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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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ALINORM 09/32/42
November 2008

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

Thirty second Session
Rome, Italy, 29 June - 4 July 2009

REPORT OF THE SECOND SESSION OF THE CODEX *AD HOC* INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE

Seoul, Republic of Korea
20-24 October 2008

NOTE: This report contains Codex Circular Letter CL 2008/33-AMR

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CX 4/100.2 **CL 2008/33-AMR**
November 2008

TO: - Codex Contact Points
- Interested International Organizations

FROM: Secretary, Codex Alimentarius Commission
Joint FAO/WHO Food Standards Programme,
Viale delle Terme di Caracalla
00153 Rome, Italy

SUBJECT: DISTRIBUTION OF THE REPORT OF THE SECOND SESSION OF THE CODEX *AD HOC* INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE (ALINORM 09/32/42)

The report of the Second Session of the Codex *Ad Hoc* Intergovernmental Codex Task Force on Antimicrobial Resistance will be considered by the 32nd Session of the Codex Alimentarius Commission (Rome, Italy, 29 June – 4 July 2009).

REQUEST FOR COMMENTS

Proposed draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (para. 22 and Appendix II)

Governments and interested international organizations wishing to comments on the above subject matter should do so in writing to the U.S. Food and Drug Administration, 7519 Standish Place, Room 177, Rockville, Maryland 20855 USA (E-mail: USAMR@fda.hhs.gov - ***preferably***, telefax: +1 240 276 9030) with a copy to the 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 (E-mail: kwakhyos@kfda.go.kr ***preferably***, telefax: + 82-2-355-6036,), the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (E-mail: Codex@fao.org - ***preferably***, telefax: +39 06 5705 4593) and the U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA (E-mail: uscodex@usda.gov - ***preferably***, telefax: +1 202 720 3157) **before 28 February 2009**.

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SUMMARY AND CONCLUSIONS

The Second Session of the Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance reached the following conclusions:

Matters of Interest to the Commission

The Task Force agreed to consolidate the three documents on Risk Assessment Guidance, Risk Profiles and Risk Management Guidance to Contain Foodborne Antimicrobial Resistant Microorganisms into a single document (para. 12) entitled “Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance” and to return the document to Steps 2/3 for redrafting by an electronic working group, circulation for comments at Step 3 and further consideration at its third session (para. 21 and Appendix II).

LIST OF ABBREVIATIONS USED IN THIS REPORT

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial Resistance
AMRD	Antimicrobial Resistance Determinant
AMRM	Antimicrobial Resistant Microorganism
AMU	Antimicrobial Use
CAC	Codex Alimentarius Commission
CL	Circular Letter
CRD	Conference Room Document
DALY	Disability Adjusted Life Year
FAO	Food and Agriculture Organization of the United Nations
GIFSA	Global Initiative for Food-related Scientific Advice
GL	Guidelines
IDF	International Dairy Federation
IFAH	International Federation for Animal Health
JEMRA	Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment
OIE	World Organization for Animal Health
RA	Risk Assessment
RM	Risk Management
RMO	Risk Management Option
SPS	Sanitary and Phytosanitary Measures
WHA	World Health Assembly
WHO	World Health Organization
WTO	World Trade Organization

INTRODUCTION

1. The Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance held its Second Session in Seoul, Republic of Korea, from 20 to 24 October 2008, at the kind invitation of the Government of the Republic of Korea. Dr Kwang-Ho Lee, Director of Food Safety Evaluation Department, Korea Food and Drug Administration, presided over the Session. The Session was attended by 132 delegates from 33 Member countries, 1 Member organization and Observers from 7 international organizations. A complete list of participants, including the Secretariat, is given in Appendix I to this report.

2. The Session was opened by Dr Yeo-Pyo Yun, Commissioner, Korea Food and Drug Administration. Dr Yun welcomed the delegates and emphasized the importance of ensuring food safety from farm-to-table in international trade in order to protect the health of consumers. He also informed the Task Force on the activities of the national surveillance program on antimicrobial resistance.

Division of Competence

3. The Task Force noted the division of competence between the European Community and its Member States, according to paragraph 5, Rule II of the Procedure of the Codex Alimentarius Commission, as presented in document CRD 1.

ADOPTION OF THE AGENDA (Agenda Item 1)[1]

4. The Task Force agreed to amend the Provisional Agenda and to include, as a new Item 4, the proposal of Japan to discuss the "Structure of the Integrated Document" that was placed on the supplementary list. The Task Force adopted the amended Agenda as the Agenda of the Session with the addition of the item as mentioned above and renumbered the Provisional Agenda Items 4 through 9 as new Items 5 through 10.

5. The Task Force noted the numerous comments received on the proposed draft Risk Management Guidance to Contain Foodborne Antimicrobial Resistant Microorganisms (renumbered Item 7). The Task Force agreed to the proposal of the Delegation of France to establish an in-session working group, open to all interested parties, lead by Denmark and working in English only, to prepare proposals on how to best address the comments received on this document.

MATTERS REFERRED TO THE TASK FORCE BY THE COMMISSION AND OTHER CODEX COMMITTEES (Agenda Item 2)[2]

6. The Task Force noted matters presented in document CX/AMR 08/2/2 arising from the 31st Session of the Codex Alimentarius Commission regarding the Terms of Reference (Objectives) and the new work of the Task Force.

INFORMATION ON THE WORK BY FAO, WHO AND OIE ON ANTIMICROBIAL RESISTANCE (Agenda Item 3)[3]

7. The Representative of FAO informed the Task Force about the recommendations made by the FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, held in Rome (Italy) in November 2007. The Task Force noted that a stakeholders meeting had been held prior to the expert meeting to allow representatives from different sectors to express their opinion on this matter.

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1 CX/AMR 08/2/1; CX/AMR 08/2/1Add.1.
2 CX/AMR 08/2/2
3 CX/AMR 08/2/3; CRD 7 (Joint FAO/WHO/OIE Expert Meeting omn Critically Important Antimicrobials – executive summary and recomendations)

8. The Representative of FAO also informed the Task Force of other joint FAO/WHO activities on provision of scientific advice and on FAO field activities to support member countries in their efforts to apply relevant codes of practices that contribute to the prevention and containment of antimicrobial resistance. The Representative of FAO indicated that the joint FAO/WHO Global Initiative for Food-related Scientific Advice on Food Safety (GIFSA) could support developing countries' efforts to generate and analyse data for risk assessments.

9. The Task Force's attention was drawn to the information on relevant OIE activities, included in document CX/AMR 08/2/3.

10. The Representative of WHO informed the Task Force about WHO activities on containment of foodborne antimicrobial resistance (AMR). These activities have been strengthened for the last ten years following a resolution taken by the 51st World Health Assembly (WHA 51.17), which requested WHO to address the alarming increase of antimicrobial resistance in a holistic manner, considering human use, as well as non-human use, of antimicrobials. The Task Force noted the establishment of the WHO Advisory Group on Integrated Surveillance of Antimicrobial resistance (WHO-AGISAR). The WHO representative informed the delegates of ongoing discussion between FAO, WHO and OIE on a joint initiative on integrated surveillance of antimicrobial resistance.

11. The Task Force thanked FAO,WHO and OIE for the information submitted.

STRUCTURE OF THE INTEGRATED DOCUMENT (Agenda Item 4)[4]

12. The Task Force agreed to consolidate the three documents on Risk Assessment Guidance, Risk Profiles and Risk Management Guidance to Contain Foodborne Antimicrobial Resistant Microorganisms into a single document.

13. The Task Force agreed to establish an in-session working group co-chaired by Canada, Denmark, France and the United States of America, open to all Members and observers and working in English only, to prepare a proposal for the structure of the consolidated document to facilitate the discussion of this matter.

14. The Delegation of the United States of America briefly introduced CRD 15, prepared by the in-session working group and draw the Task Force's attention on the working group's conclusions and the proposed structure to be used as the basis for the consolidated document.

15. The Task Force generally agreed with the working group's conclusions and the structure for the consolidated document, entitled the Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance and made the following comments and conclusions.

16. The Task Force clarified that Section 6.4 dealt with Identification of AMR-RM options, while Section 6.6 covered Selection of AMR-RM options and that Appendices on risk management should be included in the proposed structure.

17. The Task Force noted that, due to time constraints, it would be difficult to appropriately merge all the three documents on risk assessment, risk profiling and risk management into appropriate sections of the structure, since some titles or the wording in these documents did not exactly correspond to the titles of the proposed structure or vice versa. The Task Force therefore agreed that additional work was necessary to appropriately move and locate these texts in the proposed structure and to address some other inconsistencies, e.g. Scope and Purpose for each of the three documents.

[4] CX/AMR 08/2/3; CRD 2 (U.S proposal to form Working Group on Harmonization); CRD 6 (prepared by Canada, Denmark, France and the United States of America); CRD 7 (Executive summary and recommendations of the Joint FAO/WHO Expert Meeting on Critically Important Antimicrobials); CRD 15 (Report from the in-session working group on harmonization).

18. The Task Force noted that CRD 6 contained texts for common elements for introduction, general principles, risk communication, documentation and definitions, which could be inserted in appropriate sections of the proposed structure and, after some discussion, agreed that these sections should be incorporated into relevant sections of the proposed structure, where appropriate.

19. The Task Force agreed that:

- Section on introduction from CRD 6 could be inserted in Section 1 of the proposed structure;
- References included in documents be moved in Section 10 - References;
- Flowchart for AMR risk analysis be transferred in Section 5 – Components of AMR-Risk Analysis/Framework for AMR-Risk Analysis;
- General principles for AMR risk analysis be moved in Section 4 – General Principles for AMR Risk Analysis and those sections containing general principles specific to risk assessment, risk profiling and risk management would be transferred to relevant sections;
- General part of Risk communication be transferred in Section 8 – Risk Communication;
- Documentation be moved in Section 9 – Documentation; and
- Section on Definitions be moved in Section 3 – Definitions, it was noted the need to make maximum use of existing Codex definition.

It was noted that for all the above sections additional work was still necessary.

Status of the consolidated document (Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance) (N01-2008, N02-2008, N03-2008)

20. The Task Force noted that significant progress had been made on the development of the three documents, however some sections in these documents and in the proposed structure were not complete and required further development.

21. The Task Force agreed to establish an electronic working group, hosted by the United States of America, open to all Members and observers and working in English only, to prepare the consolidated document entitled “Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance” taking into account decisions taken by the current session and comments to be received in response to the Circular Letter. It requested the electronic working group to prepare revised version by end of May 2009 for circulation for comments at Step 3 and further consideration at its third session.

22. In order to facilitate the work of the electronic working group, the Task Force agreed to attach to the report as Appendix II: (a) the Structure of the Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance; (b) Proposed Draft Guidelines for the Risk Assessment of Foodborne Antimicrobial Resistant Microorganisms Related to Non-Human Use of Antimicrobials; (c) Proposed Draft Guidelines on Creating Risk Profiles for Antimicrobial Resistant Foodborne Microorganisms for Setting Risk Assessment and Management Priorities; (d) Proposed Draft Guidelines on Risk Management to Contain Foodborne Antimicrobial Resistant Microorganisms; and (e) CRD 6 containing common elements for introduction, general principles, risk communication, documentation and definitions for comments by end of February 2009.

23. The Delegations of Canada, France and Denmark offered their assistance and co-operation in accomplishing this revision.

PROPOSED DRAFT RISK ASSESSMENT GUIDANCE REGARDING FOODBORNE ANTIMICROBIAL RESISTANT MICROORGANISMS (N01-2008) (Agenda Item 5)[5]

24. The Delegation of Canada, speaking as Chairperson of the physical working group on the development of proposed draft risk assessment guidance regarding foodborne antimicrobial resistant microorganisms, briefly introduced the document and highlighted the process used by the physical working group for its elaboration. The Delegation informed the Task Force that in order to facilitate discussion, it had prepared CRD 8, which contained the original text of the document CX/AMR 08/2/4 and an analysis of comments/proposals under each section from CX/AMR 08/2/4 Add.1 and CRD 3.

25. The Task Force agreed to the proposal of the Chairperson to base the consideration of this item on CRD 8 and to discuss only provisions in Sections 2, 5, 6 and 10, which required decisions of the Task Force, with the understanding that provisions in remaining Sections would be addressed while consolidating all the three documents at a later stage. In addition to editorial changes, the Task Force made the following changes throughout the document.

26. The Task Force agreed to use the term “microorganisms” instead of “bacteria” for consistency throughout the document.

Section 2 Scope

27. The Task Force amended: the first sentence in paragraph 5 to emphasize the importance of antimicrobial resistant microorganisms and resistance determinants in the food chain; and the first sentence of paragraph 6 for clarification purposes.

28. The Task Force added “management of animal and plant production” as an additional example of specific issues raised or questions asked by risk managers in paragraph 7. The Task Force did not agree to the proposal to move this paragraph to the introductory section as the wording of this paragraph was more specific to risk assessment.

29. The Task Force clarified the nature of users of the document by inserting an additional wording to the first sentence of paragraph 8 and agreed that transmission of AMR covered not only imported but also domestic food products. The Task Force also agreed to delete the reference to OIE and national/regional food safety authorities in the second sentence and to delete the last sentence of this paragraph.

Figure 1

30. The Task Force agreed to insert the references to animal feed and aquaculture in the box on Animal and/or Plant Production in Figure 1 and put this text in square brackets for further discussion. It also inserted an additional sentence at the end of paragraph 6 to clarify the relation of arrows with the components of AMR-RA presented in lower boxes in Figure 1.

31. The Task Force had discussion on the placing of antimicrobial use (AMU) in this figure. Some delegations were of the view that AMU was more relevant to risk profiling, therefore proposed to move it to that document. Other delegations were of the opinion that AMU was one of the determinants of antimicrobial resistance and therefore it was necessary to keep it in Figure 1. After some discussion the Task Force agreed to maintain the reference to AMU in Figure 1 and put it in square brackets for further consideration.

Section 5 General considerations

32. The Task Force agreed to the proposal that AMR-RA should be reassessed when significant new evidence emerge, therefore amended the last sentence of paragraph 13 to that effect and deleted the last part of the sentence as redundant.

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[5] Originally distributed as Agenda Item 4. CX/AMR 08/2/4; CX/AMR 08/2/4 Add.1 (Comments from Comments of: Argentina, Australia, Brazil, Costa Rica, Iran, Kenya, Mexico, New Zealand, Norway, Republic of Korea, United States of America, Consumers International, IDF and IFAH); CRD 3 (Comments from the European Community, Japan and Thailand); CRD 8 (prepared by Canada); CRD 9 (Comments from the European Community); CRD 12 (comments of Canada)

Section 5.1 Purpose

33. The Task Force clarified the first sentence in paragraph 14 that AMR-RA health risks were associated with "foodborne" microorganism and/or specific resistance determinant. It put in square brackets the last part of the sentence related to the impact of non-human use of antimicrobials for further consideration.

Section 5.2 Qualitative and quantitative AMR-RA

34. An additional sentence on quantitative AMR-RA was added at the end of paragraph 15.

Section 5.3 Sources of data or evidence

35. The Task Force noted that there was a redundancy in bullets 5 and 7 in relation to parts dealing with environment and agreed not to delete bullet 5, as proposed, but instead to remove examples on external environment in bullet 7 and to move them at the end of bullet 5. The reference to studies on interaction was deleted from bullet 7.

36. Bullet 6 on non human antimicrobial use data was amended to include the reference to quantities of antimicrobial drugs used at national and regional level.

37. Bullet 10 on information was amended for clarification purposes.

38. Bullet 11 was amended to clarify that fitness meant survivability and/or adaptability.

39. Bullets 12 and 13 were deleted as they were not relevant to the section.

40. The Task Force agreed with the revision of the other bullets as proposed in CRD 8.

Section 6. Process of AMR-RA

41. The Task Force agreed to reword the first paragraph of this Section as proposed in CRD 8.

Section 6.1. Hazard identification

42. The Task Force deleted the example of commensals recognizing that it was difficult to differentiate antimicrobial resistance coming from the pathogenic microorganisms or commensals and made some changes in the last sentence of paragraph 19 for clarification and consistency. It agreed that this difference could be addressed in the definition section

43. The Task Force agreed to add an additional sentence at the end of paragraph 20 for clarification purposes.

Section 6.2 Exposure assessment

44. The Task Force made some changes in paragraphs 21, 23 and 24 for clarification purposes to better explain the relation between risk question posed and factors listed in Table 1; and deleted references to national literature in paragraph 22.

45. In order to address concerns for having antimicrobial use data in the possible data requirements for exposure assessment, the Task Force agreed to substitute the current wording in paragraphs 22 and 23 with the text proposed in CRD 12 and to put this addition in square brackets for further consideration.

Table 1

46. The Task Force agreed to merge Tables 1 and 2 and to put them in square brackets for further consideration. To the concern expressed by the Delegation of Norway that the element on selection pressure was not appropriate to this Section on exposure assessment, the Task Force agreed to amend the title to clarify that these elements were possible factors which influence the development and transmission of resistant microorganisms and resistance determinants for pre-harvest and post harvest data.

47. Different proposals were made for revisions of Tables 1 and 2. After some discussion the Task Force agreed to put in square brackets the third bullet, which was revised to read "extra-label and off-label use of antimicrobial agent".

48. The Task Force also agreed to amend the fourth bullet to clarify that trends in antimicrobial use and information on emerging diseases were referred to farm production system rather than farm management.

49. The Task Force also made clarification in the bullet related to methods and routes of administration of the antimicrobial agent and deleted the bullet regarding withdrawal time/period in the second element.

50. The Task Force agreed to add an additional bullet on plant management at the end of the second element dealing with target animal or crop and microbial factors.

51. The Task Force agreed to the proposal to add two additional bullets to the first element in Table 2 and clarify that the third bullet related to food product formulation.

52. The second element on Food production factors in Table 2 was expanded by inserting five additional bullets on Factors affecting frequency and level of resistant microorganism contamination.

53. The reference to catering was deleted from the element on consumer behaviour with the understanding that the bullet on catering and food service was included in the second element; and “sanitation’ was substituted with “personal hygiene’ in the third bullet related to human-to-human transmission of microorganisms.

54. The Task Force agreed to add an additional bullet on growth and survival characteristics of resistant microorganisms in the fourth element of Table 2.

Section 6.3 Hazard characterization

55. The first sentence of paragraph 25 was amended to link the pathogen characteristics described in the hazard identification Step; and a reference to national literature was deleted in the end of this paragraph.

56. The title of Figure 2 was amended for clarification purposes.

57. The Task Force agreed to add some text at the end of paragraph 26 to refer to names of models listed in Figure 2.

58. There was a proposal to merge paragraphs 27 and 28, however the Task Force did not agree to this proposal and retained paragraph 27 unchanged, as presented in CRD 8.

59. The Task Force noted that the first sentence of paragraph 28 was more relevant to the document on risk management, therefore decided to consider moving it into that document and deleted the rest of the paragraph.

Table 3

Element: Resistant microorganisms and resistance determinants

60. The Task Force agreed to amend the first bullet to clarify that it should include not only resistance genotype and phenotype but also cross-resistance and co-resistance.

Element: Antimicrobial agent

61. The Task Force noted that the bullet on pharmacodynamics/pharmacokinetics was more related to exposure assessment therefore decided to move it to Table 1. The Task Force also noted that the third bullet was more relevant to risk characterization, therefore moved it to Table 4. The Task Force deleted the second bullet and as a consequence, the element on Antimicrobial Agent was deleted in Table 3.

Element: Dose-response

62. The bullet in Section on Dose-response was substituted by new simplified text.

Section 6.4 Risk Characterization

63. The Task Force amended the last sentence in paragraph 30 for clarification purposes and did not agree to delete paragraph 31 as proposed.

64. The Task Force agreed to amendments for clarification purposes in bullets 1, 5, 6 and 7 in paragraph 33. It also agreed to add a reference to the FAO/WHO/OIE expert meeting held in Rome in 2007 in relation to data gaps at the end of the last bullet.

Table 4

65. The Task Force, noting that the bullet was moved from Table 3 to Table 4 (see para. 61) and that the bullet 6th bullet in Table 4, covered similar situations decided to put both bullets in square brackets for further consideration.

Section 10 Appendices

Appendix I

66. The Task Force added some language to the introductory paragraph of Appendix 1 to reflect limitations of a qualitative risk assessment.

67. The Task Force also agreed to add a sentence regarding illustration of potential approaches that could be used to conduct a qualitative risk assessment at the beginning of the second sentence in Appendix 1.

68. The Task Force noted that illustrative exposure scoring could be examples, therefore inserted "e.g." in brackets with the scores.

Appendix II

69. The Task Force noted that Appendix II could be revised in light of the discussions and agreed to put it in square brackets.

Status of the proposed draft risk assessment guidance regarding foodborne antimicrobial resistant microorganims (N01-2008)

70. See paras 20-22.

PROPOSED DRAFT GUIDANCE ON CREATING RISK PROFILES FOR ANTIMICROBIAL RESISTANT FOODBORNE MICROORGANISMS FOR SETTING RISK ASSESSMENT AND MANAGEMENT PRIORITIES (N03-2008) (Agenda Item 6)[6]

71. The Delegation of United States of America, speaking as Chairperson of the physical Working Group on the proposed draft Guidance on Creating Risk Profiles for Antimicrobial Resistant Foodborne Microorganisms for Setting Risk Assessment and Management Priorities, briefly introduced the report of the Working Group. The Delegation informed the Task Force that in order to facilitate discussion, it had prepared CRD 11, which contained the original text of the document CX/AMR 08/2/5 and comments/proposals under each section extracted from CX/AMR 08/2/5 Add.1 and CRD 4.

72. The Task Force agreed to the proposal of the Chairperson to base the consideration of this item on CRD 11 and to discuss provisions only in Sections 1 and 4 (including sub-sections 4.1 through to 4.7) and the Annex, which required decisions of the Task Force, with the understanding that provisions in remaining sections and matters of editorial nature would be addressed while consolidating all the three documents at a later stage.

73. The Task Force agreed with most of the changes proposed in CRD 11 and, in addition, made the following comments and decisions.

Section 4.1 - Identification of an antimicrobial resistance food safety issue

74. In paragraph 8, the Task Force deleted the last part of the second sentence starting with "by reducing the therapeutic value…." to improve the clarity of the paragraph and because potential adverse effects of resistance were more accurately described in other part of the document. The Task Force agreed to replace throughout the document the term "bacteria" with "microorganisms" for consistency with earlier decision.

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[6] Originally distributed as Agenda Item 5. CX/AMR 08/2/5; CX/AMR 08/2/5 Add.1 (Comments of Argentina, Australia, Brazil, Canada, Costa Rica, Iran, Mexico, New Zealand, Norway, IDF and IFAH); CRD 4 (Comments of European Community, Japan and Thailand); CRD 11 (Development of Guidance on Creating Risk Profiles for Antimicrobial Resistant Foodborne Microorganisms for Setting Risk Assessment and Management Priorities, prepared by USA); CRD 16 (Comments of USA)

75. In paragraph 10, the Task Force agreed to replace the term “public input” with “and interested parties”. In this regard it was noted that the definition for “interested parties” should be included in the “Definitions” section of the consolidated document. It was further agreed to add an additional sentence to refer to the information on plant production and food processing that may be useful to identify food safety issues.

Section 4.2 - Development of antimicrobial resistance risk profile

76. In paragraph 12, and in other paragraphs of the document, the Task Force agreed to change the term “stakeholders” with “interested parties”, to be defined in the “Definitions” section of the consolidated document.

77. The Delegation of Brazil was of the view that the reference to lists developed by “national” groups included in the third bullet of paragraph 13 was not relevant in the context of international trade. In this regard, other delegations indicated that the use of lists of critically important antimicrobials developed by national groups provided useful elements in the preparation of risk profiles.

78. The Task Force discussed whether paragraph 15 on “provisional decision” needed to be moved in other parts of the document. In noting that some provisions on “provisional decision” were also included in the Risk Management part of the document, the Task Force agreed to put the entire paragraph into square brackets and to decide on its location at a later stage.

Section 4.4 - Establishment of broad risk management goals

79. The Task Force had an extensive discussion on this section, especially on whether it should be part of the risk management or risk profile activities. Some delegations were of the view that the section was part of the risk profile activities because of the ranking of food safety issues. Other delegations were of the opinion that the section was a deviation from the Codex risk analysis working principles; and that there was a need to clearly differentiate between risk management goals and options and define these terms.

80. It was further noted that the physical Working Group had attempted to describe in this section the various steps of risk profiling as a process of events; that the structure of the antimicrobial resistance risk analysis did not necessarily follow the structure of the Codex risk analysis principles; that the inclusion of this section could be justified by the specificity of the antimicrobial resistance risk analysis; and that the “establishment of broad risk management goals” was described as part of “Preliminary Risk Management Activities” in the FAO Food Safety Risk Analysis document that considered the most recent development on this matter.

81. The Task Force agreed on the need to clarify the section and more clearly describe the sequence of activities that leads to the decision on the need for a risk assessment, and to review the factors listed in para. 21that may influence this decision. The Task Force agreed to replace paragraphs 18-22 with a proposal, as contained in CRD 16. However, in view of the impossibility to consider the proposal in detail, the Task Force agreed to put the revised paragraphs 18-21 in square brackets for further consideration.

Section 4.5 - Establishment of risk assessment policy

82. The Task Force noted that paragraph 24 had been reviewed in view of the decision to merge the three documents (see Agenda Item 4). It was agreed to change the term “adopt” with “refer” as more appropriate and to replace the term “guidance” with “guidelines” throughout the text, as more appropriate.

Section 4.6 - Commission of a risk assessment

83. The Task Force agreed to put the proposed new last sentence in paragraph 26 and the last three bullet points in paragraph 27 into square brackets and to reconsider a more appropriate location during the harmonisation process of the consolidated document.

Section 4.7 - Consideration of results of the risk assessment

84. The Task Force agreed to revise paragraph 30 to make a better transition with the other parts of the document and put the entire paragraph in square brackets for further consideration during the harmonization process of the consolidated document.

ANNEX (Suggested Elements to Include in an Antimicrobial Resistance Risk Profile)

85. The Task Force agreed to consider the suggestion to include tables on possible data requirements to be collected/applied during the various steps of a risk profiling, during the harmonization process of the consolidated document.

1. Definition of the hazard-food commodity combination(s) of concern

86. The first bullet was deleted as inconsistent with the header of the sub-section.

2. Description of the public health problem (i.e. the adverse human health consequences)

87. The Task Force agreed that it was more appropriate to refer to “disease” (instead of “illness”) throughout the entire document for consistency with WHO terminology.

88. The first white bullet under “Characteristic of the antimicrobial-resistant infection or disease” was put in square bracket, pending a decision on the definition of “adverse health effect”, to be included in the consolidated document.

4. Description of antimicrobial(s) use associated factors (Pre-harvest factors)

89. The Task Force decided to revise the header to read “Description of antimicrobial(s)”.

90. In the third bullet, the terms “withdrawal period” was deleted in order to more generally refer to the time period between administration and milking or slaughtering.

91. The sixth bullet was replaced with a new bullet on “quantity of use in relevant animal and plant species”. The eighth bullet and the new proposed bullet on “availability of alternative treatments and preventive measures” were moved under point 6 “Other Risk Profiles Elements”, as more appropriate.

6. Other Risk Profiles Elements

92. The last bullet was deleted as outside the scope of a risk profile.

93. The Task Force noted the comments regarding the need for the establishment of databases and training/capacity building activities on antimicrobial risk analysis and it was of the view that these needs could not be addressed in this document but rather in the implementation of the activities and that international organizations could assist to address these needs.

Status of the proposed draft guidance on creating risk profiles for antimicrobial resistant foodborne microorganisms for setting risk assessment and management priorities (N03-2008)

94. See paras 20-22.

PROPOSED DRAFT RISK MANAGEMENT GUIDANCE TO CONTAIN FOODBORNE ANTIMICROBIAL RESISTANT MICROORGANISMS (N02-2008) (Agenda Item 7)[7]

95. The Delegation of Denmark, speaking as co-Chairperson of the in-session Working Group on the proposed draft Risk Management Guidance to Contain Foodborne Antimicrobial Resistant Microorganisms (see para. 5), briefly introduced the report of the Working Group, as presented in CRD 13.

96. The Task Force noted that the Working Group had concentrated mainly on Section 2 “Purpose and Scope” and on Section 4 “Identification of risk management options”, had skipped those parts that would be covered during the integration of the three documents (i.e. Introduction and General Principles) and had not proceed beyond paragraph 9, due to time constraints.

[7] Originally distributed as Agenda Item 6. CX/AMR 08/2/6; CX/AMR 08/2/6 Add.1 (Comments of Argentina, Australia, Brazil, Canada, Costa Rica, Iran, Mexico, New Zealand, Norway, IDF and IFAH); CX/AMR 08/2/6 Add.2 (Comments of IFT); CRD 5 (Comments of Japan and Thailand); CRD 10 (Comments of European Community); CRD 13 (Report of the Working Group on Agenda Item 7); CRD 14 (Comments of France and Denmark)

97. The Task Force agreed to base the consideration of this item on CRD 13 (for the parts revised by the Working Group, i.e. paras 1-9) and on CRD 14, which contained a proposal prepared by the two co-chairpersons of the Working Group, based on comments included in documents CX/AMR 08/2/6 Add.1, Add.2 and CRD 5.

Section II – Purpose and Scope

98. The Task Force agreed to a proposal to revise Section II and clarified that the main purpose was to reduce the risk of foodborne AMR microorganisms and resistance determinants from the non-human use of antimicrobials following risk profiling and/or risk assessment.

99. The Task Force agreed to revise the text in relation with further revision in paragraph 8 in order to include several important references on relevant works developed by the two parent organizations (FAO and WHO) and OIE.

Section IV – Identification of the Available Options

100. The Task Force agreed to revise the second part of paragraph 5 to make the examples of options for pre- and post-harvest more specific. Some delegations questioned whether the option of reducing the use of antimicrobials was appropriate as they felt that the purpose of the document was on the reduction of the risks associated with antimicrobial resistance and not on the reduction of antimicrobials' use. Other delegations were in support of the revised text and were of the opinion that the reduction of antimicrobials' use was an appropriate example of an option for reducing antimicrobial resistance. As a compromise, the Task Force agreed to place the suggested revision in square brackets.

101. The Task Force agreed to delete paragraph 6 and to move paragraph 7 to section 8.

102. In paragraph 8, the Task Force agreed to limit the list of codes of practices that "should be followed as a minimum" to only include Codex texts, and to delete reference to other texts. It was also noted that paragraph 4 clearly stated that other texts, including OIE and WHO, should be read in conjunction with the document..

103. The Task Force noted that the in-session Working Group had an extensive discussion on paragraph 9 regarding additional risk management options. In discussing this paragraph, proposals were made to amend bullet (b) with language from Article 5 point 7 "Assessment of risk and determination of the appropriate level of sanitary and phytosanitary measures" of the WTO/SPS Agreement. It was noted that in other parts of the document there were provisions that allowed the possibility for making a provisional decision and that on these issues similar language were included in another part of the document (i.e. paragraph 20) and in the risk profile document (paragraph 15). After some discussion and noting the bullets (a) and (b) were not specifically related to the implementation of additional options but rather to their selection, the Task Force agreed to delete the second bullet and to move the first bullet to Section 6 "Selection of Risk Management Option" .

A. Pre-harvest options

A.1. General

104. The Task Force agreed to move the first bullet on monitoring of the use of antimicrobials to Section VIII "Monitoring and Review of Risk Management Options" as more appropriate to that section. With regard to the second bullet, the Task Force considered whether it was necessary and agreed that, although licensing of veterinary drugs was taken into account in several Codex documents, it was not generally believed to be part of the Codex remit and that the retention of the bullet required several amendments. The Task Force also agreed to delete the entire bullet, with the exception of part of sub-bullet (c) that was moved to section A.2 "Food animal production" as a new bullet. As a result of these decisions the Task Force noted that the entire section remained empty.

A.2.Food animal production

105. The Task Force revised the text of the new bullet (see para. 104) to include references to pre- and post-approvals and off-label prohibition. A reference to consideration of Critically Important Antimicrobials (CIA) for human health[8] was added in the bullet in recognising that their consideration was part of risk management's responsibilities.

106. The Task Force agreed to merge the second and fourth bullets and to make some amendments to improve their clarity. The Task Force noted that the document should not include aspects already covered in the *Code of Practice to Minimise and Contain Antimicrobial Resistance* (CAC/RCP 61-2005) and agreed to delete the third bullet.

107. The Task Force amended the fifth bullet to delete reference to treatment lines of antimicrobial treatment's choices, in recognising that aspects of veterinary medicine's practice were outside the scope of the guideline and that CAC/RCP 61-2005 included directed to veterinary professional organizations to develop species and disease specific clinical practice guidelines on the responsible use of veterinary antimicrobial drugs.

108. The alternative wording proposed for the sixth bullet was not agreed and the second and last sentences were deleted. The Observer from IDF commented that prophylactic use of antimicrobial agent was an important animal health measure and expressed concern that the restriction of use was not qualified in this bullet.

109. The last part of the seventh bullet was amended to refer to the reduction of the risk associated with the use of antimicrobials. All sub-bullets were put in square brackets for further consideration.

110. The Task Force agreed to delete the remaining bullets (from the 8th through to the 12th) because they were either outside the mandate of Codex (i.e. 10th bullet) or already included in other bullets or covered in CAC/RCP 61-2005.

111. In view of time constraints, the Observer from Consumers International proposed to consider the inclusion of a section on animal feed production under at a later stage.

A.3 Plant production

112. The Task Force agreed to rename the title for this section "Food crop production" in order to avoid confusion with plants which were used for animal feed and to add a similar bullet on approval and licensing of antimicrobials to that inserted in Section A.2 (see para. 105) in this section. Due to time constraints, the Task Force could not consider several proposals contained in CX/AMR 08/2/6 Add.1 and Add.2 and CRDs 5 and 10.

B. Post-harvest options

113. The Task Force amended the first sentence to clarify that target interventions were directed towards microbial contamination of food including microorganisms. It was noted that this sentence was a bullet and not an introduction to the section.

114. The Task Force deleted specific example for novel intervention, i.e."such as bacteriophages" in the second bullet and deleted the third bullet. The fourth and fifth bullets were put in square brackets for further discussion on their feasibility and practicability.

Section V Evaluation of Risk Management Options (RMO)

115. The Task Force put the entire section into square brackets in recognising the need for further work to clarify its scope and to include possible advantages and disadvantages of the most important management options and examples on experiences of voluntary application of guidelines on prudent use versus restrictive actions could be described in this section or elsewhere.

116. In view of time constraint the Task Force did not consider the remaining parts of the document.

[8] FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials. Rome, 2008

Status of the proposed draft risk management guidance to contain foodborne antimicrobial resistant microorganisms (N03-2008)

117. See paras 20-22.

OTHER BUSINESS AND FUTURE WORK (Agenda Item 8)

118. The Task Force noted that there was no item proposed to be discussed under “Other Business and Future Work”.

DATE AND PLACE OF NEXT SESSION (Agenda Item 9)

119. The Task Force noted that its Third Session was tentatively scheduled to be held in October 2009.

SUMMARY STATUS OF WORK

SUBJECT MATTERS	STEP	ACTION BY:	DOCUMENT REFERENCE (ALINORM 09/32/42)
Proposed draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (N01-2008, N02-2008, N03-2008)	2/3	Electronic working group Members and Observers 3rd Session of the Task Force	Paras 12, 20-22 and Appendix II

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Appendix II

PROPOSED DRAFT GUIDELINES FOR RISK ANALYSIS OF FOODBORNE ANTIMICROBIAL RESISTANCE

Part1

Structure for Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance

1. Introduction
   A. Risk communication
2. Scope
3. Definitions
4. General Principles for AMR-Risk Analysis
5. Components of AMR-Risk analysis/ Framework for AMR-Risk Analysis (flowchart)
6. Risk Management
   - 6.1 General principles of AMR-RM
   - 6.2 General Considerations
   - 6.3 Preliminary AMR-Risk Management Activities
     - 6.3.1 Identification of an AMR food safety issue
     - 6.3.2 Development of an AMR- Risk Profile
     - 6.3.3 Ranking of food safety issues and setting priorities for risk assessment and management
     - 6.3.4 Establishment of broad risk management goals
     - 6.3.5 Establishment of Risk Assessment Policy
     - 6.3.6 Commission the AMR-RA
     - 6.3.7 Consideration of results of AMR-RA
   - 6.4 Identification of AMR-RM options
   - 6.5 Evaluation of AMR-RM options
   - 6.6 Selection of AMR-RM Options
   - 6.7 Implementation of AMR-RM Options
   - 6.8 Monitoring and Review of AMR-RM Options
7. Risk Assessment
   - 7.1 General Principles for AMR-RA
   - 7.2 General Considerations
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    Decide on placement of RA, RP and RM appendices

Part 2

PROPOSED DRAFT GUIDELINES FOR THE RISK ASSESSMENT OF FOODBORNE ANTIMICROBIAL RESISTANT MICROORGANISMS RELATED TO NON-HUMAN USE OF ANTIMICROBIALS

SECTION 1. INTRODUCTION

(This section may be revised with merged document – The AMR Risk Analysis Document)

1. Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue. When pathogens become resistant to antimicrobial agents, they can pose a greater health risk as a result of potential treatment failure and increased likelihood and severity of disease. AMR is inherently related to antimicrobial use in any environment including human and non-human uses. Food is an important vehicle for spread of resistant microorganisms from animals to humans.

2. In accordance with the Codex principles, risk assessment is an essential tool in assessing the overall risk to human health from foodborne antimicrobial resistant microorganisms. In this context, AMR risk assessment (AMR-RA) described in this document characterizes the adverse effects to human health resulting from exposure via food to antimicrobial resistant microorganisms or resistance determinants in animal feed, food animals (including aquaculture), food production/processing and retail foods, arising from the non-human use of antimicrobials.

3. Over the past decade, there have been significant developments with respect to AMR-RA. A series of FAO/OIE/WHO expert consultations on AMR have identified 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 and 2008). The OIE guideline on risk analysis of AMR is a major development in addressing the potential public health impact of antimicrobial resistant microorganisms of animal origin (OIE, 2007). However, it is necessary to capture the multidisciplinary aspects of AMR within the entire farm to table continuum. In order to address the existing gaps and controversies in the methodologies and approaches, there is a need to develop a consolidated guidance document specific to AMR-RA.

4. The objective of this guidance document is to provide a structured risk assessment framework to assess the risk to human health associated with the presence in food and animal feed (including aquaculture), and the transmission through food and animal feed, of antimicrobial resistant microorganisms or resistance determinants linked to non-human use of antimicrobial agents. 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) (FAO/WHO, 2007), the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999) (FAO/WHO, 1999) and the proposed guidelines on AMR risk profile and AMR risk management (currently under development). 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).

SECTION 2. SCOPE

5. The scope of this guidance document encompasses the overall risk to human health relating to antimicrobial resistant microorganisms and resistance determinants in microorganisms, in particular in food, food animals, food production/processing, and plants arising from the non-human use of antimicrobials.

6. Essentially, this AMR-RA guidance document provides 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. A schematic presentation in Figure 1 shows the scope and relationship of the components of AMR-RA. The arrows connecting each of the lower boxes in Figure 1 represent a multitude of steps, each a potential intervention or critical control point.

7. The extent of the farm-to-table pathway covered by the AMR-RA should fit its intended purpose. The scope of the risk assessment is determined by the risk managers in consultation with risk assessors. Considering the complexity of the AMR issue, specific issues raised or questions asked by risk managers should be as precise as possible (e.g. combinations of microorganism/antimicrobial class, particular use of antimicrobial, target species, specific geographical area, management of animal and plant production) for risk assessors to specifically address the risk issue.

8. Intended users of this document include member countries and their national/regional food safety authorities conducting risk assessment on transmission of AMR in food products (included domestic and imported food). It can be taken into account by the joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA), or international organizations. Industries/organizations involved in food production, and/or manufacture, distribution and use of antimicrobials may find it useful in assessing the AMR risks.

9. The risk assessment of AMR marker genes in recombinant-DNA plants[1] or microorganisms[2] or of certain food ingredients, which could potentially carry AMR genes such as probiotics[3] and residue issues are outside the scope of this document.

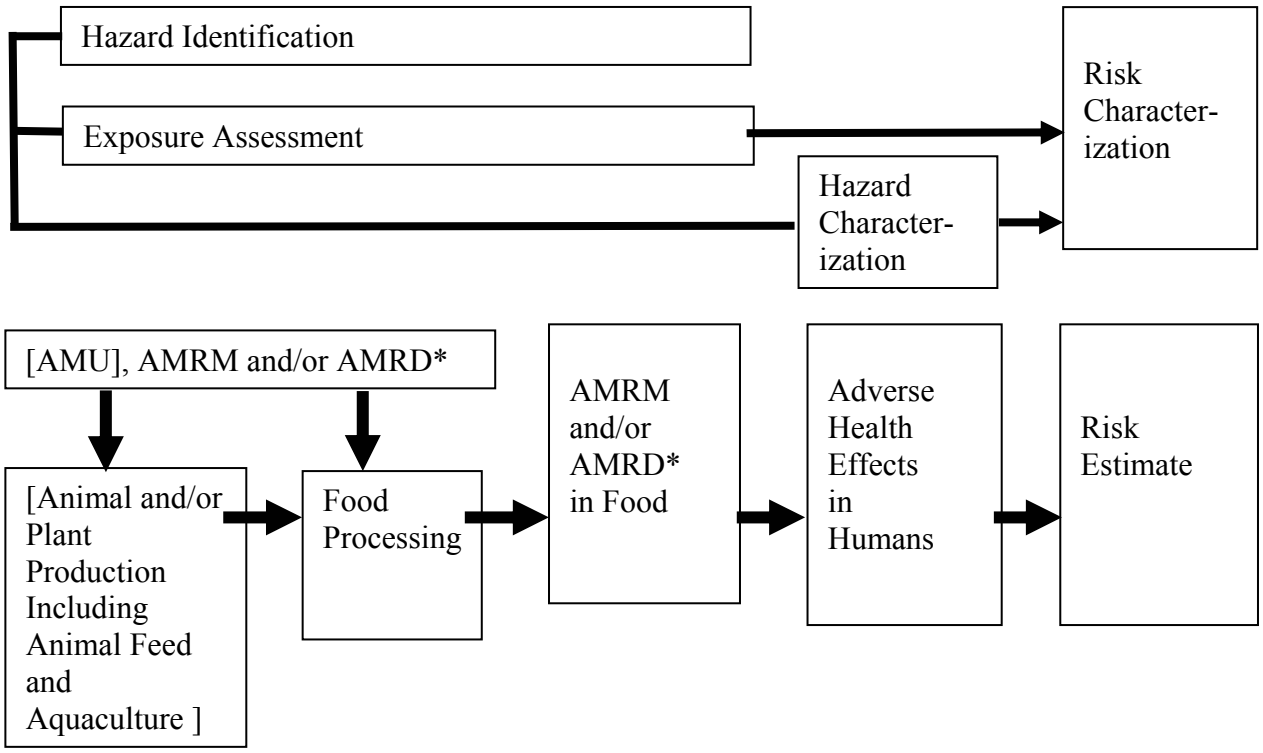

Figure 1. Schematic showing the scope and relationship of the components of AMR-RA
(*: AMU, antimicrobial use; AMRM, antimicrobial resistant microorganism; AMRD, antimicrobial resistance determinant)

SECTION 3. DEFINITIONS

(This section may be revised with merged document – The AMR Risk Analysis Document)

10. 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. Some established Codex definitions are cited in *italics*. Definitions cited from existing FAO/OIE/WHO documents are referenced as appropriate.

[1] The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA plants is addressed in the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003) (FAO/WHO, 2003b).
[2] The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA microorganisms is addressed in the Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms (CAC/GL 46-2003) (FAO/WHO, 2003c).
[3] The food safety assessment on the use of probiotics in foods is addressed in a Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Foods (FAO/WHO, 2002).

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 illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality (FAO/OIE/WHO, 2003).

Antimicrobials (Antimicrobial Agents) - Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target (FAO/OIE/WHO, 2008).

Antimicrobial class: Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of 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 - The ability of a microorganism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species (FAO/OIE/WHO, 2008).

Commensal – Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected.

Co-resistance: Various resistance mechanisms, each conferring resistance to an antimicrobial class, associated within the same bacterial 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 agent, in general the higher the activity, the lower the level of resistance. Cross-resistance implies cross-selection for resistance (FAO/OIE/WHO, 2008).

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.

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 their 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 the hazard*.

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 groups of food.*

Pathogen – A microorganism that causes illness or disease.

Pre-Harvest – The stage of food animal or plant production prior to the slaughtering or harvesting.

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

Resistance Determinant – The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial. They are located in a chromosome or a plasmid, and may be associated with transmissible genetic elements such as integrons or transposons, thereby enabling horizontal transmission from resistant to susceptible strains.

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 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 Estimate - *Output from Risk Characterization.*

Weight of Evidence - A measure that takes into account the nature and quality of scientific studies intended to examine the risk of an agent. 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.

SECTION 4. GENERAL PRINCIPLES

(This section may be revised with merged document – The AMR Risk Analysis Document)

11. AMR-RA is considered a specific form of microbiological risk assessment. The approach of AMR-RA should be consistent with the Working Principles for Risk analysis for Food Safety for Application by Governments (FAO/WHO, 2007) and the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (FAO/WHO, 1999). Additional principles more specific to AMR-RA are highlighted below:

- AMR-RA should address the risk question taking into account the whole farm-to-table continuum approach, where appropriate, encompassing the food pathway of production, processing, storage, distribution and consumption.
- AMR-RA should essentially consider the principal contributing factors, such as non-human antimicrobial use (including both therapeutic and non-therapeutic uses in animals or plants), to the emergence and dissemination of AMR among pathogenic and commensal microorganisms that have food reservoirs.
- AMR-RA should consider the impact of AMR on the effectiveness/efficacy of the available antimicrobial agents in human medicine which are needed to treat related and unrelated human infections.
- AMR-RA should consider the dynamics of genetic resistance determinants within microbial populations (e.g., in animal feeds, aquaculture or environment) as well as their persistence and spread within humans and animals.

SECTION 5. GENERAL CONSIDERATIONS

12. In accordance with the Working Principles for Risk Analysis for Food Safety for Application by Governments (FAO/WHO, 2007), AMR-RA should clearly document the scope and purpose as well as the output format assessed, which are generally defined by the risk manager commissioning the work. Scientific evidence related to AMR risks originates from studies of diverse sources, which often may not have been designed for the purpose of an AMR-RA.

13. Given the complexity of AMR issues, AMR-RA will require the expertise that spans multiple scientific disciplines and a multidisciplinary team with effective interaction is important to the endeavour. Involvement of appropriate experts will help select the data of high quality, and identify their strengths and limitations. Similarly, input from stakeholders should be sought in identifying available data or information for AMR-RA. AMR-RA should consider the weight of evidence and uncertainty of scientific data used, and should transparently record the sources of data and the data selection process. AMR-RA should particularly demonstrate how the risk estimates are reached. Appropriate selection of the presentation formats or the order of data presentation may facilitate transparency. Similarly, AMR-RA should be reassessed when significant new evidence emerges.

5.1. PURPOSE

14. The purpose of AMR-RA is to determine the human health risk associated with specific foodborne antimicrobial resistant microorganism(s) and/or specific resistance determinant(s) [and the impact of non-human antimicrobial use]. It can provide guidance to risk managers on appropriate risk management options.

5.2. QUALITATIVE AND QUANTITATIVE AMR-RA

15. The principles of AMR-RA apply equally to both qualitative and quantitative risk assessment. While the design differences may yield different forms of output, both approaches are complementary. Based on the purpose or the type of questions to be answered and data availability for a specific AMR-RA, the decision on selection of a qualitative or quantitative approach should be made. 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. Appendix 1 provides examples of the outputs from a qualitative AMR-RA. The Appendix is not intended to imply that a qualitative AMR-RA is the preferred approach but merely to illustrate ways in which qualitative findings can be presented. Quantitative risk assessment can be divided into two types, deterministic or probabilistic and these will result in different forms of output (FAO/WHO 2006b).

5.3. SOURCES OF DATA OR EVIDENCE

16. Given the fact that multiple data sources are likely required for an AMR-RA and that these data can be limited, their strengths, limitations, discrepancies, and gaps should be clearly presented using a weight of evidence approach (e.g., FAO/OIE/WHO, 2008).

17. Possible sources of information:

- Monitoring and surveillance programs including active and passive surveillance (phenotypic and if applicable genotypic information) for AMR derived from humans, food, animal feed, animals, or plants taking into consideration epidemiologic and microbiological breakpoints.
- Epidemiological investigations of outbreaks and endemic cases associated with resistant microorganisms.
- Clinical studies including case reports on the relevant foodborne-related infectious disease prevalence, primary and secondary transmission, antimicrobial therapy, and impacts of resistance on disease frequency and severity.
- Regional treatment guidelines for zoonotic pathogens including information on the medical importance of and potential impacts of increased resistance in target or other microorgansims to alternative treatments.
- Studies on interaction between microorganisms and their environment through the farm-to-table (litter, water, faeces, and sewers).
- Non-human antimicrobial use data such as quantity of antimicrobial drugs used at national and regional levels, daily dosage, species-specific (including plants), route of administration, and duration.
- Investigations of the characteristics of resistant microorganisms and resistance determinants (in-vitro and in-vivo studies).
- Research on properties of antimicrobials including their resistance selection (in-vitro and in-vivo) potential and transfer of genetic elements and the dissemination of resistant microorgansims in the environment.
- Field animal trials addressing the linkage of antimicrobial usage and resistance.
- Information on factors influencing the transfer of resistance determinants.
- Information on the link between resistance, virulence, and/or fitness (e.g. survivability or adaptability) of the microorganism.
- Data on the pharmacokinetics / pharmacodynamics related to the application of drugs.

SECTION 6. PROCESS OF AMR-RA

18. At the beginning of the work the specific purpose of the particular AMR-RA being carried out should be clearly stated. The output form and possible output alternatives of the AMR-RA should be defined. The microbiological risk assessment may require a preliminary investigation phase to define and map the work to be undertaken within the framework of the AMR-RA.

19. According to the established working principles for risk analysis for food safety (FAO/WHO, 2007), the process of an AMR-RA is composed of **Hazard Identification**, **Exposure Assessment**, **Hazard Characterization**, and **Risk Characterization**[4] (Exposure Assessment and Hazard Characterization can be conducted in parallel). This proposed process utilizes the microbiological risk assessment (FAO/WHO, 1999) and integrates the structured approach described in the OIE guideline (i.e., hazard identification, release assessment, exposure assessment, consequence assessment and risk estimation) (OIE, 2007).

6.1. HAZARD IDENTIFICATION

20. The process of hazard identification recognizes that the hazards, resistant pathogenic and commensal microorganisms and/or resistance determinants of food, animal feed, and/or of animal/plant origin, have the potential to cause an adverse human health effect. The resistance determinants from resistant microorganisms can disseminate both vertically and horizontally. Intra- or inter-species transfer occurs for mobile resistance determinants from both pathogenic and commensal microorganisms. In this document, hazard includes antimicrobial resistant microorganisms (pathogenic and commensal) and their resistance determinants (from feed, animals, plants and food derived from animals or plants). The conditions under which the hazard produces adverse health effects include scenarios through which humans could become exposed to a microorganism which contains the resistance determinant. The scope of hazard identification (e.g., combinations of microorganisms/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) is guided by the question posed by risk managers for a specific AMR-RA.

21. Data in the hazard identification step may include: description of the microorganisms and their genotypic and phenotypic characteristics including molecular characterization of resistance determinants, virulence and pathogenicity, in-vivo studies in laboratory animals, surveillance or epidemiological studies of resistant infections or resistance determinants, and clinical studies. Additionally, interaction of resistant microorganisms or resistance determinants with the 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. Where necessary, opinions should be sought from relevant experts and consideration given to using studies on analogous microorganisms.

6.2. EXPOSURE ASSESSMENT

22. The exposure assessment will address all the pathways as a consequence of non-human uses of antimicrobials resulting in the emergence and dissemination of resistant microorganisms and resistance determinants to humans via the food chain. This step covers the release and exposure assessments of the OIE guideline (OIE, 2007). The fundamental preliminary 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.

23. 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 antimicrobial resistance development or they can pose questions regarding exposure to existing antimicrobial resistant microorganisms/resistant determinants found on food. The first part of Table 1 (pre-harvest factors) includes possible factors for modelling the likelihood for the development and spread of resistance within animal or plant populations [(similar to the release assessment of the OIE guideline (OIE, 2007)], whereas the second part of the table considers possible factors related to the exposure to food containing antimicrobial resistant microorganisms and/or resistant determinants (post-harvest factors). The factors outlined in Table 1 reflect points along the food chain that may influence the level of antimicrobial resistant microorganisms (microbial load) or resistant determinants and are a consolidation of recommendations from Principles and Guidelines for the Conduct of Microbiological Risk Assessment (FAO/WHO, 1999) and OIE guideline (OIE, 2007) as well as with information available from literature (FAO/WHO, 2003a, 2006a and 2008b; FAO/OIE/WHO, 2008; and OIE, 2003).

[4] Recent practical guidelines from the Joint FAO/WHO Experts Meeting on Microbiological Risk Assessment (JEMRA) are available, respectively, with respect to the food safety risk analysis (FAO/WHO, 2006a), the use of microbial risk assessment outputs to develop practical risk management strategies (FAO/WHO, 2006b), the assessment for hazard characterization (FAO/WHO, 2003a), exposure assessment (FAO/WHO, 2008b), and risk characterization (in press).

24. An AMR-RA addressing the overall risk to the general population will examine the load and likelihood of contamination of all foods (domestic and imported) by resistant microorganisms/resistance determinants and to the extent possible the factors that could influence their prevalence in food. The direction of factors included in assessment of risk can either add to or subtract from the final estimate.

25. When the hazard of interest is the resistance determinant including those in commensal microorganisms, then exposure assessment should consider whether they 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* (CAC/RCP 54-2004)). There is a potential for environmental microorganisms to be a reservoir of resistance determinants for subsequent transfer to pathogens/commensals that have human health implications, AMR-RA may need to consider these factors.

[Table 1. Possible factors that influence the development, prevalence and transmission of resistance microorganism and resistance determinants - pre-harvest and post harvest data

Element	Description or scope of data
Selection pressure	Extent of antimicrobial agent use or proposed use • Number of animal, crop or target farms exposed to the antimicrobial agent in the defined time period • Geographical distribution of use and/or farms • [Extra- and off-label use of antimicrobial agent] • 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
	Intensity of non-human use of antimicrobials • How much is used per target (as quantitative as possible) in the defined time period • Methods and routes of administration of the antimicrobial agent (individual/mass medication, local/systemic application) • Dosing regimen and duration of use • Number of administrations/administration periods in the defined time period • Cumulative effects of use of other antimicrobials in the defined time period
Target animal or crop and microbial factors affecting resistance development and spread	• Seasonal changes in microorganism prevalence • Rate of resistance development in commensal and zoonotic microorganisms in targets after administration of an antimicrobial agent • 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) • Primary and secondary transmission among targets • Animal management factors affecting immunity • Plant management

	• Pharmacokinetics and pharmacodynamics
Other possible sources of resistant microorganisms for the target	• Prevalence of other targets carrying microorganisms of interest; fraction that are resistant to antimicrobial agent in question • Prevalence of animal feed contaminated with resistant microorganisms • Prevalence of resistant microorganisms in soil or water, animal and human waste products
Possible outcome	Estimate or probability of the prevalence of the target animal or crop carrying resistant commensal and/or resistant zoonotic microorganisms presented for food harvest that is attributable to the use of the antimicrobial, and the level of contamination
Initial level of contamination of the food product	Prevalence and level of commensals and zoonotic microorganisms present in/on the target at slaughter or time of crop harvest and proportion resistant to the antimicrobial agent • Antimicrobial resistance rate of microorganisms present in/on the target at slaughter or time of crop harvest • Antimicrobial resistance rate of microorganisms present in the retail food • Food matrix factors (food product formulation)
Food production factors	Factors affecting the frequency and level of resistant microorganism contamination: • Sanitation and process controls, such as GMP, GHP and HACCP • Methods of production and processing • 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 • Regional or seasonal differences in quantity of food products produced • Catering and food services
Consumer behaviours	• Storage, cooking and handling • Cross-contamination • Human-to-human transmission of the microorganisms, including personal hygiene • 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
Possible outcome	Estimate of the likelihood and level of contamination of the food product at the time of consumption with resistant microorganisms and attendant uncertainty

]

6.3. HAZARD CHARACTERIZATION

26. The hazard characterization step considers the characteristics of the pathogen as already described in the hazard identification step, matrix and host in order to determine the probability of disease upon exposure to the pathogen (FAO/WHO, 2003a and 2006a). AMR-RA 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 (OIE, 2003 and 2007). The overall structure of the consolidated hazard characterization step in the AMR-RA is presented in Figure 2 (FAO/WHO, 2003a and 2006a; OIE, 2007) and the hazard characterization step has incorporated the consequence assessment of the OIE guideline that considers the relationship between the exposure and the adverse effect with the emphasis on the severity of the adverse health consequence (OIE, 2007).

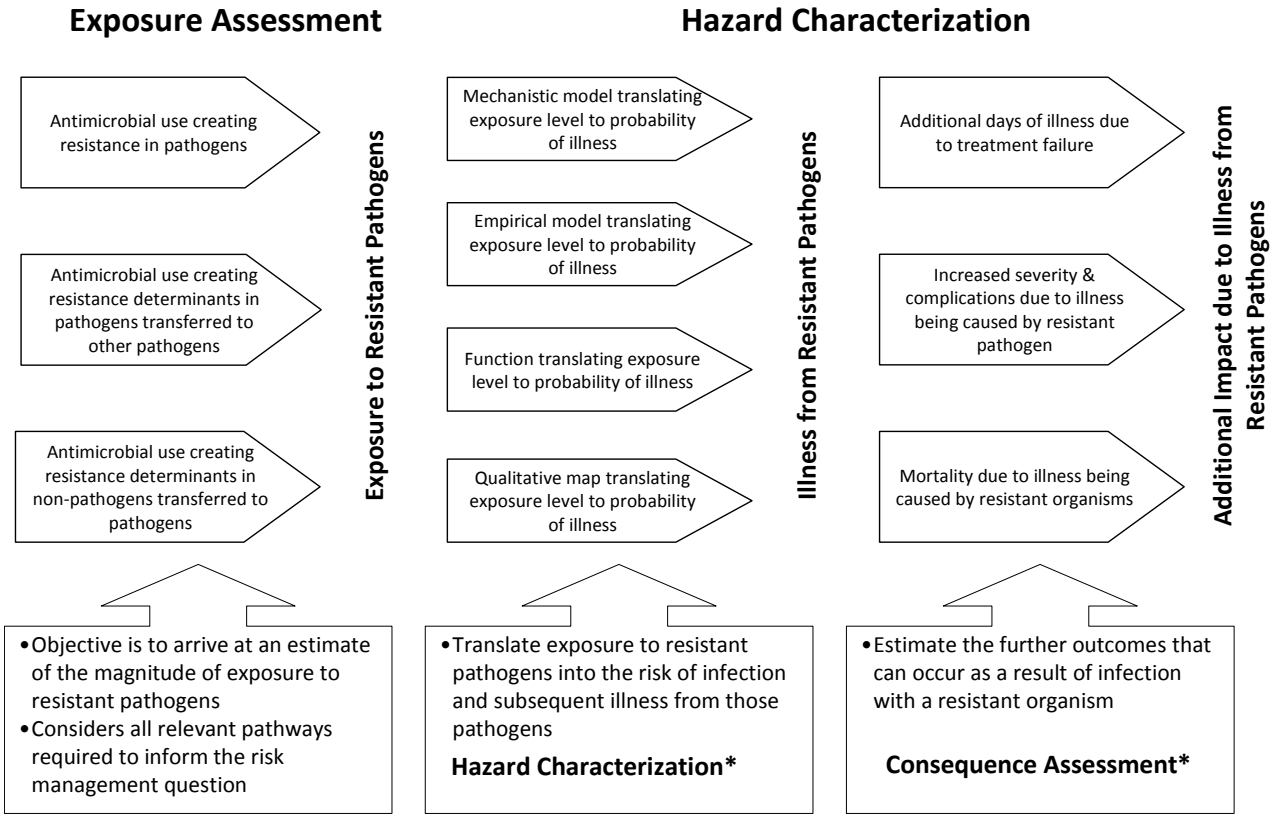

Figure 2. Scheme for Hazard Characterization in AMR-RA
(consolidated from the JEMRA (FAO/WHO, 2003a and 2006a) and from the World Organisation for Animal Health (OIE, 2007))

27. The output from the hazard characterization, including the dose-response relationship where available, assists in translating levels of exposure to a likelihood of an adverse outcome. Paramount to this is that the exposure assessment step provides an estimate of the level of exposure of the human population to resistant pathogens or resistance determinants from food. In order to translate this exposure to risk, the appropriate models can potentially be employed. A comprehensive model with high quality data will have a higher degree of confidence on 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. Figure 2 includes examples of different types of models (i.e. mechanistic models, empirical models, functions, or qualitative mapping) that could link exposure to diseases. The choice of modeling approach will be guided by the risk question(s) and the risk manager's needs.

28. Determining the number of infections 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 AMR-RA, like microbiological risk assessments, will focus on diseases, except in this case the focus is specifically on disease attributed to resistant pathogens. It considers the subsequent risk of treatment failure or other complications as a result of infection from microorganisms that have acquired resistance. It is important to recognize that, compared to non-AMR-RA, 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, estimates 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.

29. The major factors that can have an impact on the hazard characterization are included in Table 3.

Table 3. Possible data requirements for hazard characterization

Element	Description or scope of data
Resistant microorganisms and resistance determinants	• 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 gastro-intestinal tract.
Adverse health effect characteristics	• Nature of the infection/disease • Host factors and susceptible population • Diagnostic aspects • Treatment with antimicrobial agent and hospitalization • Severity of adverse health effects • Epidemiological pattern (outbreak or endemic) • Persistence of hazards in humans
Dose-response	• Dose-response assessments between resistant microorganisms and probability of human diseasees
Possible outcome	• Probability of disease and additional consequences attributed to the resistance (severity of the adverse health effect)

6.4. RISK CHARACTERIZATION

30. The risk characterization step of AMR-RA integrates the information from the preceding components of the risk assessment and synthesizes overall conclusions about risk that is 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 guidance 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 (DALY's), or preventable fraction, will need to be established at the onset of the assessment process in conjunction with risk managers.

31. Additional outcomes of risk characterization, which would have been defined in the purpose of AMR-RA, may include scientific evaluation of risk management options within the context of the risk assessment (FAO/WHO, 2006b).

32. The adverse human health effects of concern in AMR-RA 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 risk, important subgroups; 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 AMR-RA, during the commissioning of the AMR-RA, in order to determine the appropriate exposure assessment and hazard characterization outcomes for risk characterization.

33. 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 were adequately characterized?
- What were the key scientific assumptions used (stated in clear language and understandable by non-mathematicians)? How do these assumptions 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 ensure that risk managers understand the impacts of these aspects on the risk characterization.
- Sensitivity and uncertainty analysis (Table 4). 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.
- What alternatives were considered, i.e., to what extent are there plausible alternatives, or other opinions? Does the AMR-RA adequately address the questions formulated at the outset of the work? What confidence do the assessors have about whether the conclusions can be relied upon for making decisions?
- Key conclusions as well as important data gaps and research needs[5].

34. The potential points for consideration in the risk characterization are presented in Table 4 (OIE, 2007).

Table 4. Potential Points for Consideration in the Risk Characterization

Element	Description or scope of data
Factors in risk estimation	• Number of people falling ill and the proportion of that number with resistant strains of microorganisms • 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

[5] FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials (Rome, 2008)

	the population or a member of a specific more exposed or more vulnerable subgroup) • Importance of pathology caused by the target microorganisms. • [Absence of alternative antimicrobial agent and alternatives with potential toxicity • Alternatives available in case of resistance, and potential impact of switching to alternative antimicrobial agent] • 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
Scientific evaluation of risk management options	• Comparison of public health burden before and after interventions
Sensitivity analysis	• Effect of changes in model input values and assumption on model output • Robustness of model results (output)
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

Section 7. DOCUMENTATION

(This section may be moved, potentially expanded, and included in the integrated AMR Risk Analysis Document)

35. The AMR-RA should be fully documented to be consistent with the established principles in Codex CAC/GL-62 document (FAO/WHO, 2007).

Section 8. RISK COMMUNICATION

(This section may be moved, potentially expanded and included in the integrated AMR Risk Analysis Document)

36. Throughout the process of AMR-RA, there should be an effective communication between risk assessors and risk managers. Similarly, effective communication should be maintained between risk assessors and affected and interested stakeholders for gathering relevant input and to maintain the transparency of the AMR-RA process. The outcome of risk assessment, and management interventions where appropriate, should be communicated to all stakeholders and the general public in a timely fashion.

SECTION 9. REFERENCES

(This section may be harmonized with reference section for overall AMR Risk Analysis Document)

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OIE (World Organisation for Animal Health). 2003. OIE international standards on antimicrobial resistance, 2003. *http://www.oie.int/eng/publicat/ouvrages/a_119.htm*.

OIE. 2007. Terrestrial Animal Health Code (2007). *http://www.oie.int/eng/normes/mcode/en_titre_1.3.htm*.

SECTION 10. APPENDICES

Appendix 1. Examples of Qualitative AMR-RA

Although quantitative risk assessments are encouraged, qualitative risk assessments are often preferred due to its 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 that a quantitative approach is subjected to.

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;

- 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.

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

Example 1

Illustrative Exposure Assessment Scoring

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

- **Negligible (0):** Virtually no probability that exposure to the hazard can occur (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)

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

Illustrative Hazard Characterization Scoring

The hazard characterization translates the outcomes of this step into qualitative statements that reflect the implications of exposure to a hazard. 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 organisms 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 the potential for treatment failures requiring lengthy hospitalization

Illustrative Risk Characterization Output

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

- No Additional Risk: Value of 0
- Some Additional Risk: Value between 1 and 2
- High Additional Risk: Value between 3 and 4

- Very High Additional Risk: Value between 5 and 6

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

		Exposure Assessment		
		Negligible	**Moderate**	**High**
Hazard Characterization	**Negligible**	**0**	**0**	**0**
	Mild	**0**	**1**	**2**
	Moderate	**0**	**2**	**4**
	Severe	**0**	**3**	**6**

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

Example 2

Illustrative Exposure Assessment Scoring

The ranking 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 plants. 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

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/forms/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

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 5.

Table 5. Integration of the Outputs of Hazard Characterization and Exposure Assessment into the Qualitative Risk Estimation

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

Exposure Assessment -Probability of Exposure	Hazard Characterization -Severity of Adverse Health Effect	Qualitative Risk Estimation
High (Almost Certain)	Very High (Fatal)	Very High

[Appendix 2. Outline of Information for an AMR-RA

This appendix lists the suggested elements to include in an AMR-RA and the level of details of the data may vary case-to-case.

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 (and non-human antimicrobial use)

2.2. The antimicrobial and its properties

2.2.1. Description of the antimicrobial – name, formulation, etc.

2.2.2. Class of antimicrobial

2.2.3. Mode of action and spectrum of activity

2.2.4. Pharmacokinetics of antimicrobial

2.2.5. Existing or potential non-human uses of the antimicrobial and related agents

2.2.6. Intrinsic and acquired resistance in pathogenic and commensal microorganisms

2.2.7. Mechanism of resistance and their prevalence among human and non-human microflora

2.2.8. Importance of antimicrobial(s) in human medicine

2.3. Microorganisms and resistance related information

2.3.1. Potential human pathogens (species/strain) that likely acquire resistance in non-human hosts

2.3.2. Commensals (species/strain) that likely acquire resistance determinants in non-human hosts and transmit them to human pathogens

2.3.3. Potential routes of transmission

2.3.4. Mechanisms of antimicrobial resistance

2.3.5. Association of resistance with virulence and pathogenicity

2.3.6. Location of resistance determinants and their frequency of transfer to related and unrelated microorganism species

2.3.7. Co- and cross-resistance and/or multiple resistance, and importance of other antimicrobials whose efficacy is likely to be compromised

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

2.4.1. Clinical studies

2.4.2. Epidemiological studies and surveillance

3. Exposure Assessment

3.1. Factors affecting prevalence of hazard on-farm (pre-harvest)

3.1.1. Resistance selection pressure: frequency, quantity and duration of non-human use of antimicrobials

3.1.2. Methods and routes of antimicrobial administration

3.1.3. Resistance transferability

3.2. Factors affecting prevalence of hazard in food (post-harvest)

3.2.1. Frequency and level of resistant organism/resistance determinants in food

3.2.2. Microbial ecology in food: survival capacity and redistribution of microorganism in the food chain

3.2.3. Occurrence and probability of resistance gene transfer from resistant microorganisms to human commensals/pathogens

3.2.4. The level of sanitation and process control in food processing, and likely environmental contamination

3.3. Transfer of hazard

3.3.1. Transmission of resistance determinants/resistant microorganisms among animals, food, feed, environment and humans

3.3.2. Resistance gene transferability

3.3.3. Potential human exposure from direct contact to primary production environments

3.3.4. Potential human to human transmission of resistant organism

3.4. Exposure to hazard

3.4.1. Quantity of various food commodities consumed

3.4.2. Point of food consumption (home or commercial establishment)

3.4.3. Human demographics, socio-cultural etiquettes in relation to food consumption and susceptibility

3.4.4. Food handlers as a source of contamination

3.4.5. Factors favouring resistance enrichment (e.g., use of antimicrobial for unrelated purpose)

3.4.6. Consumption of a particular food commodity could be qualitatively classified as low, medium or high

4. Hazard Characterization

4.1. Resistant microorganisms and resistance determinants

4.1.1. Description of microorganism including pathogenicity

4.1.2. Resistance occurrence

4.1.3. Epidemiological patterns

4.2. Antimicrobial

4.2.1. Use data and pattern, and selective pressure

4.2.2. Importance in human medicine

4.3. Human host and adverse health effects

4.3.1. Host factors and susceptible population

4.3.2. Nature of the infection, disease

4.3.3. Persistence of hazard in humans

4.3.4. Diagnostic aspects

4.3.5. Epidemiological pattern (outbreak or endemic)

4.3.6. Treatment with antimicrobial therapy and hospitalization

4.3.7. Drug selection for infections

4.3.8. The overall antimicrobial drug importance ranking

4.4. Dose-Response relationship: Mathematical relationship between the exposed dose and probability of adverse outcome (e.g. infection, disease, and treatment failure).

5. Risk Characterization

5.1. Risk estimate

5.1.1. Integrates the outcome of hazard identification, hazard characterization and exposure assessment to determine the probability and severity of adverse human health impacts

5.1.2. Probability and severity should be calculated for each endpoint defined, and for general population as well as specific (e.g., susceptible) sub-populations

5.2. Uncertainty and variability analyses

5.3. Sensitivity analysis]

Part 3

DEVELOPMENT OF GUIDANCE ON CREATING RISK PROFILES FOR ANTIMICROBIAL RESISTANT FOODBORNE MICROORGANISMS FOR SETTING RISK ASSESSMENT AND MANAGEMENT PRIORITIES

INTRODUCTION *[to be harmonized]*

1. Antimicrobial resistance resulting from the non-human use of antimicrobials is a recognized food safety concern. Given the complexity surrounding the field of antimicrobial resistance, food safety regulators require a structured approach to manage those concerns. Risk analysis has been implemented as a decision-making tool to estimate risks posed by food hazards and to determine appropriate risk mitigation strategies to control those hazards. General frameworks for managing foodborne risks have been developed by international and national authorities to establish principles and guidelines for the conduct of risk analysis. The Codex *Ad Hoc* Task Force on Antimicrobial Resistance is establishing such a risk management framework; this document is one of three guidance documents that describe those principles and guidelines specific to antimicrobial resistance risk analysis.

2. The initial phase of the risk management 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. This document describes the steps to be used by Codex or national/regional authorities in conducting preliminary risk management activities as they relate to antimicrobial resistance. For the purpose of this guidance, preliminary risk management activities are taken to include identification of a food safety problem; development of a risk profile, ranking of the hazard for risk assessment and risk management prioritization; establishment of broad risk management goals; establishment of risk assessment policy for the conduct of the risk assessment, commissioning of the risk assessment, and consideration of the results of the risk assessment.

3. This document should be read in close conjunction with the *Principles and Guidelines for the Conduct of Antimicrobial Resistance Risk Assessment* and the *Principles and Guidelines for the Conduct of Antimicrobial Resistance Risk Management*, documents that are currently under development, as well as the *Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials* (Rome 2007) and the *Working Principles for Risk Analysis for Food Safety for Application by Governments (CAC/GL 62-2007)*. In addition, this guidance incorporates the prior work on microbial risk assessment, as described in the Codex documents *Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30 - 1999)* and *Principles and Guidelines for the Conduct of Microbiological Risk Management (CAC/GL 63 - 2007)*. Additional background material with relevant technical information that should be consulted include documents developed by the World Health Organization, the Food and Agriculture Organization and the Codex Alimentarius (*e.g.*, *The Interaction between Assessors and Managers of Microbial Hazards in Food*, Kiel, Germany, March 2000; *Principles and Guidelines for Incorporating Microbiological Risk Assessment in the Development of Food Safety Standards, Guidelines and Related Texts*, Kiel, Germany, March 2002; *The Use of Microbiological Risk Assessment Outputs to Develop Practical Risk Management Strategies: Metrics to improve food safety*, Kiel, Germany, April 2006; and *Food Safety Risk Analysis, A Guide for National Food Safety Authorities* – FAO Food and Nutrition Paper 87, Rome, 2006).

1. Scope

4. This document is intended for use by Codex and/or national/regional authorities for the conduct of preliminary risk management activities to address the food safety issues associated with the presence of antimicrobial resistant microorganisms and resistance determinants in food and feed, including aquaculture, and the transmission through food and feed of antimicrobial resistant microorganisms and antimicrobial resistance genes. In the course of implementing these preliminary risk management activities, the risk managers should consider the different areas of use of antimicrobials, such as veterinary applications, aquaculture, plant protection or food processing.

2. Definitions *(to be considered in harmonized document)*

5. The definitions of risk analysis terms related to food safety contained in the Procedural Manual of the CAC [6], shall apply. In particular, see definitions of hazard, risk, risk analysis, risk assessment, risk

[6] Codex Alimentarius Commission, Procedural Manual.

management, risk communication, risk assessment policy, risk profile, risk estimate, hazard identification, and hazard characterization.

6. Risk manager[7] is defined as follows: a national or international governmental organization with responsibility for antimicrobial resistance risk management activities.

3. General Principles *(to be considered in harmonized document)*

PRINCIPLE 1: Protection of human health is the primary objective in antimicrobial resistance risk management.

PRINCIPLE 2: Antimicrobial resistance risk management activities should take into account the emergence and dissemination of both resistant foodborne pathogens and resistance determinants through the whole food chain.

PRINCIPLE 3: Antimicrobial resistance risk management activities should focus on clearly defined combinations of the food, antimicrobial drug, antimicrobial use, and foodborne human pathogens and/or resistance determinants.

PRINCIPLE 4: Antimicrobial resistance risk management activities should follow a structured approach.

PRINCIPLE 5: The activities conducted in all phases of antimicrobial resistance risk management should be transparent, timely, consistent, fully documented, and openly communicated.

PRINCIPLE 6: Risk managers should ensure effective consultations with relevant interested parties.

PRINCIPLE 7: Risk managers and risk assessors should ensure effective interactions.

PRINCIPLE 8: Risk managers should take into account risks resulting from regional differences in human exposure to foodborne antimicrobial microorganisms and resistant determinants and regional differences in available risk management options.

PRINCIPLE 9: Antimicrobial resistance risk management decisions should be subject to monitoring and review and, if necessary, revision.

PRINCIPLE 10: Risk management activities should take into account recent work by international organizations on antimicrobial resistance.

4. Guidelines for Activities

7. These guidelines provide an outline of a series of steps that comprise the preliminary risk management activities, part of the general framework for antimicrobial resistance risk analysis. These activities are conducted by, or under the guidance of, the risk managers.

4.1. Identification of an antimicrobial resistance food safety issue

8. In the context of this document, a potential food safety issue may arise when antimicrobial resistant microorganisms and antimicrobial resistance determinants are present in food and feed, including aquaculture, or are transmitted through food and animal feed. Foodborne exposures to resistant microorganisms or resistance determinants may adversely impact human health. The risk manager initiates the risk management process to evaluate scope and magnitude of the food safety issue and, where necessary, to commence activities to manage the identified risk.

9. Food safety issues may be identified by the risk manager or be the result of collaboration between different interested parties. Within Codex, a food safety issue may be raised by a member government, or by an intergovernmental or observer organization.

10. Antimicrobial resistance food safety issues may be identified on the basis of information arising from a variety of sources, such as antimicrobial resistance surveillance in animals and in foods of animal origin, food safety monitoring, antimicrobial usage surveys, animal and human surveillance data (including post-

[7] The definition of Risk Manager is derived from the definition for risk management, which may not include all of the individuals who are involved in the implementation phase and related activities associated with managing the risks resulting from antimicrobial resistance; i.e., risk management decisions are largely implemented by industry and other interested parties. The focus of the definition of risk manager in this document is restricted to governmental organizations with authority to decide on the acceptability of risk levels associated with foodborne hazards.

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 antimicrobial resistance 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).*

11. 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.

4.2. Development of an antimicrobial resistance risk profile

12. The antimicrobial resistance 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 risk management options that have been identified to date, if any, and the food safety policy context that will influence further possible actions. The risk profile is usually developed by personnel with specific scientific expertise on the food safety issue of concern and some understanding of antimicrobial resistance risk assessment techniques. Interested parties who are familiar with the relevant production chain and related production techniques should be consulted.

13. The depth and breadth of the antimicrobial resistance risk profile may vary depending on the needs of the risk managers and the complexity and urgency of the food safety issue. An extensive list of suggested risk profile elements is provided in the Annex as guidance to risk managers at the national/regional level, and for bringing forward newly proposed work within the Codex process. Whenever possible, a comprehensive risk profile should be conducted to minimize the chances of important data or information being missed that might influence risk management decisions. In certain situations, however, it may be necessary to develop an abbreviated risk profile that could be used as a basis for further preliminary risk management activities. These include prioritizing the development of more comprehensive risk profiles or determining the need for commissioning a risk assessment. An abbreviated risk profile may be particularly useful for resource-challenged countries in determining priorities for further activities. Caution should be exercised in implementing these abbreviated risk profiles, as they may not provide as complete a picture of the food safety issue as needed for effective decision making by the risk managers. The fundamental elements that should comprise an abbreviated risk profile include:

- Description of the hazard and public health problem (the antimicrobial resistance food safety issue);
- Identification and characterization of the food commodity + antimicrobial resistant microorganims + 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.

14. 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 antimicrobial resistance risk assessment, establishing additional information gathering pathways, or implementing immediate risk mitigation for those food safety issues that require an immediate action[8] by the risk manager without further scientific consideration (e.g. requiring withdrawal / recall of contaminated products).

[8] 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

15. [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.]

4.3. Rank food safety issues and set priorities for risk assessment and management

16. Given the potentially high resource costs associated with conducting risk assessments and/or implementing risk management goals, a risk ranking or prioritization process is important in placing the risks from a specific food commodity + antimicrobial resistant microorganism + antimicrobial use combination in context with other risk scenarios that require the attention of risk managers. The output from the risk profile provides the principal criteria that should be used by risk managers in this risk ranking or prioritization process.

17. Beyond the description of the 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 include:

- Perceived relative level of risk to consumers;
- Capability to implement effective food safety control measures;
- Potential international trade implications associated with food safety control measures;
- Regulatory challenges; and
- Policy concerns/public demand.

4.4. [Establish broad risk management goals[9]

18. Following development of the risk profile and the conduct of the risk ranking/prioritization steps, 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.

19. 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.

20. Often critical in establishing and achieving risk management goals is determining 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;
- 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.

21. 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.]

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constitutes a serious and as yet uncontrolled foodborne risk to public health that requires urgent action. Emergency measures may be part of immediate action.

[9] *Food Safety Risk Analysis, A Guide for National Food Safety Authorities* – FAO Food and Nutrition Paper 87, Rome, 2006).

4.5. Establish a risk assessment policy

22. Determination of risk assessment policy should be included as a specific component of preliminary risk management. Risk assessment policy should be established by risk managers in advance of risk assessment; after consideration of the outcome of the risk profile 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. Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different risk management options.

23. For antimicrobial resistance risk assessment policy, risk managers may refer to the General Principles in the Risk Assessment portion of the guidelines or relevant Codex or FAO documents.

24. Additional elements specific to the food safety issue related to antimicrobial resistance should also be included in order to provide guidelines to risk assessors conducting the risk assessment. For example, the risk assessment policy should provide the risk assessors with guidance on the need to address uncertainty and what assumptions to use when the available data are inconsistent. Further assessment of the severity of the adverse human health effects attributed to and/or associated with different categories of antimicrobials, as previously defined (FAO/OIE/WHO 2008), should be given due consideration.

4.6. Commission of a risk assessment

25. Based on the established risk management goals, risk managers may commission a risk assessment to provide an objective, 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 and that the risk assessment meets the needs of the risk manager. It is also important that all aspects of the commissioning and conduct of the risk assessment are documented and transparent.

26. 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 type (e.g., quantitative, qualitative) of risk assessment to be conducted;
- The expertise and resources required to carry out the risk assessment;
- Timelines for milestones and completion of the risk assessment;
- [Criteria to validate the risk model;
- Criteria to assess the scientific and technical adequacy of the risk assessment; and
- Analysis of any future data needs.]

27. It is important to ensure that the composition of the risk assessment team is appropriate in terms of expertise and be free of conflicts of interest or bias. The risk managers should also ensure that there are effective and iterative communication pathways between the risk assessors and risk managers during the risk assessment process, and that the risk assessment be adequately reviewed by the scientific community and if appropriate, the public.

28. The risk manager should refer to the Principles and Guidelines for the Conduct of Antimicrobial Resistance Risk Assessment section of this guideline (under development).

4.7. Consider the results of the risk assessment

29. [The conclusion 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. In reviewing the completeness of the risk assessment, risk managers need to understand the nature, sources and extent of uncertainties and variability of the risk estimates expressed.]

ANNEX

Suggested Elements to Include in an Antimicrobial Resistance Risk Profile

A risk profile should present, to the extent possible, information on the following:

1. **Definition of the hazard-food commodity combination(s) of concern:**
   - Food commodity;
   - Antimicrobial resistant pathogen; and
   - Antimicrobial use pattern
   - Description of the food commodity and the associated cause for concern (e.g., antimicrobial resistant foodborne disease, trade restrictions) due to the hazard
   - Occurrence of the hazard in the food chain.
2. **Description of the public health problem (*i.e.*, the adverse human health consequences):**
   - Characteristics of the resistant microorganism(s) or resistance determinants, including key attributes that are the focus of its public health impact (e.g., cross resistance, co-resistance, horizontal gene transfer);
     - Growth rate
   - Characteristics of the antimicrobial-susceptible infection, disease, including:
     - Susceptible populations;
     - Annual incidence rate in humans including, if possible, any differences between age and sex;
     - Severity of clinical manifestations (e.g., case-fatality rate, rate of hospitalization; and
     - Nature and frequency of long-term complications;
   - Characteristics of the antimicrobial-resistant infection, disease:
     - Added burden of the infection, disease due to antimicrobial resistance, if readily available (e.g., medical and/or hospital costs; working days lost due to disease, etc.); and
     - Evidence of links between resistance, virulence, and/or fitness of the antimicrobial resistant microorganism
   - Characteristics of treatment of the antimicrobial resistant infection, disease:
     - Options for treating the infection, disease (e.g., importance of antimicrobial drug for treatment of human adverse health effect, possible side effects of alternate treatments);
     - Extent of human use of the antimicrobial agent for which resistance is the concern;
     - Availability and nature of treatment; and
     - Prevalence of resistance in human populations;
3. **Description of food commodities associated with the antimicrobial resistant microorganisms or resistance determinants (Post-harvest factors);**
   - Characteristics of the food commodity (commodities);
   - Food use and handling that influences transmission of the hazard;
   - Frequency and characteristics of foodborne sporadic cases;
   - Epidemiological data from outbreak investigations;
   - Prevalence of resistance on food commodity; and
   - Evidence of a relationship between the presence of the antimicrobial resistant microorganisms or resistance determinants on the food commodity and the occurrence of the adverse health effect in humans.

4. Description of antimicrobial(s);

- Chemical, physical and pharmacological properties of the antimicrobial agent;
- Type of use (treatment/prevention/control/growth promotion);
- Dose regimen and route of administration;
- Final product specifications;
- Specific rules of usage for the country concerned;
- Quantity of use in relevant animal and plant species;
- Factors influencing the persistence of resistance in the pre-harvest production stage;
- Associations between usages and development and persistence of resistance;
- Factors that may affect the dissemination of antimicrobial resistant microorganisms through the food chain;
- Evidence of a relationship between the use of the antimicrobial and the occurrence of antimicrobial resistant microorganisms, or resistance determinants, in the food commodity of concern;
- Persistence of the antimicrobial in the environment, and factors affecting the maintenance of antimicrobial resistant microorganisms and/or resistance determinants; and
- Contribution of alternative (non-foodborne) sources of antimicrobial resistance

5. Antimicrobial resistance genes and resistance determinants:

- Factors that may affect the frequency of transfer of genetic elements through the food chain; and
- Description of the molecular genetics of the antimicrobial resistance of concern

6. Other Risk Profile Elements:

- Summary of the extent and effectiveness of current risk management practices including food safety production/processing control measures, educational programs, and public health intervention programs (e.g., vaccines);
- Identification of additional risk mitigation strategies that could be used to control the hazard;
- The extent of international trade of the food commodity;
- Existence of regional/international trade agreements and how they may affect public health with respect to the specific hazard-food commodity combination(s);
- Public perceptions of the problem and the risk;
- Initial assessment of the need and benefits to be gained from requesting an antimicrobial resistance risk assessment, and the feasibility that such an assessment could be accomplished within the required time frame;
- Importance of antimicrobial drug to animal medicine; and
- Availability of alternative treatments and preventive measures.

7. Assessment of available information and major knowledge gaps:

- Existing antimicrobial resistance risk assessments on the food commodity + antimicrobial resistant pathogen + antimicrobial use combination(s) including, if possible;
- Other relevant scientific knowledge and data that would facilitate risk management activities including, if warranted, the conduct of a risk assessment;
- Existing Codex guidance documents (including existing Codes of Hygienic Practice and/or Codes of Practice);

- International and/or national governmental and/or industry codes of hygienic practice and related information; and
- Areas where major absences of information exist that could hamper risk management activities, including, if warranted, the conduct of a risk assessment.

Part 4

PROPOSED DRAFT GUIDELINES ON RISK MANAGEMENT TO CONTAIN FOODBORNE ANTIMICROBIAL RESISTANT MICROORGANISMS

I.- INTRODUCTION

(to be harmonized)

II.- PURPOSE AND SCOPE

1. 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. Guidance on the identification, evaluation, and selection of risk management options will be provided. In addition, consideration will be given to the implementation of risk management options and how to measure and monitor the effectiveness of the selected risk management options, including establishing a baseline against which subsequent changes can be compared.

2. 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 antimicrobial resistant (AMR) microorganisms and resistance determinants.

3. This document should be read in conjunction with the Codex *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC-RCP 61-2005) as the main text for pre-harvest, *Recommended International Code of Practice-General Principles of Food Hygiene* CAC/RCP 1-1969 as a main text for post-harvest, the relevant sections of the OIE Terrestrial Animal Health Code (2008)[10], 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[11].

III.- GENERAL PRINCIPLES *(to be considered in harmonized document)*

PRINCIPLE 1: Protection of human health is the primary objective in antimicrobial resistance risk management. Animal health should also be considered when evaluating risk management options to the greatest extent possible.

PRINCIPLE 2: Antimicrobial resistance risk management activities should take into account the emergence and dissemination of both resistant foodborne pathogens and resistance determinants through the whole food chain.

PRINCIPLE 3: Antimicrobial resistance risk management activities should focus on clearly defined combinations of food, antimicrobial drug (AM), antimicrobial use and the human pathogens and/or resistance determinants

PRINCIPLE 4: Antimicrobial resistance risk management activities should follow a structured approach[12]

PRINCIPLE 5: The activities conducted in all phases of antimicrobial resistance risk management should be transparent, timely, consistent, fully documented and openly communicated

PRINCIPLE 6: Risk managers should ensure effective consultations with relevant interested parties[13].

PRINCIPLE 7: Risk managers and risk assessors should ensure effective interaction.

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[10] http://www.oie.int/eng/normes/Mcode/en_sommaire.htm

[11] http://www.who.int/foodborne_disease/resistance/en/index.html

[12] See para. 7 in GL 62-2007.: "*The risk analysis should follow a structured approach comprising the three distinct but closely linked components of risk analysis (risk assessment, risk management and risk communication) as defined by the Codex Alimentarius Commission, each component being integral to the overall risk analysis.*"

[13] *For the purpose of the present document, the term "interested parties" refers to "risk assessors, risk managers, consumers, industry, the academic community and, as appropriate, other relevant parties and their representative organizations".*

PRINCIPLE 8: Risk managers should take into account risks resulting from regional differences in human exposure to AMR microorganisms & determinants from the food chain and regional differences in available risk management options.

PRINCIPLE 9: Antimicrobial resistance risk management decisions should be subject to monitoring and review and, if necessary, revision

PRINCIPLE 10: Activities of risk management should take into account all work by Codex and work by international organizations on antimicrobial resistance and that Codex Guidelines (GL) and Recommended Code of Practice (RCP) should be fully implemented

[PRINCIPLE 11: Risk managers should consider implementing additional and/or alternative risk management options when monitoring and review of effectiveness indicates consumer protection or food safety goals are not being satisfactorily met].

IV.- IDENTIFICATION OF THE AVAILABLE OPTIONS

4. Risk management options should consider the relevant practice throughout the food chain and could be divided in pre-harvest and post-harvest aspects. Pre-harvest options would contain aspects such as Responsible Use Guidelines and Codes of Practice for antimicrobial agents [and possibilities to modify the use of antimicrobial agents as related to the risk of the development of antimicrobial resistance microorganisms used in food production.] Post-harvest options would contain aspects contributing to minimising the contamination of food by resistant microorganisms such as food hygiene practices for handling and avoiding cross contamination.

5. Risk management options described in the following section may be implemented, at the discretion of national/regional authorities and in a manner that is proportional to the level of risk, as a minimum, the existing Codes of Practice should be followed. These codes of practice describe the respective roles and responsibilities of authorities and groups to minimize and contain antimicrobial resistance:

- Codex *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC/RCP 61-2005);
- Codex *Recommended International Code of Hygiene 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;
- Risk management options for animal feed, such as the Codex *Code of Practice on Good Animal Feeding* (CAC/RCP 54-2004); and
- *Code of Hygienic Practice for Fresh Fruits and Vegetables* (CAC/RCP 53-2003).

6. Following risk profiling and/or Risk Assessment national/regional Authorities might find a need for Risk Management activities additional to those outlined in the above mentioned documents. The following are examples of supplemental risk management options (RMOs) that go beyond those described in existing texts and may be considered by various stakeholders. These RMOs may be used in combination with RMOs already in place.

A.- Pre-harvest options

A.1- General

A.2- Food animal production

- Additional risk management options in the pre- and post-approval and licensing of antimicrobials for food animals could include regulatory controls on conditions of use, such as marketing status limitation, extra-/off-label prohibition, extent of use limitation. The level of control could be implemented in a stepwise fashion proportionate to the risk with consideration of Critically Important Antimicrobials (CIA) for human health (FAO/WHO/OIE, Rome 2008), or as needed to obtain a consumer protection or food safety goal.

- Whenever possible, a microbial diagnosis and susceptibility testing should be performed prior to treatment for a given AM and microbial infection. National authorities may support the development and dissemination of standards for establishing culture and susceptibility testing, breakpoints, and interpretive criteria determinations for important pathogens and antimicrobials approved for use in food animals.
- Recommend on different AM to be used, if several antimicrobials can be used for a given indication in an animal. Professional bodies could develop prudent use guidelines that are species- and disease condition-specific. These specific guidelines should be regularly updated.
- Disease prevention/prophylactic use in healthy animals not considered to be at risk of infection or prior to the onset of clinical infectious disease, should be avoided.
- Minimize the presence and transmission of foodborne microorganisms and determinants between animals, from animals to humans and between flocks/holdings by implementing animal health and infection control programs so as to reduce the risk associated with the use of antimicrobials.
    - **[** Active control programs to reduce zoonotic infections without using antimicrobials.
    - Changes in production systems (e.g. closed pig farms instead of bringing piglets together from different farms at a certain age)
    - Improved housing/ventilation systems to prevent respiratory infections
    - Reduced density of animals
    - Improved hygiene (e.g. at hatcheries), sanitary measures (disinfection between rounds, rodent controls, control at the entry of holdings and houses, …)
    - Vaccination when appropriate (not only for zoonotic infection but also for other infections such as viral respiratory infection).
    - Training for the improvement of specific husbandry practises]

A.3- Food crop production

Additional risk management options in the pre- and post-approval and licensing of antimicrobials for food crop production could include regulatory controls on conditions of use, such as marketing status limitation, extent of use limitation. The level of control could be implemented in a stepwise fashion proportionate to the risk with consideration of Critically Important Antimicrobials (CIA) for human health (FAO/WHO/OIE, Rome, 2008), or as needed to obtain a consumer protection or food safety goal.

Competent authorities and/or professional bodies should elaborate crop species-specific prudent use treatment guidelines in consultation with all relevant interested parties. Prudent use guidelines should contain information such as use of culture and susceptibility, breakpoints, and interpretive criteria.

National authorities may support the development and dissemination of standards for establishing culture and susceptibility, breakpoints, and interpretive criteria for important pathogens and antimicrobials approved for use in crops.

Prophylactic use on healthy crops should be discouraged. Preventative uses of antimicrobials on crops known to be “at risk” of developing disease (exposed to pathogens, unusual stress, trauma) are acceptable.

Prevent the presence and transmission of foodborne resistant microorganisms and resistance determinants between crops and from crops to humans by implementing biosecurity and infection control programs.

See *Code of Hygienic Practices for Fresh Fruits and Vegetables* (CAC/RCP 53/2003)

- The spread of AMR microorgansims through other possible sources of contamination, such as direct use in agriculture of human and animal waste (manure), should be controlled, if there is sufficient evidence of risk and if practical, feasible and supported by science.
- Adopt proper treatment procedures (e.g composting, pasteurization, heat drying, UV irradiation, alkali digestion, sun drying or combinations of these) that are designed to reduce or eliminate pathogens in manure, biosolids and other natural fertilizers.

- The use of antimicrobial agents significant to human and animal therapy should be avoided.
- Antimicrobial agents not significant to human and animal therapy should be used only when unavoidable and in accordance with good agricultural practices and in a manner that achieves this objective.

Additional risk management options in the pre and post approval and licensing of antimicrobials for food crop production could include regulatory controls on conditions of use, such as marketing status limitation, extra/off-label prohibition, extent of use limitation. The level of control could be implemented in a stepwise fashion proportionate to the risk with consideration of Critically Important Antimicrobials (CIA) for human health (FAO/WHO/OIE 2008) ,or as needed to obtain a consumer protection or food safety goal.

B.- Post-harvest options

- Target interventions towards microbial contamination of food including microorganisms that are resistant to antimicrobials of critical importance to public and animal health; the WHO and OIE lists of CIAs may be used as a guide
- In addition to the specific process steps (chilling, thermal processing, irradiation, drying, chemical preservation, vacuum or modified atmospheric packaging) described in CAC/RCP 1-1969, Section 5.2.2 Specific Process Steps, national authorities may facilitate the development of novel interventions~~,~~**.**
- **[** Prevent the food containing AMR microorganisms & AMR determinants, at a level presenting a risk for human health reaching the consumer. The presence of AMR determinants in the pathogenic microorganisms should be regarded as an additional risk factor.
- Withdraw food containing AMR pathogenic microorganisms , at a level presenting a risk for human health from the market for reprocessing or destruction. The presence of AMR determinants in the pathogenic microorganisms should be regarded as an additional risk factor.]

V.- EVALUATION OF IDENTIFIED RISK MANAGEMENT OPTIONS (RMO)

7. [Animal health should also be considered when evaluating risk management options, to the extent possible, consistent with the requirement of GENERAL PRINCIPLE 1.]

8. [Evaluation of the identified Risk management options should be performed]

9. [Risk management options should be assessed in terms of the scope and purpose of risk analysis and the level of consumer health protection they achieve. The option of not taking any action should also be evaluated.]

10. [Risk management options should be evaluated by risk managers, taking into account the options' feasibility, effectiveness, economic implications, enforcement and compliance; proportionality to the amount of risk, and consumer protection they are expected to provide; and as compared to the option of taking no action. The level of control or reduction of risk that is necessary, should be specified, when feasible.]

VI.- SELECTION OF RISK MANAGEMENT (RM) OPTIONS[14]

11. The selection of RM options should be based on their ability to mitigate the risks effectively and on the practical feasibility and consequences of the options. Where available, a risk assessment can often help in the evaluation and selection of RM options.

12. The selection of risk management options should be supported by mechanisms to monitor and evaluate effectiveness to contain AMR microorgansims that may be transmitted through the food chain.

13. [The various interested parties should be involved when developing regulatory programs.]

14. The implementation of additional options is subject to the resources, legislative and other constraints of the country/region.

[14] CAC/GL 63 – 2007 provides general guidance on the selection of risk management options (sections 4 & 6).

A.- Identifying an appropriate level of consumer health protection[15]

15. Risk management decisions on appropriate options should be achieved by considering and integrating all evaluation information obtained from preliminary risk management activities and/or the risk assessment.

A.1- Benefit-risk approach

16. Because antimicrobials play a major role in animal health, animal health should be considered when evaluating risk management options, but this must be considered secondary to protecting consumers. When evaluating restrictions on the use of antimicrobial products it is necessary to consider substitutes or alternative practices that would reduce the need for the product. Substitutes could be other less important antimicrobials, non-antimicrobial products, or changes in livestock husbandry that promote animal health. The impact of reduced antimicrobial resistance on animal health should also be considered when evaluating restrictions on antimicrobial use.

A.2- Threshold approach

17. Given the geographic variations in the levels of resistance and the increasing emergence of resistance, it may be necessary to explore the need to develop resistance thresholds for specific antimicrobial-species-pathogen combinations, above which any of a range of risk management options may be triggered. However, this approach needs to be carefully assessed as it should be put in perspective with the current use of antimicrobials and the current level of resistance.

A.3- Provisional approach:

18. When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, it may be appropriate for countries to select a provisional decision, while obtaining additional information that may inform and if necessary modify the provisional decision. In those instances, the nature of the provisional 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 completion of a risk assessment) should be articulated when the decision is communicated initially.

[A.4- ALARA approach

(Further comments to be submitted by Philippines)]

B.- Selection of preferred risk management options

19. A decision on the preferred risk management options should also consider factors other than restricting antimicrobial use. Some of the important factors that may be considered include: hygienic food handling practices, reduction of prevalence of pathogens in animals or plant production, implementation of HACCP, etc.

20. Cross-resistance, co-resistance issues should be considered.

21. Control measures may be placed on the use of specific antimicrobial agent in some species or some route of administration or specific production processes (see GENERAL PRINCIPLE 3)

VII.- IMPLEMENTATION OF RISK MANAGEMENT OPTIONS

22. [Risk managers should develop an implementation plan that describes how the options will be implemented, by whom, and when

23. National/regional authorities should ensure an appropriate regulatory framework and infrastructure.

24. Additional measures could be envisaged following a stepwise approach (see annex 2).]

VIII.- MONITORING AND REVIEW OF RISK MANAGEMENT OPTIONS

- [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 microorgansims and determinants. For making

[15] "Appropriate Level of Protection" (ALOP). ALOP is defined in the SPS Agreement as "the level of protection deemed appropriate by the Member establishing a sanitary or phytosanitary measure to protect human, animal or plant life or health within its territory". ALOPs may range from general to specific depending upon the level of information available with regards to the source of hazards and risks and will depend on the public health goals.

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.**]**

a) Monitoring should, to the extent possible, include all antimicrobials used in food animal and crop production

b) Monitoring of antimicrobial usage in animals should be compatible with existing monitoring programs taking into account relevant aspects of the drug/microorgansims/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 risk management options.

c) Authorities should preferably plan the collection and analysis of data on the dissemination of antimicrobial resistance and on antimicrobial usage

d) AMR data should be analyzed with AM usage data together with other relevant data to assess possible relationships.

[With regard to post-harvest, the aim should be to minimize and contain AMR microorgansims on food. A system to monitor trends in antimicrobial resistance and prevalence of foodborne microorgansims should be in place. Targeted interventions aimed at reducing antimicrobial resistant microorgansims during food processing should be implemented.]

25. Governments should define an evaluation process to assess whether the risk management options have been properly implemented and an assessment whether or not an outcome has been successful (see also GENERAL PRINCIPLES).

26. Monitoring and surveillance should be supported by regulation and the enforcement of control measures

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

28. Monitoring schemes should be harmonized (CAC/RCP 61-2005 & GL 63) between countries, to the extent possible (in a general consideration about sharing info between countries; more comments are requested on this issue & review OIE Terrestrial Animal Code for existing wording).

29. Risk management options should be reviewed and evaluated, regularly, or at a predetermined moment in time, or whenever new relevant information becomes available

30. Monitoring/control points related to specifically implemented risk management options should be measured to assess the effectiveness and need for potential adjustment

31. Additional Monitoring/control points may be measured to identify new information (e.g., emerging hazard, virulence of a pathogen, prevalence and concentration in foods, sensitivity of sub-populations, changes in dietary intake patterns,...).

IX.- RISK COMMUNICATION

(to be harmonized)

Annex 1: possible endpoints

Annex 1 also applies to plants or vegetables that are intended for human consumption In order to monitor the effects of risk management measures and variations in AMR, possible endpoints include:

a. Nature and extent of antimicrobial resistance.

b. Nature and extent of antimicrobial resistance in animal-derived food products at retail level.

c. Prevalence of antimicrobial-resistant microorgansims on farm level.

d. Prevalence of antimicrobial-resistant microorgansims in animal-derived food products at retail level.

e. Prevalence of antimicrobial-resistant microorgansims or resistant genes in human clinical isolates from foodborne diseases

f. Development of new microorgansimsl resistance patterns.

g. Prevalence of foodborne pathogens on farms.

h. Prevalence of foodborne pathogens in food.

i. Prevalence of food borne disease in humans.

j. Number of deaths attributable to foodborne antimicrobial-resistant microorgansims.

k. Number of treatment failures attributable to foodborne antimicrobial-resistant microorgansims.

l. Other adverse health effects such as loss of treatment option and severity of infection (e.g., prolonged duration of disease, increased frequency of bloodstream infections, increased hospitalization, and increased mortality) associated with resistant infection

m. Frequency of human infections attributable to foodborne antimicrobial-resistant microorgansims.

n. Frequency of adverse human health effects attributable to foodborne antimicrobial resistant microorgansims.

o. Mortality due to foodborne infection caused by antimicrobial resistant microorganisms in “vulnerable populations”.

p. [Level of awareness of antimicrobial resistance risk (producers, consumers, industry and others).]

q. Level of compliance with specific drug use restriction or compliance with prudent use guidelines.

r. Trends in usage of antimicrobials in food-producing animals.

s. Trends in usage of critically important antimicrobials (CIA) in food-producing animals.

t. Technical and economic feasibility of the measures to be applied

[Annex 2: Suggested step wise approach

Step 1

a) Ensure adequate veterinarian (or equivalent animal health professionals) coverage for the country, veterinarian training in judicious/appropriate/responsible antimicrobial use and animal production practices, and appropriate involvement in food production and food safety processes.

b) Ensure adequate infrastructure for food production/food hygiene with respect to existing Codex standards and guidelines.

c) Ensure training, awareness and communication on prudent use of veterinary drugs for farmers and persons handling food animals.

d) National authorities should capitalize upon regulatory precedents and expertise of "peer" authorities in the region when capabilities are limited.

e) Communicate to the public the necessity of proper food preparation and hygiene.

Step 2

f) Implement responsible use guidelines via professional veterinary organizations.

g) Ensure reliable national food safety authority oversight of food safety activities consistent with Codex food hygiene guidance.

h) Implement adequate infrastructure and enforcement capacity to ensure compliance with quality product availability and veterinary involvement in antimicrobial usage.

i) Implement local/regional surveillance programs for foodborne disease.

Step 3

j) Implement national surveillance programs for foodborne disease, including AMR pathogens associated with foodborne disease.

k) Implement national resistance monitoring program, and where possible, usage monitoring.

l) Implement regulatory review of new antimicrobial agents prior to product approval.

m) Work in collaboration with food producing companies to maintain vigilance for implementation of food hygiene practices (i.e. HAACP) that safeguard against food contamination.

n) Work with professional associations (e.g. veterinary profession, species specific groups, etc.) to ensure compliance with responsible use guidelines by all members. Implement research programs to fill data gaps that will improve antimicrobial use practices, or minimize the need for antimicrobial use by preventing disease, etc.

o) Encourage animal health companies to develop products that will avoid resistance selection of currently used human use antibiotic classes.**]**

Part 5

GUIDELINES ON AMR RISK ANALYSIS ENCOMPASSING AMR RISK MANAGEMENT, RISK PROFILING, AND RISK ASSESSMENT

Common Elements for Introduction, General Principles, Risk Communication, Documentation and Definitions

(Prepared by Canada, Denmark, France and the United States of America)

Introduction

Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue. When pathogens become resistant to antimicrobial agents, they can pose a greater human health risk as a result of potential treatment failure 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 antimicrobial agents in food-producing animals provides a potentially important pathway for spread of resistant microorganisms from animals to humans.

In accordance with the 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 antimicrobial resistance. 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 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 production to consumption continuum, and the need to implement appropriate risk mitigation strategies, this guidance document presents a consolidated framework specific to AMR risk analysis.

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

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 is identification, selection, and implementation of appropriate risk management actions to minimize and contain the identified human health risks.

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).

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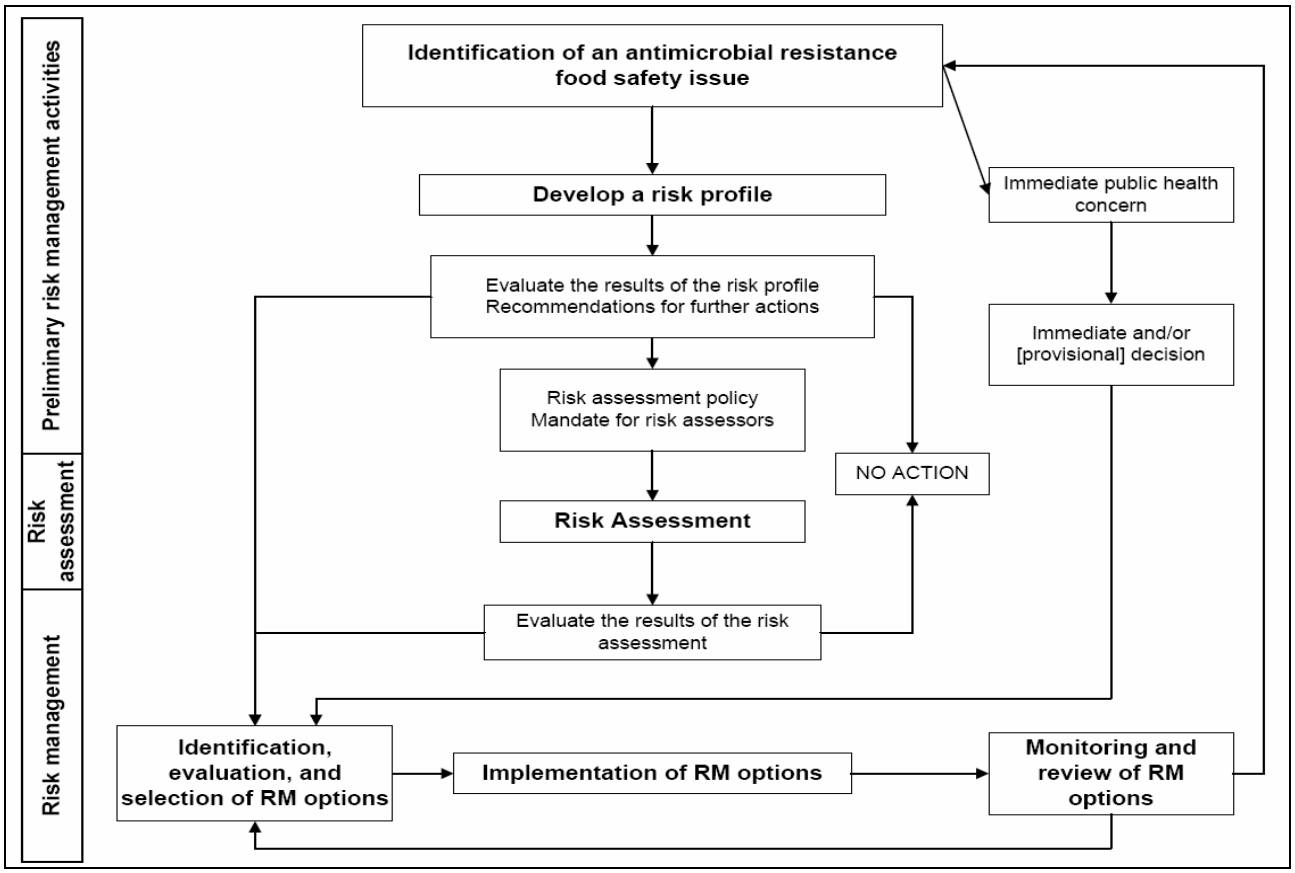
Flowchart for AMR Risk Analysis

Background: At the inter-session working group held in Brussels May 26-30, 2008, it was suggested that a flowchart or other diagram would be a helpful adjunct to the Introduction of an integrated document. The diagram would aid readers of the document by placing the components of risk analysis in relation to one another and providing a frame of reference for the elements such as: 1) sequencing of steps prior to risk assessment (preliminary risk management activities), 2) the process for identification, selection, implementation, and monitoring/review of risk management options, and 3) describing the process for implementing and reviewing a provisional decision.

The diagram may require additional modification to fit with the major content areas.



General Principles for AMR Risk Analysis

Principle 1: Protection of human health is the primary objective of antimicrobial resistance (AMR) risk analysis.

Principle 2: AMR risk analysis should be consistent with the approach elaborated in the *Working Principles for Risk Analysis for Food Safety for Application by Governments* (CAC/GL 62-2007).

Principle 3: AMR risk analysis should follow a structured approach.

Principle 4: AMR risk analysis should be evaluated and reviewed as appropriate in light of newly generated scientific data.

Principle 5: Risk managers and risk assessors should ensure effective interactions throughout the process of AMR risk analysis. However, the process of risk assessment should be functionally separated from that of risk management.

Principle 6: AMR risk analysis should involve consultations with relevant interested stakeholders.

Principle 7: The activities conducted in all phases of AMR risk analysis should be transparent, timely, consistent, fully documented, and openly communicated.

Principle 8: AMR risk analysis should consider regional differences in human exposure to foodborne antimicrobial resistant microorganisms and genetic determinants of resistance as well as in available risk management options.

General Principles for AMR Risk Management

Principle 9: AMR risk management activities should be consistent with the *"Principles and Guidelines for the Conduct of Microbiological Risk Management"* (CAC/GL 63-2007).

Principle 10: AMR risk management activities should consider the emergence and dissemination of both resistant foodborne pathogens and genetic determinants of resistance through the whole food chain.

Principle 11: AMR risk management decisions should be subject to monitoring and review and, if necessary, revision.

Principle 12: National authorities should implement, as much as possible, the Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC-RCP 61-2005), the relevant sections of the OIE Terrestrial Animal Health Code (2007), the Codex Codex of Food Hygiene (CAC/RCP 1-1969, Rev. 4 (2003)) and relevant WHO documents/guidelines on containment of antimicrobial resistance in food animals.

General Principles for AMR Risk Profiling

Principle 13: AMR risk profiling activities should clearly describe the AMR food safety problem, its public health context, availability of pertinent scientific information, and possible risk mitigation actions consistent with established approach (CAC/RCP 61-2005).

Principle 14: AMR risk profiling 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 15: AMR risk profiling activities should focus on clearly defined combinations of the food, antimicrobial drug(s), antimicrobial use practice, and resistant foodborne microorganisms/or genetic determinants of resistance.

Principle 16: AMR risk profile should provide as much information as possible to risk managers to facilitate decision-making.

General Principles for AMR Risk Assessment

Principle 17: An AMR risk assessment is a microbiological risk assessment that additionally needs to consider factors relating to the antimicrobial susceptibility of the microorganism(s) in question and related consequences to treatment of human disease. Consequently, the approach should be consistent with the *"Principles and Guidelines for the Conduct of Microbiological Risk Assessment"* (CAC/GL 30-1999).

Principle 18: AMR risk assessment should addresses the risk question posed by the risk managers by taking into account the whole farm-to-table continuum approach, where appropriate, encompassing the food production, processing, distribution, and consumption.

Principle 19: AMR risk assessment should consider the principal contributing factors to the emergence and dissemination of AMR among pathogenic and commensal microorganisms that have food reservoirs.

Principle 20: AMR risk assessment should consider the dynamics of genetic resistance determinants within microbial populations (e.g., in animal feeds, aquaculture, plants, or the environment) as well as their persistence and spread within humans and animals.

Principle 21: AMR risk assessment should consider the impact of AMR on the treatment effectiveness/efficacy of antimicrobials used in human medicine.

8. Risk Communication

8.1. General

Risk communication is fundamentally a two-way process. Through risk communication, decision-makers can obtain vital information, provide information and solicit feedback from affected/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.

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

Communicating effectively with different audiences requires considerable knowledge, skill, and thoughtful planning. It is not always a simple matter to know specifically who those parties are or to get them engaged in a particular risk analysis process; it is also important to avoid choosing inappropriate risk communication tools/mechanisms.

Mechanisms may be established for engaging interested parties in food safety decision-making at the national/regional level in a general, ongoing way. For antimicrobial resistance (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.

Effective risk communication is crucial to achieving the objectives of AMR risk management given the complex nature of the risk and the variety of stakeholder needs and concerns. Communication with public health authorities that are not integrated in food safety authorities is especially important, in view of the importance of integrating scientific information from all aspects of monitoring hazards throughout the food chain, human health surveillance and epidemiological data.

8.2. During preliminary risk management activities

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 and affected 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 risk management options, which are also to be communicated timely to the interested and affected parties.

8.3. During risk assessment

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, and possible risk management options, where appropriate, should be communicated to all interested parties and the general public in a timely fashion.

During the implementation of Risk management options

Risk managers should communicate decisions on risk management options to all interested parties, including the rationale, and how those affected will be expected to implement them, where appropriate.

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

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

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

Ranking risk management options 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.

Information on veterinary antimicrobial products considered essential by the national authority to ensure their safe and effective use, in compliance with GVPs (?), should be made available by the veterinary drug industry, in the form of labelling, data sheets, or leaflets…

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.

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

Training should be undertaken to assure the safety to the consumer of animal derived food and therefore the protection of public health. Training should involve all the relevant professional organisations, regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes, professional associations and other approved users[16].

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 labelling, and public interest messages. Consumer organisations can play a significant role in getting this information to consumers.

When risk management options include consumer information, outreach programmes 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.

Documentation

The process (including consultations between risk managers, risk assessors and stakeholders, the data source identification/selection, constraints, uncertainties and assumptions made etc.) and specific outputs of AMR risk analysis, including risk assessment, risk management and risk communication, should be fully and transparently documented in conformity with the approach established in other Codex documents (CAC/GL

[16] See para. 36 in *CAC/RCP 61-2005 – CODE OF PRACTICE TO MINIMIZE AND CONTAIN ANTIMICROBIAL RESISTANCE – TRAINING OF USERS OF VETERINARY ANTIMICROBIAL DRUGS*, for the scope of relevant training programmes.

30-1999; CAC/GL 62-2007; and CAC/GL 63-2007). While respecting legitimate concerns to preserve confidentiality, documentation should be accessible to all interested parties.

Definitions for Harmonized Document

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. Some established Codex definitions are cited 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 illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality (FAO/OIE/WHO, 2003).

Antimicrobials (Antimicrobial Agents) - Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target (FAO/OIE/WHO, 2008).

Antimicrobial class: Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of 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 - The ability of a microorganism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species (FAO/OIE/WHO, 2008).

Commensal – Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected.

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 agent, in general the higher the activity, the lower the level of resistance. Cross-resistance implies cross-selection for resistance (FAO/OIE/WHO, 2008).

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.

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.

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 their 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 the hazard*. 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 groups of food.*

Pathogen – A microorganism that causes illness or disease.

Pre-Harvest – The stage of food animal or plant production prior to the slaughtering or harvesting.

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

Resistance Determinant – The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial. They are located in a chromosome or a plasmid, and may be associated with transmissible genetic elements such as integrons or transposons, thereby enabling horizontal transmission from resistant to susceptible strains.

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 antimicrobial resistance 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 Estimate - *Output from Risk Characterization.* 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 an agent. 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.