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Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin

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This report, prepared by the OIE Ad hoc Group of experts on antimicrobial resistance, has not yet received the approval of the International Committee of the OIE

Summary

The Ad hoc Group of experts on antimicrobial resistance, appointed by the Office International des Epizooties, has developed an objective, transparent and defensible risk analysis process, providing a valid basis for risk management decisions in respect to antimicrobial resistance. The components of risk analysis and of different possible approaches in risk assessment (qualitative, semi-quantitative and quantitative) are defined. The Ad hoc Group recommended the following: an independent risk assessment based on scientific data; an iterative risk analysis process; a qualitative risk assessment systematically undertaken before considering a quantitative approach; the establishment of a risk assessment policy; and the availability of technical assistance for developing countries.

Keywords

Antimicrobial resistance – Containment of resistance – Food – Human medicine – International standards – Public health – Risk analysis – Risk assessment – Risk management – Veterinary medicine.

Introduction

This document presents the concept of risk analysis, comprising the components of hazard identification, risk assessment, risk management and risk communication, as applicable to antimicrobial resistance. The inter-relationship of these components is described and the respective distinct responsibilities of risk assessors and risk managers are identified. An example of a risk analysis methodology is given both in relation to animal health and to human health.

Background

Use of antimicrobials in animals for therapeutic, preventative and growth promotion purposes can reduce the therapeutic value of antimicrobials used in animal and human medicine because of losses in susceptibility of pathogenic bacteria. This risk may be represented by the loss of therapeutic value of one or several antimicrobial drugs and includes the emergence of multi-resistant bacteria.

The principal aim of risk analysis of antimicrobial resistance in bacteria from animals is to provide Member Countries of the Office International des Epizooties (OIE) with an objective and defensible method of assessing and managing the human and animal health risks associated with the development of resistance due to the use of antimicrobial drugs in animals, including appropriate communication measures. The procedure should be transparent and clearly separate responsibilities in risk assessment and risk management. Risk assessment should be based on the available scientific data. Transparency is essential because data are often uncertain or incomplete, and without full documentation, the distinction between facts and value judgements may not be clear. Risk management should also be a structured approach so that all stakeholders (for example, agricultural and pharmaceutical industries, healthcare providers and consumer groups) are provided with clear reasons for the imposition of risk management controls (for example, on the animal use of the antimicrobial in question, more stringent slaughtering or processing requirements, or import restrictions on products from animals that have been treated with antimicrobials).

A policy framework for the authority regulating antimicrobials should be established to provide risk managers and risk assessors with a consistent set of legal, regulatory and political rules within which risk analyses must be conducted.

This Guideline explains the recommendations of the OIE Ad hoc Group on antimicrobial resistance for guidelines and principles for conducting transparent, objective and defensible risk analyses to control the impact of using antimicrobials in animals, and provides recommended definitions of terms used in risk analysis.

Two principal sets of terminology are currently in use in risk analysis relating to this topic, namely: the United States (US) National Academy of Science (NAS) system on which the Codex Alimentarius Commission (Codex) approach is based, developed for food safety issues, and the Covello-Merkhofer system on which the OIE *International Animal Health Code* risk analysis is based. Beyond their apparent differences, both systems are very similar and largely contain the same components. The way these components are ordered in each of these two systems has evolved because of the type of risks that are being addressed. The terminology presented in this document follows the Covello-Merkhofer system. Comparison between the two systems and definitions of terms are given in Appendix C.

The risk analysis process

Risk analysis is defined in the OIE *Code* as 'The process composed of hazard identification, risk assessment, risk management and risk communication'. It is a term frequently used to describe the complete process of properly addressing a risk issue. It encompasses assessing and managing the risk together with all the appropriate communication between risk assessors, stakeholders and risk managers. A typical risk analysis proceeds as detailed below.

a) A policy framework will previously have been established by risk managers that describes the types of risk that need to be addressed, implying, among other things, the ranking of these risks among the other risk issues. In consultation with technical experts and risk assessors, a strategy for the assessment of the risk is then formulated. The policy framework also provides an explanation of the type of risk management options that can be considered under the legislative and regulatory framework of the country. Finally, the policy framework should explain the risk decision-making process, including methods of evaluating and quantifying risks and the level of risk deemed to be acceptable.

b) A risk issue and plausible risk management actions that could be taken to reduce or eliminate the risk are identified by management.

c) In consultation with technical experts, risk assessors and other stakeholders, a strategy for a preliminary assessment of the risk is formulated, including precisely how the risk is to be evaluated.

d) Risk assessors execute a preliminary qualitative assessment (scoping study) and advise management on the feasibility of assessing quantitatively the risk and on the identified risk management strategies. This report is made public.

e) Managers will determine from this scoping study whether the risk is sufficiently severe to warrant further action, including whether resources (which could be very limited) can be dedicated to the issue. If the risk is considered sufficiently important, and if feasible, risk managers may then instruct risk

assessors to fully assess the risk (qualitatively, and/or quantitatively) and the reduced level of risk that would exist after each identified risk reduction option. Refining of the risk reduction options and risk assessment may go through several iterations.

f) The risk assessment may be presented for review at various stages until the final risk assessment report has been produced, which is then made public. This aspect of risk communication is particularly helpful in ensuring transparency of the risk analysis as a whole and the efficient collection of data.

g) Risk managers use the results of the risk assessment in order to determine, in line with previously defined policy, the appropriate actions to take in order to manage the risk in question in the most efficient manner.

h) The risk management decision by a regulatory authority is made public with the greatest possible clarity.

i) The risk managers have to implement their decision and to organise the follow-up of these regulatory and other measures in order to evaluate the impact of these decisions with regard to the expected results.

j) The data acquired by the follow-up must be assessed in order to allow a possible amendment of the risk analysis policy, of the assessment strategy, of the outcome of the scientific assessment, and of the regulatory and other actions that have been taken.

The following sections elaborate on these stages, categorised into four parts according to the Covello-Merkhofer system. References refer to where in the above bullet points each stage appears:

– hazard identification (*b*)

– risk assessment (*c, d, e, f*)

– risk management (*b, g, i, j*)

– risk communication (*c, d, f, h*).

Hazard identification

Hazard identification is defined under the OIE system as 'The process of identifying the pathogenic agents that could potentially be introduced in the Commodity considered for importation'. It is the identification of 'risk agents' (hazards) and the conditions under which they might potentially produce adverse consequences. In terms of risk issues related to antimicrobial-resistant bacteria, the risk agent is most generally represented by the resistance determinant that emerges as a result of the use of a specific antimicrobial in animals. This definition then reflects the development of resistance in a species of bacterium that is pathogenic, as well as the development of a resistance determinant that may be passed to other bacteria that are pathogenic. The conditions under which the risk agent might potentially produce adverse consequences include any feasible scenarios via which humans or animals become exposed to pathogens which contain that resistance determinant, fall ill and where the human or animal would be treated with an antimicrobial that is no longer effective because of the resistance.

Risk management

Risk management policy

Risk management policy is a new term defined as 'The regulatory policy framework for monitoring, measuring, assessing and managing risks involved in the use of antimicrobials in food producing animals'. A critical precursor to the risk analysis process is the development and public explanation of such a policy framework. This framework, aimed at providing the guidelines for conducting an appropriate risk assessment, has to be developed by the risk managers with the technical support of the scientific experts in charge of the risk assessment.

The policy framework explains the philosophy behind monitoring and controlling risks involved in the use of antimicrobials in food producing animals. It must explain methods for involving risk assessment in the approval of new drug use, the various restrictions of use that might be applied to control and reduce any adverse impact and the procedure for retracting approval of use of the drug. It must also explain how the human or animal impact due to resistance will be measured, what level of impact will be considered unacceptable and how this information is used in the registration of new drugs.

The policy framework may also address the additional importance of certain antimicrobial drugs needed to treat infectious diseases in human medicine for which there are no effective alternative therapies. Furthermore, it should explain the range of risk reduction actions that management can select within legislative and regulatory restrictions.

The framework should explain the impact of uncertainty on the risk management decision. It should also address what actions will be taken in the event of identifying an unquantifiable risk due to antimicrobial use.

The establishment of a population of resistant bacteria as a result of the use of an antimicrobial in animals means that the human or animal health impact may continue long after the animal use of an antimicrobial has ceased. The policy framework should therefore address how to measure a long-term impact, and may include some cut-off period or discount factor that recognises the reduced value of a therapeutic drug as new drugs become available.

However, the policy framework should not necessarily restrict risk management from considering potential risk management options that may be outside the current domain of the

regulatory authority. Clear explanation of these conditions allows the pharmaceutical and agricultural industries and the veterinary and healthcare professional bodies to plan and test current and future antimicrobial products in a predictable environment and modify their use to achieve clear objectives.

Clearly stating the policy framework ensures transparency during the risk management phase of a risk analysis. People react to risk in very different and often emotional ways: a clear policy on how to measure risk and what is deemed acceptable implicitly recognises that a zero risk policy is unachievable and greatly reduces any suspicion of false argument.

Risk management components

Risk management is conducted by risk managers who have a comprehensive understanding of policy, and an appropriate level of technical background to communicate effectively with the risk assessors. The OIE defines risk management as consisting of the steps described below.

Risk evaluation

The process of comparing the risk estimated in the risk assessment with the appropriate level of protection of the Member Country.

Option evaluation

The process of identifying, evaluating the efficiency and feasibility of, and selecting measures in order to reduce the risk associated with an importation in line with the appropriate level of protection of the Member Country. The efficacy is the degree to which an option reduces the likelihood and/or magnitude of adverse biological and economic consequences. Evaluating the efficacy of the options selected is an iterative process that involves their incorporation into the risk assessment followed by comparison of the resulting level of risk with that considered acceptable. The evaluation for feasibility normally focuses on technical, operational and economic factors affecting the implementation of the risk management options.

Implementation

The process of following through with the risk management decision and ensuring that the risk management measures are in place.

Monitoring and review

The ongoing process by which the risk management measures are continually audited to ensure that they are achieving the results intended.

Risk decision when data are insufficient or inadequate

In the event that insufficient or inadequate data are available to reasonably assess the importance of a potential risk issue, and it is considered that the risk is potentially of such severity that one cannot wait for sufficient data before taking action, it is reasonable for the risk managers to take a temporary risk avoidance action that minimises any exposure to the risk. There are five extremely important considerations when faced with this situation, as follows:

a) a risk assessment must first be attempted, and all reasonable efforts made to acquire the necessary data, within the allowable timeframe, before taking the temporary risk avoidance action

b) the risk avoidance action must be chosen to provide the required level of protection in the manner least restrictive to trade

c) the risk avoidance action should be commensurate with the potential severity of the risk

d) in all cases, particularly in international trade, the risk avoidance action should be taken in conjunction with a commitment to acquire the necessary data, within a reasonably short and defined time, to help assess the severity of the risk and the most appropriate risk reduction strategy

e) the process must remain transparent.

Risk assessment

Risk assessment is defined in the OIE *Code* as 'The evaluation of the likelihood and the biological and economic consequences of entry, establishment, or spread of a pathogenic agent within the territory of an importing country'. There are a number of approaches to assessing the magnitude of a risk and the value of potential risk reduction options. These can be broadly categorised into three types: qualitative, semi-quantitative and quantitative risk assessments. Whichever approach is taken, the risk assessment must be designed to address the specific question posed by the risk managers.

The risk assessment process is usually sub-divided into four components: risk release assessment; exposure assessment; consequence assessment; and risk estimation. Their meanings are described below and examples of factors that may be considered in each component are listed in Appendices A and B.

Release assessment

Defined in the OIE *Code* as 'Description of the biological pathways necessary for the use of an antimicrobial in animals to release resistant bacteria or resistance determinants into a particular environment, and estimating the probability of that complete process occurring either qualitatively or quantitatively'.

Exposure assessment

Defined in the OIE *Code* as 'Describing the biological pathways necessary for exposure of animals and humans to the hazards released from a given source, and estimating the probability of the exposure occurring, either qualitatively or quantitatively'.

Consequence assessment

Defined in the OIE *Code* as 'Description of the relationship between specified exposures to a biological agent and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring. This estimate may be either qualitative or quantitative'.

Risk estimation

Defined in the OIE *Code* as 'Integration of the results from the release assessment, exposure assessment, and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. Thus risk estimation takes into account the whole of the risk pathway from hazard identified to unwanted outcome'.

The policy framework will provide guidelines to the risk assessors on how to assess the complete impact of any risk issue and risk reduction strategies. For example, removing an antimicrobial from veterinary use may mean that another antimicrobial is used in its place with potentially worse consequences. Unless these secondary impacts, whether positive or negative, are addressed, the risk management strategy may be sub-optimal.

The initial planning stages of a risk assessment can be performed as described below.

a) The risk issue in question is formally expressed to ensure that all participants agree on the problem to be addressed. The potential mechanisms and pathways via which the hazard can result in an adverse effect are also described. This system, as understood by the risk assessment team, can be explained using one or more flow diagrams. At this point, the diagram is purely conceptual and there is therefore no need for data. The purpose of such diagrams is to focus thought on what data would be useful, what possible risk management options exist, and to integrate and review the level of knowledge about the system in general. It is advisable to involve a broad participation in the exercise and to circulate widely to stakeholders and relevant experts.

b) A preliminary data search is conducted to assess what components of the system might be adequately quantified. Components might include, for example: the prevalence of resistant bacteria in faeces, water or carcasses; the distribution by animal species, season and geographical region of use of an antimicrobial; the frequency of the use of the antimicrobial in human medicine and the health status of those receiving the antimicrobial. At this stage, it is sufficient to know of the availability of data. Requests for data that might help quantify the components of the system can also be made to stakeholders and relevant experts. Strong consideration should also be given to useful data that may not be immediately available, but that could become available within a reasonable period, perhaps with some research effort. The interpretation of what constitutes a reasonable period will reflect the imminence and severity of the risk issue in question. It may be appropriate to consider completing a risk assessment rapidly to help decision makers identify the immediate actions to be taken, recognising that a re-evaluation of the risk issue when more data become available may lead the decision makers to alter the preliminary actions that were taken.

c) A review of the system, as perceived by the risk assessment team, together with the data available to quantify the components of that system can provide important guidance. It can illustrate which risk management options can be properly assessed for their effectiveness. It can also guide the risk assessor regarding the production of a quantitative risk assessment, if required, that would be based on data as well as supplying guidance as to whether such a model could be validated in some way. It is the combination of feasible risk management options, together with the data that could be available to assess those options, that should direct the risk assessment team towards the form of their assessment. If the system is not sufficiently well understood, or insufficient data are available to meaningfully quantify the model, it may only be possible to produce a qualitative risk analysis. However, quantification of certain aspects of the system may also be possible, which could enable the evaluation of a restricted number of risk management options. The risk assessment model can be kept as simple as possible to support the range of risk management decisions being considered. The model structure may not include a complete pathway analysis of the risk scenario if there are limited risk reduction strategies the benefits of which can be addressed in a far simpler model. Flexibility in the approach to modelling will reduce the effort required to produce the assessment and limit the number and type of assumptions that may have to be made in the model. However, the model may not then be useful in addressing other questions that arise over the same risk issue and may not help other stakeholders contribute to efficiently managing the risk. It may also be difficult to demonstrate consistency between models where different model structures have been used together with quite different assumptions.

A full assessment of the risk to human and animal health from antimicrobial-resistant bacteria resulting from use of antimicrobials in food-producing animals can be divided into three parts, as follows:

a) production of the resistant bacteria of interest as a result of antimicrobial use, or more particularly, production of the resistant determinants if transmission is possible between bacteria. (If it is the use of the antimicrobial in animals that is being considered as the hazard, there may be several different species of bacteria to consider.)

b) consideration of the realistic pathways via which humans can become exposed to these resistant bacteria or resistance determinants, together with the possible range of bacterial load ingested at the moment of exposure

c) consideration of the response of the person to the exposure.

Risk assessment of antimicrobial issues can be technically difficult, and it is essential that the assessment is the work of a team of professionals with broad expertise in risk analysis modelling, microbiology, veterinary medicine and animal husbandry, human healthcare and medicine, chemistry and any other relevant disciplines. Published chemical, microbial and genetic risk assessments can provide useful generic illustrations for modelling components of the risk assessment.

Qualitative risk assessment

Qualitative risk assessment is defined in the OIE *Code* as 'An assessment where the outputs on the likelihood of the outcome or the magnitude of the consequence are expressed in qualitative terms such as high, medium, low or negligible'. A qualitative risk assessment is always completed first as part of a preliminary evaluation (scoping study), whether or not one progresses to a semi-quantitative or fully quantitative assessment. It is the collation of all available information that will enable the determination of the probability and impact of the risk in question. A qualitative risk assessment discusses the steps necessary for the risk to occur, which pathways are feasible and which can be logically discounted. In a risk assessment of a human health impact due to use of a specific antimicrobial in food producing animals, for example, factors would include patterns of use of the antimicrobial, rates of resistance acquisition in exposed bacteria, the ecology of these resistant bacteria, pathways via which these bacteria may directly or indirectly transfer resistance to pathogens that infect humans, and the rates at which antimicrobials analogue to the animal antimicrobial are prescribed for the infected humans.

A qualitative risk assessment would also need to discuss the level of loss of benefit of the human medicine antimicrobial. All of these factors constitute a risk scenario on which one can overlay possible risk reduction strategies and discuss the benefits they might provide. Appendices A and B list factors that may be useful in an assessment. At this stage, a risk may be determined to be logically insignificant because, for example, the biological pathway is not possible or the risk is logically less severe than another for which a full analysis has been completed and determined to be acceptably small. As more risk assessments are conducted on antimicrobial issues, there may be broad agreement concerning the likely risks associated with particular hazards. In such cases, a qualitative assessment may frequently be the sole requirement. Qualitative assessment does not require mathematical modelling skills and so will often be the type of assessment used for routine decision-making.

When all easily-obtainable information has been collected, a preliminary report to the risk managers is necessary to advise of any further information that will be needed to complete the picture, or perhaps any additional information that will be necessary to complete a more quantitative analysis. It should also be apparent at this stage whether data are or can be made available to assess each risk reduction strategy and communicating this to the risk managers enables them to assess which risk reduction strategies are worth pursuing in greater depth.

Quantitative risk assessment

Quantitative risk assessment is defined in the OIE *Code* as 'An assessment where the outputs of the risk assessment are expressed numerically'. The purpose of quantitative risk assessment is to numerically evaluate the probability and impact(s) associated with a risk issue. Two principal mathematical approaches are feasible: the most common is to use a Monte Carlo simulation model to describe the risk event (the development of the hazard into an actual impact), together with its uncertainty (lack of knowledge) and variability (inherent randomness); the second method is to use the algebra of probability theory to produce a formulaic model of the risk event. Monte Carlo simulation is almost always preferred over algebraic methods because it is far simpler to execute, particularly with modern software. It offers greater modelling flexibility, is easy to understand, check and explain, and less prone to human error in model development. However, Monte Carlo simulation of rare events can become onerous, in which case a combination of calculating some simpler parts of a risk scenario and simulating the remainder may sometimes prove more efficient.

A quantitative risk assessment produces a mathematical model that estimates the effect of possible risk management actions. It may be desired that any possible action between and including production of the food animal and the final human health effect be evaluated quantitatively. If so, the quantitative risk assessment model must simulate all important microbial pathways between the farm and the exposed human or animal in sufficient detail to evaluate possible changes in the system as a result of a risk management action. For risk management purposes, it may only be necessary to evaluate changes in the human or animal health impact as a result of a risk management action, not the underlying base health risk, although it may be informative to be able to estimate the base health risk for other purposes.

Thus, a full risk assessment model may need to consider a wide range of pathways. For example, *Enterococcus faecium* is a hardy organism that can survive for long periods outside its original host. Feasible pathways may include, for example, runoff from manure lagoons or fields sprayed with manure entering waterways used by swimmers, or the consumption of vegetables that have been grown in fields sprayed with manure. By contrast, these pathways would not be important for *Campylobacter* which succumb rapidly to changes in their environment. Failure to appreciate the range of pathways

could lead to a misevaluation of the effect of some risk management action. For example, irradiation of poultry carcasses may be effective against *Campylobacter* if consumption of meat were to be considered the primary exposure pathway. However, irradiation might prove ineffective for *E. faecium* if the primary exposure pathway was from consumption of raw vegetables.

Microbial food safety risk assessments have for some time attempted to model very similar risk issues to those posed by antimicrobial resistance. A variety of modelling techniques exists for microbial risk assessments, based around the principles of stochastic simulation of risk scenarios (14, 18, 19, 22). Spreadsheet models are generally used together with Monte Carlo simulation add-ins to create simulations of the entire 'farm-to-fork' continuum, finishing with the way in which the consumer is affected by consumption of the bacteria. Other commercially available dynamic simulation applications can achieve much the same effect. There are a variety of formula-based models available from the field of predictive microbiology to estimate the growth and attenuation of various bacteria when exposed for different amounts of time to different environments, particularly level of moisture, temperature and pH. Thus, a quantitative risk assessment combines probability mathematics (11, 17), usually from the binomial and Poisson processes, with empirical curve-fitting equations and sometimes theoretically based formulae from predictive microbiology, to attempt to characterise the exposure events. Microbial food safety models consider the redistribution, growth and attenuation of bacteria during the various actions in slaughtering, processing, food handling and cooking. For example, the microbial load on contaminated carcasses will be reduced drastically through correct handling, removal of the most contaminated parts of the carcass, scalding and washing. In contrast, cross-contamination between carcasses through aerosols, splashing, workers, etc., may mean that the proportion of contaminated carcasses leaving the slaughter plant is greater than the proportion of contaminated animals entering the plant. Much of the modelling principles necessary in antimicrobial resistance risk assessment parallel those used in microbial food safety risk assessment. At the time of writing (November 2000), very few antimicrobial resistance risk assessments have been published (http://www.fda.gov/cvm/fda/mappgs/antitoc.html; 23) but a significant number of microbial food safety risk assessments have been completed which provide practical illustrations of the techniques employed (2, 8; http://www.fsis.usda.gov/ophs/risk/index.htm; http://www.foodriskclearinghouse.umd.edu/risk_assessments.htm; http://www.fsis.usda.gov/OPHS/ecolrisk/home.htm; http://www.nal.usda.gov/fnic/foodborne/risk.htm).

Microbial risk assessments typically use logarithmic scales in estimating the microbial load because of the range of numbers that can be involved and the multiplying nature of bacterial growth and attenuation. Subsequent estimations of the probability of infection, illness or perhaps death from specific exposures are made through dose-response equations to produce a final estimate of the total human health impact. Risk assessments that model the complete microbial pathway from the farm to final ingestion are sometimes called 'farm-to-fork' or 'farm-to-table' risk assessments, though these are potentially misleading terms in cases where significant exposure pathways are associated with ingestion via other means (e.g. consumption of vegetables, ingestion through soil or water, and human-to-human or animal-to-human transmission). A full 'farm-to-fork' model invariably contains a host of potentially contestable assumptions because of the inherent complexity of the system being modelled and the gaps in knowledge of that system. It also relies a great deal on the validity of a dose-response model, the weaknesses of which are well known (21).

In general, a risk assessment model should only be as complex as necessary to evaluate the risk management options available to the regulatory authority, therefore a full 'farm-to-fork' model may not be necessary. For example, the risk assessment completed by the United States Food and Drug Administration Center for Veterinary Medicine (USFDA-CVM) on the human health effect of fluoroquinolone-resistant *Campylobacter* (http://www.fda.gov/cvm/fda/mappgs/antitoc.html) considered only the effect of removal of fluoroquinolone use in poultry. This assessment avoided any modelling of the 'farm-to-fork' pathways. It estimated the number of human cases of campylobacteriosis that would have been affected by the fluoroquinolone-resistance from poultry, to provide an estimate of the current risk. The argument was that removing fluoroquinolone from poultry would have the effect of reducing the human impact by this amount, which was supported by the low survivability of *Campylobacter* outside its host, so resistance would rapidly disappear. The assessment then related this risk to the level of prevalence of fluoroquinolone-resistant *Campylobacter* contaminated broiler carcasses at the end of the slaughter plant. The argument then presented was that changes in that prevalence and/or the load on the contaminated carcasses can be mapped to a corresponding change in the human health impact. The structure of models like this can be used very effectively in other countries, using data appropriate to that country, where similar assumptions would apply.

All parameters in a quantitative risk assessment model must be quantified. The most transparent approach, least likely to attract criticism, is to use published data from peer-reviewed papers. However, such data will frequently not be available and reasonable surrogates may be used in their place, together with supporting arguments for the surrogacy. Expert opinion may also be used, but it is more transparent if any data from which the expert has based his or her opinion can be used in its place (12). Unpublished data from reliable sources may also be used. Regardless of the source, all data used in the risk assessment must be critically reviewed.

A quantitative risk assessment must explicitly model the uncertainty associated with the model parameters using techniques like the bootstrap (5, 6), Bayesian inference (9, 20) and classical statistics (1, 10, 13). Bayesian inference is particularly useful at explicitly stating the contribution arising from observations, interpretation of those observations and any subjective estimation. Bayesian inference also allows the analyst to combine information from different sources, such as two different random surveys of a population for contamination with different test sensitivities and specificities.

The results of the risk assessment are presented as a report to the risk managers, explaining the methods used, characterising the risk in appropriate terms according to policy, together with the benefits of any risk reduction strategies that could be assessed. All quantified terms should be reported with their uncertainties in an easily understandable form. The relative frequency distribution provides an excellent visual representation of the level of uncertainty, whilst cumulative distribution plots allow the risk manager to evaluate the risk at any desired level of confidence. Sensitivity analyses should be performed to determine the key uncertainty parameters of the model and illustrated using techniques such as spider plots and tornado charts. Key assumptions must also be explicitly described, together with a balanced argument of the reasoning for the assumptions and a discussion of the inaccuracy of the predictions of the model should those assumptions be false. This model uncertainty must be keenly analysed, and possible methods of validating assumptions must be considered, perhaps through scientific experiments or comparison with the experience of other nations. Inclusion and discussion of all types of uncertainty in the risk assessment report allow the risk managers to apply the appropriate level of conservatism in valuing the risk and any risk reduction options. It should be emphasised that failure to properly address uncertainty in the risk assessment report equates to an implicit value judgement of the risk that is not the remit of the risk assessor.

Semi-quantitative risk assessment

Semi-quantitative risk assessment is a new term defined as 'An assessment where estimates of the likelihood of the outcome and the magnitude of the consequences are expressed in semi-quantitative terms via some scoring mechanism'. It will frequently not be possible to perform a complete quantitative risk assessment on each item in a portfolio of risk issues facing risk managers because of lack of appropriate data. In such circumstances, it would nonetheless be useful to have a method for comparing the magnitude of risks and the benefits of risk reduction strategies for those risks. Semi-quantitative risk assessment, when properly executed, is a transparent approach that supports the efficient management of a portfolio of risk issues without requiring complete quantification of the risks or excessive risk avoidance. Semi-quantitative risk assessment techniques are commonly used for risk analysis in commercial projects, but are currently not widely accepted in international risk issues because of the difficulty in retaining transparency and because the process is open to abuse without proper guidelines.

The principle of semi-quantitative risk assessment (22) is initially to estimate the probability and size of the potential consequences into broad, but well-defined categories, then convert these estimates using a scoring system to produce a severity score for the risk. Various risk management options can be evaluated according to the degree to which they would reduce the severity score of the risk. The technique has a number of advantages, as follows:

– the risks can be compared in a systematic fashion

– a severity threshold can be set for unacceptable risk

– an efficient and consistent policy framework can be developed which minimises the total severity scores for all risks given the resources available.

Risk communication

As defined in the OIE *Code*, 'Risk communication is the interactive exchange of information on risk among risk assessors, risk managers and other interested parties'. There are many aspects to risk communication. Failure to pay proper attention to risk communication may easily result in failure of the risk analysis process. Both risk managers and risk assessors should be well versed in the concepts of risk analysis. The risk assessors should have a clear understanding of policy. Similarly, the risk managers should be fully conversant with the taxonomy and terminology of risk assessment and appreciate the level of effort and variety of disciplines involved in producing a reliable risk assessment. The goals of risk communication are the following:

– to promote awareness and understanding of the specific issues under consideration during the risk analysis process, by all participants

– to promote consistency and transparency in arriving at and implementing risk management decisions

– to provide a sound basis for understanding the risk management decisions proposed or implemented

– to improve the overall effectiveness and efficiency of the risk analysis process

– to strengthen working relationships and mutual respect among all participants

– to promote the appropriate involvement of all stakeholders in the risk communication process

– to exchange information on the knowledge, attitudes, values, practices and perceptions of stakeholders concerning the risks in question.

The joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Consultation on the application of risk communication to food standards and safety measures, held in 1998 in Rome, provides an in-depth discussion on the subject (7).

Communication between assessors and managers

Management must provide clear instructions for the risk issue that is to be analysed, together with the preferred method(s) of characterisation (e.g. person days of illness per year). Assessors must ensure that the managers have reasonable expectations of the assessment and may also advise of other potential information the assessment may provide that would help the management with their decision-making. There should be communication between the risk assessors and risk managers throughout the assessment process to ensure that the assessment is completed in a timely fashion and that the required resources are made available.

Communication between assessors and stakeholders

It is extremely helpful to widely publicise the intended method of assessment, including model structure and assumptions at the earliest possible opportunity, together with an expression of flexibility in the eventuality of any new information or ideas. This allows stakeholders to provide input, improves transparency of the process and improves support for the assessment and any resultant risk management decision.

Communication between managers and stakeholders

Risk managers will usually need to advise stakeholders of the intention to perform a risk analysis at the beginning of the project. At this stage, communication with stakeholders is an important opportunity to gather political and scientific support for the risk assessment, as well as a data gathering exercise. When the risk assessment has been completed, it is advisable to make the report publicly available with a reasonable comment period to ensure that there are no large errors in the assessment or additional data available. The World Wide Web is an excellent means for maximising the availability of the assessment and may include downloadable, self-contained versions of the risk assessment. Publishing comments received, together with any responses from the risk assessment and risk management teams, underlines the transparency of the process. These can be included in the final risk analysis document that explains the results of the risk assessment together with the risk management decision that has been made.

Recommendations

To effectively manage antimicrobial resistance risk issues, the OIE Ad hoc Group recommends that:

– risk analysis should be conducted in an objective and defensible manner

– the risk analysis process should be transparent and consistent

– risk analysis should be conducted as an iterative and continuous process

– risk management and risk assessment functions should be kept separate to ensure the independence of decision-making and evaluation of the risk

– risk management should be conducted in reference to a policy framework setting out the domain of the regulator and the range of risk reduction actions that may be considered

– the risk assessment should be based on sound science and conducted according to a strategy established by the risk managers in co-operation with the risk assessors

– risk assessment requires a multidisciplinary team and should be conducted in broad consultation with available scientific expertise

– qualitative risk assessment should always be undertaken, and provides information on whether progression to full quantitative risk assessment is feasible and/or necessary

– risk assessment of antimicrobial resistance issues requires very specific, technical skills that may not be available to developing countries. The OIE and its Member Countries should work towards helping these countries to develop or access these skills, to ensure that risk assessment itself does not become a barrier to trade

– communication between managers, assessors and stakeholders is essential. Effort should be made to establish such communication early in the process, to allow opportunity for responses, and should be continued throughout the risk analysis process.

Antibiorésistance : méthodologie d'analyse du risque appliquée à l'impact potentiel sur la santé publique des bactéries d'origine animale résistantes aux antibiotiques

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Résumé
Le Groupe ad hoc d'experts sur l'antibiorésistance créé par l'Office international des épizooties a élaboré une procédure d'analyse du risque à la fois objective, transparente et justifiée, offrant une base valable pour les décisions de gestion du risque relatives à l'antibiorésistance. Les auteurs définissent les éléments constitutifs de l'analyse du risque et les différentes approches possibles de l'évaluation du risque (qualitative, semi-quantitative et quantitative). Les recommandations du Groupe ad hoc portent sur les points suivants : évaluation du risque indépendante basée sur des données scientifiques ; processus itératif d'analyse du risque ; réalisation systématique d'une évaluation qualitative du risque avant toute approche quantitative ; élaboration d'une politique d'évaluation du risque ; enfin, prestation d'une assistance technique pour les pays en développement.

Mots-clés
Analyse du risque – Antibiorésistance – Denrées alimentaires – Évaluation du risque – Gestion du risque – Maîtrise de la résistance – Médecine humaine – Médecine vétérinaire – Normes internationales – Santé publique.

Resistencia a los antimicrobianos: metodología de análisis de riesgos para determinar la eventual incidencia en la salud pública de bacterias de origen animal resistentes a los antimicrobianos

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Resumen
El Grupo Ad hoc de expertos sobre la resistencia de las bacterias a los productos antimicrobianos, creado por la Oficina Internacional de Epizootias, ha elaborado un proceso de análisis de riesgos objetivo, transparente y defendible, brindando con ello una sólida base para tomar decisiones de gestión de riesgos ligados a la

resistencia a los antimicrobianos. Los autores exponen los elementos que configuran el análisis de riesgos y los distintos planteamientos que se pueden aplicar (cualitativo, semicuantitativo y cuantitativo). El Grupo Ad hoc recomendó los siguientes procedimientos: una evaluación de riesgos independiente y basada en datos científicos; un proceso iterativo de análisis de riesgos; una evaluación cualitativa sistemática previa a la eventual aplicación de un método cuantitativo; la definición de una política de evaluación de riesgos; y la prestación de asistencia técnica a los países en desarrollo.

Palabras clave
Alimentos – Análisis de riesgos – Contención de las resistencias – Evaluación de riesgos – Gestión de riesgos – Medicina humana – Medicina veterinaria – Normas internacionales – Resistencia a los productos antimicrobianos – Salud pública.

Appendix A

Risk assessment of human health impact due to the use of antimicrobials in animals

The following lists, although not exhaustive, describe factors that may need consideration in a risk assessment of human health impact.

Definition of the risk

The infection of humans with bacteria that have acquired resistance to the use of a specific antimicrobial in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the human infection.

Hazard identification

Two types of hazard exist, as follows:

– bacteria that have acquired resistance due to the use of a particular antimicrobial in animals

– resistance determinants selected as a result of the use of a particular antimicrobial in animals.

The identification of the hazard must include considerations on the class or subclass of antimicrobial.

Release assessment

Release assessment consists of describing the biological pathways necessary for the use of a specific antimicrobial in animals to lead to the release of resistant bacteria or resistant determinants into a particular environment, and estimating the probability of that complete process occurring either qualitatively or quantitatively. The release assessment describes the probability of the release of each of the potential hazards under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures. Examples of the kind of inputs that may be required in the release assessment are as follows:

– species of animal treated with the antimicrobial in question

– number of animals treated, geographical distribution of those animals

– variation in methods of administration of the antimicrobial

– bacteria developing resistance as a result of the antimicrobial use

– mechanism of direct or indirect transfer of resistance

– capacity of resistance transfer (chromosomes, plasmids)

– cross-resistance and/or co-resistance with other antimicrobials

– surveillance of animals, animal products and waste products for the existence of resistant bacteria.

Exposure assessment

Exposure assessment consists of describing the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring, either qualitatively or quantitatively. The probability of exposure to the identified hazards is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed. Examples of the kind of inputs that may be required in the exposure assessment are as follows:

– human demographics and consumption patterns, including traditions and cultural practices

– prevalence of food and/or the animal environment contaminated with resistant bacteria

– prevalence of animal feed contaminated with resistant bacteria

– microbial load in contaminated food at the point of consumption

– survival capacity and redistribution of resistant bacteria during the agrofood process (including slaughtering, processing, storage, transportation and retailing)

– disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those waste products

– point of consumption of food derived from the food-producing animal (professional catering, home cooking)

– variation in consumption and food-handling methods of sub-populations

– capacity of resistant bacteria to settle in human intestinal flora

– human-to-human transmission of the bacteria under consideration

– capacity of resistant bacteria to transfer resistance to human commensals

– exposure to resistance determinants from other sources

– amount of antimicrobials used in response to human illness

– dose, route of administration (oral, injection) and duration of human treatment

– pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

Consequence assessment

Consequence assessment consists of describing the relationship between specified exposures to resistant bacteria or resistance determinants and the consequences of those exposures. A causal process must be believed to exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring. This estimate may be either qualitative or quantitative. Examples of consequences include the following:

– dose-response relationships

– variation in susceptibility of sub-populations

– variation and frequency of human health effects resulting from loss of efficacy of antimicrobials

– changes in human medicine practices resulting from reduced confidence in antimicrobials

– changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks

– associated costs

– interference with a classical first line antibiotherapy in humans

– perceived future of the drug (time reference).

Risk estimation

Risk estimation consists of integrating the results from the release assessment, exposure assessment and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. Thus, risk estimation takes into account the whole of the risk pathway from the hazard identified to the unwanted outcome. For a quantitative assessment, the final outputs may include the following:

– number of people falling ill

– increased severity or duration of disease

– number of person/days of illness per year

– deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)

– importance of the pathology caused by the bacteria

– absence of alternate antibiotherapy

– level of resistance observed in humans

– some arbitrary scale of impact to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).

Risk management options to evaluate

The following risk management measures could be implemented:

– decision not to grant a licence for use of a new antimicrobial

– review of licence authorisation and label indications

– revoking of licence

– restrict use of antimicrobial (e.g. in particular industries, therapeutic only)

– review of prudent use guidelines

– establish monitoring of veterinary use of antimicrobials

– revision of treatment guidelines.

Appendix B

Risk assessment of impact on animal health due to the use of antimicrobials in animals

The following lists, though not exhaustive, describe factors that may need consideration in a risk assessment of animal health impact.

Definition of the risk

The infection of animals with bacteria that have gained resistance from the use of a specific antimicrobial in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal infection.

Hazard identification

Possible hazards are as follows:

– bacteria that have acquired resistance due to the use of a particular antimicrobial in animals

– resistance determinants selected as a result of the use of a particular antimicrobial in animals.

The identification of the hazard must include consideration of the class or subclass of antimicrobial.

Release assessment

Examples of the type of inputs that may be required in the release assessment are as follows:

– species of animal treated with the antimicrobial in question

– number of animals treated, geographical distribution of those animals

– variation in methods of administration of the antimicrobial

– bacteria developing resistance as a result of the antimicrobial use

– mechanism of direct or indirect transfer of resistance

– capacity of resistance transfer (chromosomes, plasmids)

– cross-resistance and/or co-resistance with other antimicrobials

– surveillance of animals, animal products and waste products for the existence of resistant bacteria.

Exposure assessment

The following are examples of the type of inputs that may be required in the exposure assessment:

– prevalence of resistant bacteria in ill animals

– prevalence of food and/or the animal environment contaminated with resistant bacteria

– animal-to-animal transmission of the bacteria under consideration

– number/percentage of animals treated with the particular antimicrobial

– dissemination of resistant bacteria from animals (animal husbandry method, movement of animals)

– prevalence of animal feed contaminated with resistant bacteria

– amount of antimicrobial used in animals

– treatment (dose, route of administration, duration)

– microbial load in contaminated food at point of consumption

– survival capacity of resistant bacteria (competition of mixed populations, survival in the environment, contamination cycles including potentially the following elements: animals, humans, animal feed, environment, food, non-food producing animals, wildlife)

– dissemination of resistant bacteria and resistance determinants

– disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those waste products

– capacity of resistant bacteria to become established in animal intestinal flora

– exposure to resistance determinants from other sources

– dose, route of administration (oral, injection) and duration of human treatment

– pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

Consequence assessment

Examples of consequences include the following:

– dose-response relationships

– variation in susceptibility of sub-populations

– variation and frequency of animal health effects resulting from loss of efficacy of antimicrobials

– changes in veterinary medicine practices resulting from reduced confidence in antimicrobials

– associated costs

– perceived future of the drug (time reference).

Risk estimation

For a quantitative assessment, the final outputs may include the following:

– number of therapeutic failures due to resistant bacteria

– animal suffering (level and increase)

– economic cost (treatment with antibiotics, veterinary services, husbandry, reduced income, loss of market)

– deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)

– level of resistance observed in animals.

Risk management options to evaluate

The following risk management measures could be implemented:

– decision not to grant a licence for use of a new antimicrobial

– review of licence authorisation and label indications

– revoking of licence for antimicrobials already used

– restrict use of antimicrobial (e.g. in particular industries, therapeutic only)

– review of prudent use guidelines

– establish monitoring of veterinary use of antimicrobials

– revision of treatment guidelines.

Appendix C

Comparison of systems and terms used by the Codex Alimentarius and the Office International des Epizooties

The terms used in this document comply with the OIE terminology, as defined in Section 1.4. of the *Code* (16) based on the Covello-Merkhofer system (4). The Codex Alimentarius (3) uses a different, but equally valid system, designed by the US NAS (15). The issue of antimicrobial resistance arising from the use of antimicrobials in food-producing animals bridges the domain of OIE for animal husbandry and that of the FAO for food safety. It is therefore useful to compare these two systems and define terms used in this paper, to help integrate the two approaches.

Two risk analysis terminology systems: description

Table I summarises the components of risk analysis in the OIE and Codex models.

Table I
The components of risk analysis: a comparison of the systems used by the Codex Alimentarius and the Office International des Epizooties (OIE)

Components of risk analysis system	
Codex Alimentarius	**OIE**
Risk assessment	Hazard identification
Risk management	Risk assessment
Risk communication	Risk management
	Risk communication

Table II summarises the components of risk assessment in the OIE and Codex models.

Table II
The components of risk assessment: a comparison of the United States National Academy of Science model (used by the Codex Alimentarius) and the Covello-Merkhofer model (used by the Office International des Epizooties [OIE])

Components of risk assessment model	
Codex Alimentarius	**OIE**
Hazard identification	Risk release assessment
Hazard characterisation	Exposure assessment
Exposure assessment	Consequence assessment
Risk characterisation	Risk estimate

In a system based on the NAS model (called the 'Codex system' here), there are only three components of risk analysis, whereas in the system based on the Covello-Merkhofer model (called the 'OIE system' here), four components are present. Both systems include risk assessment, risk management and risk communication as components of risk analysis. However, the OIE system also includes hazard identification as a component of risk analysis, whereas the Codex system includes hazard identification as a sub-component of risk assessment. The terms risk management and risk communication are equivalent under both systems.

The NAS system was initially developed to assess the risks to health from exposure to chemicals. Codex has adapted this system for food safety purposes. The Covello-Merkhofer system was initially developed to assess a wide range of risks from any potential hazard. The specific wording of the explanations in Table III reflects those differences.

The first difference centres around the place of hazard identification in the models. The initial report of the NAS model (15), describes hazard identification as a major undertaking. The definition relates specifically to chemicals, and even in this case, NAS indicates that it includes weighing the available evidence relevant to cause and effect, as well as evidence relating to the magnitude of effect for the specified chemical. It is essentially a qualitative process of considerable magnitude. Given the number of potential pathogen hazards present in animals and animal products, the OIE risk analysis system, with a separate hazard identification step, is more adapted to pathogenic risk management.

The second difference is the presence in the OIE system of a step called release assessment, absent in the Codex system. Covello and Merkhofer argue that this is necessary for describing the probability of a given system (e.g. an industrial complex, a meat processing plant or another risk source) to release risk agents into the environment of interest. They believe this to be an essential step in obtaining an accurate understanding of risk. From a practical standpoint, this is an essential explicit step either to assess the risks due to a particular hazard from a specific source or process, or to undertake a cost-benefit analysis of putting in place release reduction safeguards for that source or process.

'Release' comes before the possibility of exposure in actual exposure events. Thus, the Covello-Merkofer system follows release assessment by assessing the probability of exposure for each potential exposure route of interest. The third difference between the models is that the NAS system places exposure assessment after the dose response (hazard characterisation) step. The precise definitions are also slightly different.

The fourth difference is in the place and meaning of consequences in the two models. Exposure can then lead to consequences – unwanted consequences when considering a hazard. Thus, the Covello-Merkhofer system places consequence assessment after exposure assessment, and defines it broadly (any consequences that can occur can be considered, and their probability assessed). However, the NAS system looks only at the consequences of variation in dose of the chemical being considered (i.e. a dose-response assessment, also called hazard characterisation).

Table III
Definition of risk analysis terms: a comparison of the systems used by the Codex Alimentarius and the Office International des Epizooties

Term	Office International des Epizooties definition or equivalent	Codex Alimentarius definition or equivalent
Acceptable risk	Risk level judged by Member Countries to be compatible with the protection of animal and public health within their country	No equivalent defined
Consequence assessment	Description of the relationship between specified exposures to a biological agent and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of these consequences occurring. This estimate may be either qualitative or quantitative	Codex equivalent: dose-response assessment
Dose-response assessment	OIE equivalent: consequence assessment	The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response) – see 'hazard characterisation'
Exposure assessment	Describing the biological pathways necessary for exposure of animals and humans to the hazards released from a given source, and estimating the probability of the exposure occurring, either qualitatively or quantitatively	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
Hazard	In the context of the *Code*, any pathogenic agent that could produce adverse consequences on the importation of a commodity	A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect
Hazard characterisation	Embodied in the 'consequence assessment' in the OIE system	The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents that 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 process of identifying the pathogenic agents which could potentially be introduced to the commodity considered for importation	The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods
Implementation	The process of following through with the risk management decision and ensuring that the risk management measures are in place	No equivalent defined
Monitoring and review	The ongoing process by which the risk management measures are continually audited to ensure that they are achieving the results intended	No equivalent defined
Option evaluation	The process of identifying, evaluating the efficiency and feasibility of, and selecting measures in order to reduce the risk associated with an importation in line with the appropriate level of protection of the Member Country. The efficacy is the degree to which an option reduces the likelihood and/or magnitude of adverse biological and economic consequences. Evaluating the efficacy of the options selected is an iterative process that involves their incorporation into the risk assessment and then comparing the resulting level of risk with that considered acceptable. The evaluation for feasibility normally focuses on technical, operational and economic factors affecting the implementation of the risk management options	No equivalent defined
Qualitative risk assessment	An assessment in which the outputs on the likelihood of the outcome or the magnitude of the consequence are expressed in qualitative terms such as high, medium, low or negligible	No equivalent defined
Quantitative risk assessment	An assessment in which the outputs of the risk assessment are expressed numerically	No equivalent defined
Release assessment	Description of the biological pathways necessary for the use of an antimicrobial in animals to release resistant bacteria or resistance determinants into a particular environment, and estimation of the probability of that complete process occurring, either qualitatively or quantitatively.	No equivalent defined
Risk	The likelihood of the occurrence and the likely magnitude of the consequences of an adverse event to animal or human health in the importing country during a specified time period	A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food

Table III (contd)

Term	Office International des Epizooties definition or equivalent	Codex Alimentarius definition or equivalent
Risk analysis	The process composed of hazard identification, risk assessment, risk management and risk communication	A process consisting of three components: risk assessment, risk management and risk communication
Risk assessment	The evaluation of the likelihood and the biological and economic consequences of entry, establishment, or spread of a pathogenic agent within the territory of an importing country	A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterisation, (iii) exposure assessment and (iv) risk characterisation
Risk characterisation	OIE equivalent: risk estimation	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 characterisation and exposure assessment
Risk communication	Risk communication is the interactive exchange of information on risk among risk assessors, risk managers and other interested parties	The interactive exchange of information and opinions throughout the risk analysis process concerning hazards and risks, risk-related factors and risk perceptions, among 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 estimation	Integration of the results from the release assessment, exposure assessment and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. Thus, risk estimation takes into account the entire risk pathway from the hazard identified to the unwanted outcome	Codex equivalent: risk characterisation
Risk evaluation	The process of comparing the risk estimate in the risk assessment with the appropriate level of protection of the Member Country	Embodied in 'risk management' in the Codex system
Risk management	The process of identifying, selecting and implementing measures that can be applied to reduce the level of risk	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
Sensitivity analysis	The process of examining the impact of the variation in individual model inputs on the model outputs in a quantitative risk assessment	No equivalent defined
Transparency	Comprehensive documentation of all data, information, assumptions, methods, results, discussion and conclusions used in the risk analysis. Conclusions should be supported by an objective and logical discussion and the document should be fully referenced	No equivalent defined
Uncertainty	The lack of precise knowledge of the input values which is due to measurement error or to lack of knowledge of the steps required, and the pathways from hazard to risk, when building the scenario being assessed	No equivalent defined
Variability	A real-world complexity in which the value of an input is not the same for each case due to natural diversity in a given population	No equivalent defined

Table IV
Definition of new terms introduced in this document

Term	Definition
Risk management policy	The regulatory policy framework for the monitoring, measuring, assessing and managing of risks involved in the use of antimicrobials in food-producing animals
Semi-quantitative risk assessment	An assessment where estimates of the likelihood of the outcome and the magnitude of the consequences are expressed in semi-quantitative terms via a scoring mechanism

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