Food and Agriculture Organization of the United Nations

World Health Organization

World Organization for Animal Health

Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment

Geneva, December 1 – 5, 2003

Note: To allow for a rapid dissemination of the results of the meeting this draft report is published jointly by FAO, OIE, WHO. A fully edited printed copy will by published by WHO early 2004.

Contents

Executive summary

Antimicrobial agents are essential drugs for human and animal health and welfare. Antimicrobial resistance is a global public health concern that is impacted by both human and non-human antimicrobial usage. Antimicrobial agents are used in food animals, including from aquaculture, companion animals and horticulture to treat or prevent disease. Antimicrobial agents are sometimes used in food animals to promote growth. The types of antimicrobials used are frequently the same as, or closely related to, antimicrobials used in humans.

Managing human health risks from non-human usage of antimicrobials and the resulting antimicrobial resistant bacteria requires national and international interdisciplinary cooperation. This expert workshop was convened by the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) to perform a scientific assessment of antimicrobial resistance risks arising from non-human usage of antimicrobials and to formulate recommendations and options for future risk management actions to be considered by the Codex Alimentarius Commission and OIE.

The expert workshop concluded that there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented for instance by fluoroquinolone resistant human *Salmonella* infections. Evidence shows that the amount and pattern of non-human usage of antimicrobials impact on the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria. The foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist. There is much less data available on the public health impact of antimicrobial usage in aquaculture, horticulture and companion animals.

The consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in humans. Therefore, the expert workshop recommends that an expert clinical medical group appointed by WHO defines which antimicrobials are considered critically important in humans.

The expert workshop concluded that surveillance of non-human usage of antimicrobials and surveillance of antimicrobial resistance in food and animals is important for the identification of resistance problems and as a basis for choosing and evaluating interventions to limit the development and spread of resistance at all levels.

Several recent attempts to quantify the magnitude of related health impacts in the human population have been made. Estimates vary widely from small to large, depending on the organism and antimicrobial of interest, and are accompanied by considerable uncertainty.

The expert workshop concluded that residues of antimicrobials in foods, under present regulatory regimes, represents a significantly less important human health risk than the risk related to antimicrobial resistant bacteria in food.

Risk assessment approaches that adequately address the broad range of potential human health impacts need to be further developed with a view towards enabling efficient risk management of

antimicrobial resistance in the international arena. OIE is invited to continue its work on risk analysis in coordination with FAO and WHO.

The expert workshop recommended that the Codex Alimentarius Commission, where appropriate in collaboration with OIE, takes coordinated steps to define a more efficient management system for these risks focusing on the microbiological nature of the hazards.

Preamble

A joint FAO/WHO/OIE Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance was held December 1-5, 2003 in Geneva, Switzerland.

After opening remarks by Dr Hiro Endo, Director of the Control Prevention and Eradication Department, Communicable Diseases Cluster, Dr Scott McEwen was elected as chairman for the meeting and Dr Hilde Kruse was elected as rapporteur. It was decided to address the main issues of concern in four working groups. For two of these working groups, Dr Fred Angulo was elected as vice-chairman and Dr Peter Collignon was elected as rapporteur. For the two others, Dr Jacques Acar and Dr Gérard Moulin were elected as vice-chairman and rapporteur, respectively.

All participating experts had filled out the standard WHO conflict of interest declaration form before the meeting. Five experts had declared a potential conflict of interest. After further review by the organizers, it was determined that the nature of the conflict of interest for four of the experts was such that they could participate fully in the expert workshop. For one expert it was decided that he could participate in the discussions, but not in the development of recommendations. The nature of the interest is briefly described in the list of participants.

Background

Antimicrobial agents are essential drugs for human and animal health and welfare. Antimicrobial resistance is a global public health concern that is impacted by both human and non-human antimicrobial usage and the resultant development and spread of antimicrobial resistance. International interdisciplinary cooperation is essential and therefore, since 1997, WHO, FAO and OIE have organized a number of consultations to address the issues related to antimicrobial use at different steps of the food-chain, the emergence of resistant pathogens and the associated human public health problems. However, to date, no common approach dealing with the containment of antimicrobial resistance has been jointly designed by these three organizations.

Considering that antimicrobial usage and resistance is a multi-factorial problem and thus requires a multidisciplinary approach, the Executive Committee of the Codex Alimentarius Commission in its 53rd session, recommended that FAO, WHO and OIE should give consideration to convening a multidisciplinary expert consultation. All issues of antimicrobials in agriculture and veterinary use (including aquaculture) should be considered and the role played by antimicrobials as essential human and veterinary medicines should be taken into account. It was agreed that the issues raised by several Committees required a more general and multidisciplinary and multi-agency response.

This expert workshop was convened by FAO, WHO and OIE to undertake the following:

- Perform a scientific assessment considering all non-human uses of antimicrobials in animal (including aquaculture) and plants, taking into account the role played by antimicrobials as essential human and veterinary medicines.
- Analyse the findings, conclusions and recommendations of previous international expert consultations and reports.
- Review, if possible, the progress of what has been implemented in member countries.

- Formulate recommendations and options for future risk management actions to be considered by Codex Alimentarius Commission.
- Identify data gaps for research and areas for improvement.

The selection of experts followed the corresponding requirements outlined by Codex Alimentarius for advice on food safety issues.

A call for experts was published, areas of expertise to be covered and criteria for selection were agreed between the three organizations to insure scientific excellence, independence and participation of experts from developing countries. The submitted CVs were evaluated for their scientific competence by a panel composed of representatives from FAO, OIE and WHO and external independent reviewers. Based on this evaluation the three Organizations selected the experts for the expert workshop.

Prior to the meeting a group of experts were asked to prepare a background paper. This document covered the following:

- Surveillance of non-human usage
- Surveillance of antimicrobial resistance in animals and food.
- Surveillance of antimicrobial resistance in human pathogens.
- Factors contributing to emergence and spread of resistance in food production
- Evidence of associations between non-human use of antimicrobials and resistance in bacteria from humans, and the human health consequences of such resistance
- Review of risk assessment approaches for non-human use of antimicrobial agents
- The assessment procedures used by the Joint Expert Committee on Food Additives and contaminants (JECFA) in its consideration of the potential for antimicrobial resistance resulting from residues of veterinary drugs in food.
- Economical impact (agricultural production, health care) and environmental consequences.

Based on the background paper the expert workshop addressed in four working groups the following issues:

- Review of surveillance guidelines including drug use monitoring (including standardization)
- Review evidence of association between use in food animals and resistance in humans
- Review evidence of adverse human health consequences – what types of resistant bacteria are of greatest importance
- Review of risk assessment approach

In this report, the main findings in these working group are presented followed by conclusions, recommendations and data gaps /areas for improvement arising from the deliberations.

Surveillance of non-human antimicrobial usage and antimicrobial resistance

Surveillance of antimicrobial usage and antimicrobial resistance provide important data for the identification of resistance problems and contributing factors for the development and spread of this resistance at a national and local level. Such data can also be used at the international level.

Purposes of surveillance of non-human antimicrobial usage and resistance

- Documentation of the situation
- Identification of trends
- Linkage of antimicrobial usage and antimicrobial resistance
- Basis for risk assessment
- Basis for interventions
- Evaluation of effectiveness of measures implemented
- Basis for focused and targeted research

Non-human usage of antimicrobials

The non-human use of antimicrobials (which includes use in food animals, companion animals, aquaculture and horticulture) can be divided into therapeutic, prophylactic, metaphylactic and growth promoting use. Therapeutic antimicrobial use is the treatment of established infections. Metaphylaxis is a term used for group-medication procedures, aimed to treat sick animals while medicating others in the group to prevent disease. Prophylaxis means the preventative use of antimicrobials in either individuals or groups to avoid development of infections. Antimicrobial use in horticulture is mainly prophylactic and applied by spraying. Therapeutic, metaphylatic, and prophylactic use of antimicrobials can be by individual or group application. These uses involve administering antimicrobials by different routes at therapeutic levels for short periods of time. Growth promotion use is when an antimicrobial agent is used as feed supplement in food animals to promote growth and enhance feed efficiency. Growth promoters are usually administered in relatively low concentrations, ranging from 2.5 to 125 mg/kg (ppm), depending on the drug and species treated. Such levels that are usually less than therapeutic concentrations are commonly referred to as subtherapeutic doses. In many countries, these low levels are used for prophylaxis as well as for growth promotion. Historically, in the United States, "subtherapeutic" was defined as uses of antimicrobials in feeds at concentrations <200g per ton for >2 weeks, although this term is no longer used.

Recommendations from previous FAO, OIE and WHO Consultations and Meetings

The WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food ("Global Principles") provide a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health. The overall objective of the Global Principles is "*To minimize the negative public health impact of the use of antimicrobial agents in food-producing animals whilst at the same time providing for their safe and effective use in veterinary medicine".* The Global Principles were developed with the participation of the FAO and OIE, as part of a comprehensive WHO Global

Strategy for the Containment of Antimicrobial Resistance and are available at http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm

The foundation for the WHO Global Principles was laid during several previous consultations, including the WHO Consultation on the Medical Impact of the Use of Antimicrobials in Food Animals, Berlin, Germany, 13-17 October 1997 (http://www.who.int/emc/diseases/zoo/oct97.pdf) and the WHO Consultation on the use of Quinolones in Food Animals and Potential Impact on Human Health, Geneva, Switzerland, 2–5 June 1998 (http://www.who.int/emc-documents/zoonoses/docs/whoemczdi9810.pdf). The Global Principles strengthened and endorsed earlier WHO recommendations and recognized that all stakeholders concerned with the use of antimicrobials in both food animals and humans must be involved in an over-arching global strategy.

The "Global Principles" also addressed the surveillance of antimicrobial usage and resistance:

- Data generated from the surveillance of antimicrobial resistance and antimicrobial usage should play a key role in the development of national policies for the containment of antimicrobial resistance. These data are all essential in the pre- and post-licensing process and in the development and treatment guidelines for veterinary use.
- Relevant authorities should establish systems to determine the amounts of antimicrobials given to food animals. Information on the amounts of antimicrobials given to food animals should be made publicly available at regular intervals, be compared to data from surveillance programmes on antimicrobial resistance, and be structured to permit further epidemiological analysis.

In 2000 the OIE appointed an expert group on antimicrobial resistance, which established guidelines relating to standardization and harmonization of laboratory methodologies for the detection and quantification of antimicrobial resistance and also on the harmonization of national antimicrobial resistance surveillance and surveillance programmes in animals and animal-derived foods. Four guidelines were adopted by OIE in 2003 to be included in the OIE Terrestrial Animal Health Code.

Several other national and international bodies have also addressed the issue of surveillance of food, food animals and other sources for resistant bacteria and many of these were included in the review of documents that took place when the WHO Global Principles were devised.

I. Surveillance of non-human usage of antimicrobials

As a follow-up to the "global principles", WHO convened in September 2001 in Oslo, Norway, a consultation on the surveillance of antimicrobial usage in food animals for the protection of human health. Monitoring antimicrobial usage in food animals for the protection of human health. Report of a WHO consultation. Oslo, Norway, 10-13 September 2001. Accessed at http://www.who.int/emc/diseases/zoo/antimicrobial.html.

Sources of antimicrobial usage data, the degree data are obtainable, and the methods on how to collect or obtain usage data will vary from country to country because different countries have different distribution and registration systems. Access to data may require legislative support. Furthermore, economic compensation or support may be necessary.

a. Overall national usage data

A simple and cost effective surveillance system on antimicrobial usage can be achieved based upon data on overall usage for the various antimicrobial formulations. Even in developing countries, it is possible to implement a system through which some basic data on usage can be obtained, as has been previously done in Kenya. The following sources for obtaining data for the estimation of overall usage may be utilized: Import and export registration, pharmaceutical industry, wholesalers, feed mills and pharmacies.

Import data or overall national sales statistics do not give information as regard animal species, farm, geographical area, or clinical indications. However, a large proportion of the veterinary antimicrobial drugs may be species specific, making it possible to make rough estimate on usage in the different species based on overall statistics. Furthermore, overall national sales data may be split into geographical regions, e.g. communities and counties, if the national drug distribution system allows for this. Moreover, overall usage data represent several opportunities as regard pharmaco-epidemiological studies. Last but not least, overall usage data are important for the validation of other data sources.

b. Usage per species, at herd level, etc.

More sophisticated surveillance systems might make use of stratified data that gives information on usage for various animal species, usage at herd level, usage in relation to indications and in various regions. Denmark has such a comprehensive system in place. Data sources for such a stratified surveillance system may include pharmacies (prescription based data), veterinarians, feed mills and farmers and food animal producers.

These sources may be appropriate when the pharmaceutical industry or wholesalers cannot be used for the routine collection of antimicrobial usage data or when more accurate and locally specific information is required. A prescription based surveillance system will provide information about animal species and can also provide details about geographical area, farm, herd and clinical indications. However, the implementation of such an advanced system seems most feasible in countries where the veterinary drugs are dispensed by pharmacies.

Collection, storage and processing of stratified data have to be carefully designed and well managed, for example in sentinel studies. However, such systems should have the advantage of producing accurate and targeted information. Periodic or targeted collection of this type of data may be sufficient in conjunction with overall usage data. Factors such as seasonality and disease conditions, species affected, agricultural systems (e.g. extensive range conditions and feedlots), may be important factors when designing such studies.

c. Other considerations

Countries should have a regulatory approval and control system for all antimicrobial agents and products containing antimicrobial agents used in animals. Such a system could include, but not be limited to, listing of all available antimicrobial agents in the country and an approval mechanism.

Ideally, all classes and substances of antimicrobial should be included in a surveillance programme. If this is not possible, decisions need to be made on what classes of antimicrobials should be considered. Standardized national and international terminology and methodology of reporting is essential so that it is clear which antimicrobials are monitored and used. A system is required to identify and classify antimicrobials similar to the ATC (Anatomical Therapeutic Chemical)

classification system, which is used for human antimicrobials. ATCvet is the parallel system for veterinary antimicrobials. It is recommended that this classification system or a corresponding system should be used in the identification of specific antimicrobials.

Data should be collected to minimum express the annual weight in kilograms on the active ingredient of the antimicrobial(s). If a country has the infrastructure for capturing data on basic animal antimicrobial use for a specific antimicrobial, then additional information can be considered to cascade from this in a series of subdivisions or levels of detail.

Further research and development is needed to develop units of measurement that most accurately describe the antimicrobial selective pressure, in order to facilitate epidemiological analysis of usage data relative to antimicrobial resistance data and to support the comparison between different animal species, over time and with human usage. Data collected on-farm or from veterinarians may be expressed as prescribed daily dose (PDD) per weight of animal or per animal at risk and may be expressed as prevalence or incidence estimates. In human medicine, defined daily dose (DDD) is used to interpret overall sales figures of drugs because this unit allows for the comparison of usage of antimicrobial drug of varying potency. The DDD concept may be used in veterinary medicine to express prescribing patterns if usage data or estimates of usage per species are. Furthermore, where data on animals at risk are available, incidence of use or treatment frequency may be estimated by transferring the DDDs into course doses.

Countries should keep a register of all antimicrobials for specific animal species and for specific diseases. This will help to identify possible non-authorized usage. For use in risk assessments and to facilitate data comparison within and between countries as well as interpretation of trends, data on animal population and production should be provided, for example numbers of animals in the various categories slaughtered per year or animal census data.

II. Surveillance of antimicrobial resistance in bacteria from food and animals

The OIE has published a series of guidelines relating surveillance of antimicrobial resistance and these have now been included in the OIE Terrestrial Animal Health Code. These guidelines also provide guidance to initiate standardization and harmonization of both antimicrobial susceptibility testing methods and the interpretation of antimicrobial susceptibility data. Animal species and food to be considered include cattle and calves, slaughter pigs, broiler chickens, layer hens and/or other poultry and farmed fish. Different sampling points in the food production chain can be considered. Although not specifically referred to in the OIE guidelines, also non-food animals, e.g. companion animals and exotic animals might be included due to the close proximity between some of these animal species and their owners.

Since plants and vegetables of different types may have been treated with antimicrobial agents or may have been exposed to manure or sewage from livestock and therefore can become contaminated with resistant bacteria of animal origin, such foods may also be considered to be included in the surveillance. Furthermore, animal feed, including imported feed, may also be considered for inclusion into the surveillance.

Bacteria to be included in the surveillance can be subdivided into three classes; zoonotic bacteria, indicator bacteria and animal pathogens. Zoonotic bacteria should include *Salmonella* spp. and *Campylobacter* spp. Indicator bacteria such as *E. coli* and *E. faecium/faecalis* should also be included and these should be isolated from samples from healthy animals, preferably at slaughter.

Zoonotic and animal pathogens as well as indicator bacteria that may be considered in surveillance and methods used can be taken from the OIE Guidelines. However, these guidelines do not cover companion animals and horticulture, and only to a limited degree farmed fish. In implementing national surveillance programmes, countries should also consider these aspects.

National surveillance programmes should be able to detect the emergence of resistance and to determine the prevalence of resistant bacteria. The resulting data should be used in the assessment of risks to public health and should contribute to the establishment of a risk management policy. Specific aspects identified for harmonisation include the animal species, food commodities, sampling plans, bacterial species, antimicrobials to be tested, laboratory methods, data reporting, database structure and the structure of reports. Results from resistance surveillance should enable comparison of the situations in different regions or countries and also at the regional and international level and over time.

Evidence of association between non-Human usage of antimicrobial agents and antimicrobial resistance in humans

Antimicrobial resistance emerges in primary food production in response to antimicrobial selective pressure. Movement of animals, animal manure, and food- and by products facilitates spread of resistance. Bacterial factors, such as fitness of the clone, as well as resistance to antimicrobials, can promote the spread of some clones over others in the food production chain. Some resistant bacteria that have emerged in food and animals can cause human infections, whereas others can pass their resistance determinants, by mode of horizontal transmission, to human pathogenic bacteria in humans. Resistance can spread from non-human sources to humans by a multitude of routes. However, the foodborne route is the most prominent route in the transmission from food-producing animals to humans.

Since the majority of the available evidence on the association between use of antimicrobials in animals and human colonization or infection with antimicrobial resistant bacteria is found in studies investigating foodborne enteric bacteria, the remainder of this chapter will focus on that issue.

Review of previous FAO, OIE and WHO consultations and reports

Many expert panels, including WHO Consultations, national committees, and independent organizations, have examined the association between use of antimicrobial agents in food animals and antimicrobial resistance among bacteria isolated from humans. WHO organized two consultations, in Berlin in 1997 and in Geneva in 1998, to qualitatively assess the risk of human health consequences associated with the use of antimicrobial agents in food animals. At the Berlin meeting, it was concluded that "there is direct evidence that antimicrobial use in animals selects for antimicrobial-resistant non-typhoid *Salmonella* serotypes. These bacteria have been transmitted to humans in food or through direct contact with animals."

Because of the human health importance of fluoroquinolones and public health concern of increasing resistance to fluoroquinolones, particularly among *Salmonella* and *Campylobacter,* the WHO Consultation in Geneva focused on the human health risks associated with the use of fluoroquinolones in food animals. The Consultation concluded that "the use of fluoroquinolones in food animals has led to the emergence of fluoroquinolone-resistant *Campylobacter* and of *Salmonella* with reduced susceptibility to fluoroquinolones."

Similar conclusions have been presented to two committees of the Codex Alimentarius Commission: the Codex Committee on Food Hygiene (CCFH) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). A "Risk profile on antimicrobial-resistant bacteria in food" presented to the thirty-fourth session of CCFH in August 2001, stated that: "Antimicrobials are used in food animals for growth promotion, prophylaxis, metaphylaxis, and therapy. This use is the principle contributing factor to the emergence and dissemination of antimicrobial resistance among bacterial pathogens and commensials that have food animal reservoirs." Similarly, a "Discussion paper on antimicrobial resistance and the use of antimicrobials in animal production" presented to the thirteenth session of the CCRVDF in July 2001, stated that: "Animals serve as reservoirs for foodborne pathogens, including *Salmonella* and *Campylobacter*. Antibiotic resistant foodborne pathogens may be present in and on animals as a result of drug use in animals. These resistant foodborne pathogens may contaminate a carcass at slaughter and can be transmitted to humans through consumption and handling of contaminated food. In industrialized countries, the foodborne

pathogens, *Salmonella* and *Campylobacter,* are infrequently transferred from person to person. In these countries, epidemiological data have demonstrated that a significant source of antibiotic resistant foodborne infections in humans is the acquisition of resistant bacteria originating from animals that is transferred on food."

Additional evidence for an association between usage of antimicrobial agents in food animals and antimicrobial resistance among bacteria isolated from humans

Since these consultations and reports, additional evidence has been published showing that the use of antimicrobial agents in food animals is associated with antimicrobial resistance among bacteria isolated from humans. An association between use of antimicrobial agents in food animals and antimicrobial resistance among bacteria isolated from humans is most evident for *Salmonella* and *Campylobacter,* and to a lesser degree for enterococci and *Escherichia coli*.

Several lines of evidence demonstrate an association between use of antimicrobial agents in food animals and antimicrobial resistance among bacteria isolated from humans including: (1) outbreak investigations, (2) epidemiological investigations, (3) field studies, (4) case reports, (5) ecological and temporal associations, and (6) molecular subtyping. Numerous studies provide support for one or more of the lines of evidence demonstrating an association between use of antimicrobial agents in food animals and antimicrobial resistance in humans.

(1) Outbreak investigations – Although outbreaks only represent a fraction of the cases of infections caused by foodborne pathogens, including *Salmonella,* much insight into the epidemiology of foodborne diseases has been provided through investigations of outbreaks. Several outbreak investigations of antimicrobial-resistant *Salmonella* infections in humans have combined epidemiological fieldwork and laboratory subtyping techniques to trace antimicrobial-resistant *Salmonella* through the food distribution system to farms. In these studies use of antimicrobial agents on the farms was found to be associated with the antimicrobial resistance in the *Salmonella* isolated from humans. In addition to the historical literature (Holmberg et al. 1987; Spika et al. 1987), more recent evidence exists. Although use of fluoroquinolones was not confirmed on the implicated farm, an outbreak of human nalidixic acid-resistant *Salmonella* Typhimurium DT104 infections in Denmark was traced to a pig farm (Molbak et al. 1999). In contrast, an outbreak of human nalidixic-acid resistant *Salmonella* Typhimurium DT104 infections in the United Kingdom was traced to a dairy farm where fluoroquinolones were used in the dairy cattle in the month prior to the outbreak (Walker et al. 2000).

(2) Epidemiological investigations – Several recent epidemiological investigations of sporadic cases of human *Salmonella* infections have demonstrated that persons with antimicrobial-resistant infections are more likely to have visited or lived on a farm prior to illness onset than persons infected with antimicrobial-susceptible infections. These findings have been demonstrated in case-control studies of antimicrobial-resistant *Salmonella* Typhimurium DT104 infections (Glynn et al. 2004) and multidrug resistant *Salmonella* Newport infections (Gupta et al. 2004).

A case-control study in the United States of persons infected with fluoroquinolone-resistant *Campylobacter* found that persons infected with fluoroquinolone-resistant *Campylobacter* were more likely to have eaten chicken or turkey than well controls. Since chicken and turkey is not imported into the United States, this finding provides evidence that domestically-produced poultry is an important source of domestically-acquired fluoroquinolone-resistant *Campylobacter* infections in the United States (Kassenborg et al. 2004).

(3) Field studies – Levy and colleagues conducted prospective field experiments to demonstrate how antimicrobial use in food animals selects for the emergence and disseminations of antimicrobial-resistant determinants (Levy et al. 1976). Because streptothricin antimicrobial agents had not been used either in human or in veterinary medicine, the introduction of nourseothricin, a novel streptothricin antimicrobial agent, into swine production as a growth promoter in the former German Democratic Republic demonstrated the ability of antimicrobial growth promoters to select for the emergence of antimicrobial resistance in faecal *E. coli* of pigs, dissemination of resistant *E. coli* to humans and horizontal transfer of the resistant determinants to other human bacteria, including pathogens (Hummel et al. 1986). Nourseothricin resistance was subsequently detected in human *Salmonella* and *Shigella* isolates (Witte et al. 2000). Since *Shigella* is a pathogen of primates and is not found in the intestinal tract of swine, these events provide important evidence of emergence of nourseothricin-resistance in the intestinal tract in treated pigs, transfer of nourseothricin-resistant bacteria to humans, and horizontal transfer of nourseothricin-resistant determinants to *Shigella* within the intestinal tract of humans.

(4) Case reports – There are several individual case reports of farmers, members of their families, or other persons that have become directly exposed to antimicrobial-resistant bacteria from food animals. For example, the first reported case of domestically acquired ceftriaxone-resistant *Salmonella* in the United States involved the child of a veterinarian. Before the child's illness, the father was treating several herds for *Salmonella* infections. Ceftriaxone-resistant and ceftriaxone-susceptible *Salmonella* were isolated from ill cattle treated by the veterinarian. These isolates and the child's ceftriaxone-resistant isolate were indistinguishable by pulsed-field gel electrophoresis (PFGE). It appears likely that the *Salmonella* strain developed ceftriaxone resistance in the cattle and then was transmitted to the child (Fey et al. 2000).

(5) Spatial and temporal associations – In countries with surveillance data on the quantities of antimicrobial agents used in food animals, correlations have been demonstrated between the amount of antimicrobial agents used in food animals and antimicrobial resistance in selected bacteria.

Even in countries without surveillance on antimicrobial use in food animals, temporal associations have been demonstrated between the first approved use of an antimicrobial agent in food animals and an increase in antimicrobial resistance. In the United States, for example, there was a marked increase in the proportion of domestically-acquired *Campylobacter* infections that were fluoroquinolone-resistant following the first approved use of fluoroquinolones in food animals in 1995. Similar temporal associations were observed in several European countries including the United Kingdom and the Netherlands. Similar associations between resistance development in *Salmonella* and approval of use of antimicrobial agents in food-producing animals have been described.

Comparisons can also be made among countries that allow use of different antimicrobial agents in food animals. For example, domestically acquired *Campylobacter* infections are commonly fluoroquinolone-resistant in European and North-American countries that allow use of fluoroquinolones in food animals, while domestically acquired *Campylobacter* infections are susceptible to fluoroquinolones in Australia, which has not allowed use of fluoroquinolones in food animals (Unicomb et al. 2003).

(6) Molecular subtyping – Molecular subtyping provides important evidence of an association between use of antimicrobial agents in food animals and the antimicrobial-resistant enterococci in humans. Avoparcin, a glycopeptide antimicrobial agent, was approved for use as a growth promoter

in Europe in 1974. Use of avoparcin in food animals resulted in emergence and dissemination of vancomycin-resistant enterococci (VRE) in the intestinal tract of the food animals, and this resistance was commonly transmitted to humans through the food supply, predominately via contaminated meat and poultry. Prior to the EU ban on avoparcin use as a growth promoter in 1997, Europeans commonly carried VRE in their intestinal tract. Molecular subtyping of VRE isolates isolated from pigs, chickens, healthy humans from the community, and from hospitalized patients indicate genetic similarity between the isolates (Bruinsma et al. 2002).

The vancomycin-resistance determinant of vanA type VRE is carried on the transposon *Tn*1546. Importantly, this genetic element carries single nucleotide (T or G) variants. Among food animals, the G variants are found only in poultry isolates and the T variants in swine isolates. Among VRE isolates from humans, however, the G and T variants are evenly distributed. Furthermore, human isolates from a Muslim country, where swine are not raised or consumed, carry only the G mutation. These data provide evidence of an association between avoparcin use in food animals and carriage of VRE in humans (Jensen et al. 1998).

Similar molecular evidence is available to suggest an association between use of gentamicin in food animals, particularly chickens and turkeys, in the United States and high-level gentamicin-resistant enterococci in humans. When a gene conferring gentamicin-resistance gent was present in resistant enterococci from animals, the gene was also present in enterococcal isolates from food products of the same animal species. Furthermore, although much diversity was evident among high-level gentamicin-resistant enterococci, indistinguishable strains were found among human and pork isolates, and human and grocery store chicken isolates (Donabedian et al. 2003).

Molecular subtyping is also useful to demonstrate an association between *Salmonella* isolates from animals and humans. In an investigation of an increase of human fluoroquinolone-resistant *Salmonella* Choleraesuis infections in Taiwan, for example, molecular subtyping, including sequencing, concluded that swine were the source of the human infections. Additional investigations suggest that the fluoroquinolone resistance had emerged following fluoroquinolone use in pigs (Chiu et al. 2002).

Other reservoirs

Available scientific evidence shows that also antimicrobial usage in horticulture, aquaculture and companion animals can result in spread of resistant bacteria and resistance genes to humans. In general, molecular characterization of resistance genes as well as other data indicates some movement of resistant bacteria and resistance determinants from aquaculture, companion animals, and horticulture to humans.

A transposon carrying a gene for streptomycin resistance apparently evolved in *E. amylovora* in response to the spraying of apple orchards with streptomycin. This transposon has later been found in *E. coli* in pigs where a gene for trimethoprim also has been inserted. The appearance of a new resistance gene under heavy selection pressure from trimethoprim used in pig rearing and borne on a transposon earlier found in the very different context of a plant pathogen, illustrates that spread of resistance genes also can occur from horticulture (Skøld, O. 2001).

Research has shown that transfer of multiple antimicrobial resistant *Staphylococcus intermedius* and quinolone resistant *Campylobacter jejuni* can occur between humans and dogs living in the same household (Guardabassi L. et al. 2003; Damborg P et al. 2003). Thus, antimicrobial usage in

companion animals may ultimately have a public health effect, especially taking into consideration the close proximity between these animals and their owners, and the pattern of antimicrobial usage in companion animals.

Available scientific evidence shows that the same resistance genes and integrons can be found in fish pathogens as in human pathogens (Sørum H. and L'Abée-Lund T. M. 2002).

The application of molecular detection and tracking techniques in microbial ecological studies has allowed reservoirs of antimicrobial resistance genes to be investigated.

Overall themes relevant to antimicrobial resistance are (1) that propagation of resistance is an ecological problem, and thus (2) that ameliorating this problem requires recognition of long-established information on the commensal microbiota of mammals, as well as that of recent molecular understanding of the genetic agents involved in the movement of resistance genes.

Human health consequences resulting from antimicrobial resistant bacteria following non-human usage of antimicrobial agents

Although previous consultations identified limited data about treatment failures in humans due to antimicrobial resistance, examinations of previous and more recent studies provide accumulating evidence of this and other adverse human health consequences due to resistant organisms. These consequences can be divided into two categories: 1) Infections that would otherwise not have occurred and 2) Increased frequency of treatment failures and increased severity of infections. Increased severity of infection includes prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality. This new evidence of human health consequences resulting from antimicrobial resistance provides documentation of the human health impact of the antimicrobial resistance among bacteria isolated from humans resulting from the use of antimicrobial agents in food animals. It is important to note that the survival of resistant bacteria frequently appears not to be impaired by carrying these resistance genes. Another important issue is the acquisition of resistance traits by non-pathogenic, commensal organisms in food animals and that these bacteria may then be ingested by or transferred to people.

(1) Infections that would otherwise not have occurred – Use of antimicrobial agents in humans and animals disturbs the microbiota of the intestinal tract, placing such individuals at increased risk of certain infections. Individuals taking an antimicrobial agent, for any reason, are therefore at increased risk of becoming infected with pathogens resistant to the antimicrobial agent. This effect has been demonstrated in case-control studies of persons infected with antimicrobial-resistant Salmonella in which persons exposed to antimicrobial agents for unrelated reasons, such as treatment of an upper respiratory tract infection, are at increased risk of infection with Salmonella that are resistant to the antimicrobial agent.

This increased risk can be expressed in the form of an "attributable fraction", which is defined as the proportion of *Salmonella* infections that would not have occurred if the *Salmonella* were not resistant (or if the person had not been taking the antimicrobial agent for the unrelated reason). Because taking antimicrobial agents for a variety of reasons is common, antimicrobial resistance in *Salmonella* results in a number of infections, hospitalizations, and deaths that can be estimated and that would not have occurred in the absence of resistance. In a recent review on the "attributable fraction" of the over one million *Salmonella* and over one million *Campylobacter* infections each year in the United States (Barza et al. 2002), it was estimated that antimicrobial resistance in *Salmonella* and *Campylobacter* may result in about 30 000 additional *Salmonella* infections leading to about 300 hospitalizations and 10 deaths, and an estimated additional 18 000 *Campylobacter jejuni* infections leading to about 100 hospitalizations each year in the United States.

Antimicrobial agents are commonly used in animals, but the extent that antimicrobial resistance in *Salmonella, Campylobacter,* and perhaps other bacteria results in increased transmission of these bacteria between animals that are administered antimicrobial agents has not been described. It seems likely that such use may result in increased transmission between animals, and therefore may result in increased transmission to humans.

(2) Increased frequency of treatment failures and increased severity of infection – Increased frequency of treatment failures and increased severity of infection may be manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, or increased mortality. Prolonged duration of illness has been demonstrated in four recent case-control

studies of fluoroquinolone-resistant *Campylobacter*. In these studies, among persons treated with fluoroquinolones, the median duration of diarrhoea in persons infected with fluoroquinolone-resistant *Campylobacter* was several days longer than the median duration of diarrhoea in persons with susceptible infections.

The association between an increased frequency of antimicrobial resistance *Salmonella* and an increased frequency of hospitalization has been demonstrated in several studies. A study published in 1987 of 28 *Salmonella* outbreaks investigated by CDC in the USA between 1971 and 1983 found that outbreaks caused by antimicrobial-resistant *Salmonella* resulted in a greater hospitalization rate and greater case-fatality rate than outbreaks caused by susceptible infections. Recently, this analysis has been repeated on 24 *Salmonella* outbreaks investigated by CDC between 1984 and 2002. Again, outbreaks caused by antimicrobial-resistant *Salmonella* resulted in a greater hospitalization rate than outbreaks caused by susceptible infections.

A study of 758 persons with sporadic *Salmonella* infections in 1989-1990 found that persons infected with antimicrobial-resistant isolates were more likely to be hospitalized and also be hospitalized longer. A more comprehensive study of sporadic *Salmonella* infections has recently been completed for the Foodborne Diseases Active Surveillance Network (FoodNet) and National Antimicrobial Resistance Monitoring System (NARMS) in the United States. This analysis also controlled for the serotype of *Salmonella.* Among 7 370 *Salmonella* isolates tested in NARMS from 1996-2001, *Salmonella* isolates resistant to antimicrobial agents were more frequently isolated from blood than susceptible infections. A particularly high frequency of isolation from blood was observed among isolates resistant to five or more antimicrobial agents. Among 1 415 patients interviewed, persons with *Salmonella* isolates resistant to antimicrobial agents were more frequently hospitalized with bloodstream infection than susceptible infections. Again, there was a particularly high frequency of hospitalization with bloodstream infection among persons infected with isolates resistant to five or more antimicrobial agents.

Similarly, a comprehensive study of sporadic *Salmonella* Typhimurium and *Campylobacter* infections has recently been completed in Denmark among patients with culture-confirmed infections from 1995-2000. The Danish Civil Registry System was used to determine patient outcomes. Among 1 346 patients with *S.* Typhimurium infections, persons with nalidixic acid-resistant infections were more likely to have bloodstream infection or die in the 90 days following specimen collection than susceptible infections. Similarly among 3 481 patients, those persons with a fluoroquinolone-resistant or erythromycin-resistant *Campylobacter* infection were more likely to have a bloodstream infection or die in the 90 days following specimen collection than susceptible infections.

Treatment failures resulting in death have been rare among *Salmonella* but may be expected to increase as the prevalence of resistance to clinically important antimicrobial agents increases among *Salmonella*. In the best described study of such treatment failures, an outbreak of nalidixic acid-resistant *Salmonella* Typhimurium DT104 in Denmark resulted in the hospitalization of 23 patients and two deaths. Both of the patients who died had been treated with fluoroquinolones for their *Salmonella* infections; in both instances, the coroner concluded that the fluoroquinolone resistance contributed to the deaths.

A comprehensive study of mortality associated with antimicrobial resistance among *Salmonella* Typhimurium was recently conducted in Denmark among patients with culture-confirmed infections from 1995-1999 and patients were followed for two years following culture collection. To determine

the increase in mortality compared to the general population, cases were matched to 10 persons by age, sex, county, and co-morbidity. Although persons with susceptible *Salmonella* infections had a higher two-year mortality than the general population, persons with resistant *Salmonella* infections had an even higher two-year mortality. Furthermore, persons with multidrug resistant infections (that included resistance to nalidixic acid) had an estimated 10 times higher death rate in the two years following specimen collection than the general population (Helms et al. 2002).

"Critically important" Antimicrobial classes

There are many serious infections in people (including enteric infections) where there are few or no alternate antimicrobials that can be used if antimicrobial resistance develops. These antimicrobial classes can be classified under various names such as "critically important", "essential", "reserve" or "last resort".

Antimicrobial classes could be classified as critically important when the drug is in a class that is the only available therapy or one of a limited number of drugs available to treat serious human disease or enteric pathogens that cause foodborne disease. Another factor that may also be taken into account on how these drugs are classified is whether there is known linked resistance with other classes (i.e. co-selection).

The main bacteria that will need to be considered are those that are currently known to be likely transferred from food production animals to man as either zoonotic pathogens or commensal bacteria (i.e. *E.coli*, *Salmonella* spp., *Campylobacter* spp. and *Enterococcus* spp.). However, this classification also should take into account other bacteria that could be potentially transferred via foods as commensal bacteria (e.g. *Pseudomonas aeruginosa*).

Which antimicrobial classes should be defined as critically important for human medicine need to be more fully defined preferably by an expert clinical medical group appointed by WHO. These proposals should be shared with risk managers and other interested parties, including FAO and OIE. Once defined, this classification of critically important antimicrobials for people should be reviewed on a regular basis. The evidence presented at this expert workshop indicates that, based on the criteria listed previously, a list of critically important classes of antimicrobials should include; the fluoroquinolones and 3rd generation cephalosporins for *Salmonella* spp. and other *Enterobacteriaceae*; the fluoroquinolones and macrolides for *Campylobacter* spp.; and glycopeptides, oxazolidinones and streptogramins for Gram positive bacteria such as *Enterococcus* spp.

Review of risk assessment approaches for non-human usage of antimicrobial agents

This section reviews current approaches to the assessment of human risk of non-human usage of antimicrobials and describes the limitations in these approaches for their application. Currently, there are methodologies to assess the risk from the microbial hazard in foods (in combination with the antimicrobial resistance hazard) as well as methodologies to assess the chemical and microbiological hazard linked with residues of antimicrobials in foods. Risk assessment methodologies are in some areas well developed, in others the methods are under development. Chemical risk assessment in particular is well developed and already the subject of international applications.

There are two safety evaluations unique to antimicrobials: 1) Safety of ingestion of drug residues in foodstuffs (meat, milk, eggs and edible tissue) in terms of toxicity effects and perturbations of the human intestinal flora: and 2) Safety of antimicrobial agents used in animals leading to development of antimicrobial resistant bacteria and resistance determinants which could spread in bacteria to humans via the food-chain or zoonotic spread to humans. Available evidence, as described below, suggests that risk related to toxicity and flora perturbation caused by residues of antimicrobials in foods, under present regulatory regimes, is very low, while the risk related to the development of antimicrobial resistance in bacteria can be significant.

Assessment of toxicity from antimicrobial residues in foods

Various organizations and regulatory authorities have developed methods and adopted regulatory approaches to evaluate the safety of edible foodstuffs derived from animals treated with a specific drug. While regulatory approaches vary among international authorities and national agencies, objectives encompass three basic evaluations and decisions; 1) Safe ingestion level quantified in terms of an acceptable daily intake (ADI) for consumption of residues for the lifetime of an individual; 2) Maximum residue levels (MRL) allowable in all edible foodstuffs derived from treated animals to be consumed by humans; and 3) Withdrawal time needed after the drug is administered for residues to fall below the MRL so animals may be slaughtered for subsequent processing and consumption. For example, in the case of the Joint Expert Committee for Food Additives (JECFA), the ADI is based on an array of toxicological safety evaluations taking into account acute and long-term exposure to the drug and its potential impact, such as carcinogenicity, genotoxicity, reproductive toxicity, teratology, neurotoxicity, immunotoxicity and allergenicity, ocular toxicity, cardiac toxicity and, in the case of antimicrobial agents, safety for gastrointestinal microflora.

The ingestion of residues of antimicrobial compounds in food of animal origin may also pose a danger to human health by colonization barrier disruption leading to pathogenic bacteria overgrowth or by exerting a selective pressure on the intestinal microflora thus favoring the growth of microorganisms with intrinsic or acquired resistance. The ADI is determined as a conservative estimate of the safety ingestion levels by the human population, based on the lowest "no effect level" (NOEL) among a battery of toxicological safety studies. The toxicological or microbiological endpoint resulting in the lowest ADI ultimately drives the overall ADI. Thus, the ADI is determined as a conservative estimate of the safe ingestion levels by humans based on the lowest ADI among the toxicology and microbiology studies. JECFA recommends the MRL for tissues at concentrations which would lead to intakes below the ADI.

Safety evaluation of antimicrobial residues on human intestinal flora

An extensive literature review revealed no significant reported episodes of human health effects that occurred as a result of antimicrobials as residues in foods as long as the veterinary drugs are used at the correct dosages and at the levels permitted. However, the failure to find recorded adverse health effects does not necessarily mean that they have not occurred. Thus, studies have been developed which are used in regulatory submissions to determine adverse toxicological and microbiological effects of veterinary drug residues.

A harmonized approach is necessary in evaluating veterinary antimicrobial drug residues in food based on their effects on intestinal microflora. The VICH Safety Working Group is developing a unified approach in evaluating data to determine the impact of veterinary antimicrobial drug residues in food and human intestinal microflora (VICH 2004). It is quite similar to the JECFA and US FDA decision tree/pathway approach (US FDA 2003). This approach should be considered by national and international regulatory authorities and committees involved in the safety evaluation and risk assessment of chemicals in food to ensure consistency and transparency in determination of microbiological ADIs.

Assessment of human health risk caused by microbiological hazard in food

Microbiological risk assessment is a tool that is used in the management of the risks posed by foodborne pathogens and in the elaboration of standards in international trade. Codex has published principles and guidelines for the conduction of microbiological risk assessment intended to answer specific questions of importance for public health (CACgL30 1999). FAO and WHO have further developed detailed guidelines for the implementation of hazard characterization, exposure assessment and risk characterization (FAO/WHO 2003).

Both organizations have conducted a series of international risk assessments on *Listeria monocytogenes* in ready to eat foods, *Salmonella* spp. in broilers and eggs, *Vibrio* spp. in seafoods and *Campylobacter* in broilers. These risk assessments have not yet resulted in the development of international standards.

Risk assessment of antimicrobial resistance from non-human use of antimicrobials

Resistance risks to human health from non-human use of antimicrobials are inherently indirect and complex. Causal pathways for these risks include exposure of animals and plants to antimicrobials, selection of resistance in bacteria, movement of resistance genes among bacteria, and transfer of these bacteria through the food-chain and the environment to humans where they may cause a variety of adverse health effects or outcomes. Technical and logistical constraints seriously impair direct measure of risk through epidemiological study of these complex causal pathways. Nevertheless, there is great interest in the magnitude of resistance risk as an important factor in guiding antimicrobial use policy. A number of assessments of resistance risk have been performed in the period 1997 to 2003, some of them following the current OIE draft guidelines described below. Estimates of impact and attendant uncertainty ranged widely, depending on the microbial agent, antimicrobial drug and animal species included in the risk assessment models. Some of these estimates were qualitative (e.g. high, medium, low) and others were quantitative. A variety of risk assessment outcomes were used, for example, the annual number of mortalities, and annual number of cases of illness due to resistant infections treated with antimicrobial.

The risk assessments available do not fully address the broad range of potential human health impacts, or the spectrum of antimicrobials and organisms relevant to a comprehensive assessment of risk. Instead, they focus on specific antimicrobial/bacteria combinations that have been or continue to be of special interest to industry or government. Bailar and Travers made some general observations of antimicrobial resistance risk assessments that are also applicable here: Existing assessments focus on few specific clinical outcomes, few species of bacteria, and few animal species; they do not consider a more general shift toward more resistant bacterial populations (e.g. resistance transfer across bacterial species, issues of co-selection or cumulative effects in bacterial populations); they do not consider the global spread of resistant bacteria, spread of resistance genes among bacteria or multiple drug resistance; and they focus on what has already happened, which may not predict future risk (Bailar J.C. 3rd, Travers K. 2002).

Many of the individuals or groups that have undertaken or commissioned risk assessments later proposed alternative strategies or frameworks for future assessments. This is an indication that those actually conducting the assessments were not particularly satisfied with the methods available.

Various regulatory bodies and organizations have been working on approaches to assess risk from antimicrobial resistance. For example, in 2001, an OIE ad hoc group of experts proposed an approach to qualitative / quantitative risk assessment for antimicrobial resistance. The proposed process is divided into release assessment, exposure assessment, consequence assessment and risk estimation. The report further explains the rationale and approach to qualitative and quantitative assessment and the integration of risk assessment, risk management and risk communication, into the larger domain of risk analysis. The guidelines are expected to be adopted by the Member States of OIE in 2004.

Current risk assessment approaches for chemical contaminants are not adequate for antimicrobial resistance risk assessment because they deal with static chemicals that cause chronic hazards rather than dynamic bacteria such that the hazard of antimicrobial resistance continues to develop until the selective pressure is removed. The antimicrobial resistance hazard can also be amplified by continued use in any population. Moreover, the nature of the risk from antimicrobial resistance is acute and is characterized as a per meal or an annual risk rather than a lifetime cumulative risk, which is done for chemical contaminants. Currently, available risk assessment methodologies for microbial contaminants also do not address the hazard from antimicrobial resistance because the risk factors for dissemination and amplification of antimicrobial resistance are not necessarily the same as those for the bacteria. For example, there are specific biological pathways necessary for the use of the antimicrobial in animals or other non-human sources to release resistant bacteria or resistance determinants into the environment. The OIE has developed risk assessment methodology specifically for antimicrobial resistance. However, there are few risk assessments following this approach and it would benefit from additional examples.

Benefits and Costs

The societal benefits of therapeutic antimicrobial use in animals are assumed and unchallenged and have not been subjected to economic analysis. To facilitate choice of optimal risk management options for controlling problems related to antimicrobial resistance, future economic analyses of non-human antimicrobial use should attempt to segregate benefits and costs in terms of feed efficiency, disease prophylaxis and therapy on a drug and animal species-specific basis. In contrast, the economic benefits of antimicrobial growth promoters have been estimated and are debated and uncertain. Some estimates, based on targeted studies, suggest that the animal production benefits are

in the order of 1-11%, while other evidence, notably the review of Denmark's programme of antimicrobial growth promoter termination in swine and poultry production, suggests that the production gains are considerably less. There is growing evidence that when antimicrobial growth promoters still have a benefit, they derive much of their benefit from disease prophylaxis rather than enhanced feed efficiency or other effect.

Conclusions

Available scientific evidence and previous recommendations from international organizations, shows that the essential need for surveillance of non-human usage of antimicrobials and antimicrobial resistance for understanding and combating antimicrobial resistance remain valid. However, in most countries such surveillance is still inadequate. Available scientific evidence shows that non-human usage of antimicrobial agents leads to the development of bacteria that are resistant to antimicrobials used in humans. There is accumulating evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections. Evidence also shows that the amount and pattern of antimicrobial use impacts on resistant bacteria in animals and on food commodities and human exposure to these resistant bacteria. The foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist.

There is much less data available on the public health impact of antimicrobial use in aquaculture, companion animals, and horticulture. Molecular characterization of resistance genes as well as other data indicate some movement of resistant bacteria and resistance determinants from aquaculture, companion animals, and horticulture to humans. Furthermore, usage and occurrence of antimicrobial agents in these areas will exert antimicrobial selective pressure in the environment, which may impact public health.

Antimicrobial classes should be classified as "critically important" when the drug is in a class that is the only available therapy or one of a limited number of drugs available to treat serious human disease or pathogens that cause foodborne disease. Which antimicrobial classes should be defined as critically important for human medicine need to be more fully defined, preferably by an expert clinical medical group appointed by WHO. These proposals should be shared with risk managers and other interested parties including FAO and OIE. The evidence presented at this expert workshop indicates that based on the criteria listed above a list of critically important classes of antimicrobials would include, for example, the fluoroquinolones and 3rd generation cephalosporins for *Salmonella* spp.

At the international level, current risk assessment approaches for chemical and microbial hazards are not currently adequate for antimicrobial resistance risk assessment. The existing antimicrobial risk assessments, while helpful, do not adequately address the broad range of potential human health impacts, or the spectrum of antimicrobials and organisms relevant to a comprehensive assessment of risk.

Recommendations

1. **Establish a national surveillance programme on the non-human usage of antimicrobial agents**

A prerequisite for such a programme, that should take into account the OIE guidelines, is that countries have a regulatory approval and control system for antimicrobial agents and products containing antimicrobial agents. Furthermore, a system should be agreed upon internationally to identify and classify antimicrobial agents and to quantify their use in order to make data comparable. Preferably, the ATCvet classification scheme should be further developed and implemented. Further development of a system that better takes into account the potency of the drugs and differences in the dosages, such as the DDD (defined daily doses) system in human medicine, is needed.

Options for surveillance include:

- At a minimum, countries should collect data on the overall use of each antimicrobial agent and report these data in kilograms of active ingredient on an annual basis.
- Preferably, more stratified data on usage, e.g. usage per animal species or usage on farm level, should be collected.
- Presentation of data using a DDD-like concept.

Implications:

- Failure to implement surveillance of antimicrobial usage will:
  - prevent identification of trends.
  - prevent focused interventions, including development of appropriate usage guidelines.
  - prevent evaluation of interventions.

2. **Establish a national surveillance programme on antimicrobial resistance in bacteria from food and animals**

Antimicrobial susceptibility testing should be performed according to standardized methods using appropriate quality assurance. Quantitative susceptibility testing and reporting is preferred. Countries should link antimicrobial usage data with antimicrobial resistance data, preferably also with data from human medicine, and present the data to all interested parties at least on an annual basis.

Options for surveillance include:

- At a minimum, countries should perform susceptibility testing of non-typhoid *Salmonella* that at least include clinically important antimicrobial agents.
- Preferably, surveillance programmes should include testing of a wide range of bacteria from animals and food considering the OIE guidelines.
- Further consideration should be given to testing bacteria from aquaculture and companion animals, as well as bacteria isolated from the environment including irrigation waters, manure, ground water, etc.

Implications:

- Failure to implement surveillance of antimicrobial resistance will:
  - prevent identification of trends, such as the development of new emerging resistant strains.
  - prevent focused interventions, including development of appropriate usage guidelines.
  - prevent evaluation of interventions.

3. Implement strategies to prevent the transmission of resistant bacteria from animals to humans through the food production chain

Options include:

- General principles on food hygiene, Good Agricultural Practices and Good Manufacturing Practice should be developed and/or implemented at the national and international level as a mean to interrupt the flow of resistant bacteria through the food production chain. Codex has developed Recommended International Code of Practice – General Principles of Food Hygiene (latest edition 2001).
- Develop and/or implement prevention and control strategies in regard to *Salmonella* and *Campylobacter* in primary production.
- The hazard of resistant bacteria should be addressed at national and international level while developing standards for food safety and for animals in national and international trade.

Implications:

- Reduced public health risk.
- Potential economic impact.
- Reduced need for antimicrobial treatment.
- Reduction of direct antimicrobial selection pressure in animals.
- Potential impact on animal health and welfare.

4. Implement WHO Global Principles for the Containment of Antimicrobial Resistance in Animals intended for Foods and follow OIE Guidelines on Responsible and Prudent Antimicrobial Use

Management options aimed at mitigating adverse human health consequences due to resistance to all antimicrobials should aim to decrease antimicrobial selective pressure in animals.

Options include:

- Avoid group medication by feed or water wherever possible.
- Restrict the use of antimicrobials for example by prescription only.
- Remove antimicrobial use as growth promoters.
- Restrict off-label use.
- Reduce profit from sales of antimicrobials by veterinarians.

Implications:

Each of these options should reduce the quantity of antimicrobial agents used. This will decrease selective pressure, which should then decrease the development and spread of antimicrobial resistant bacteria.

5. Implement specific management strategies to prevent the emergence and dissemination of bacteria resistant to critically important antimicrobial agents for people

I. Antimicrobial classes that are "critically important" for human medicine need to be defined and identified by an expert medical group appointed by WHO. These proposals should be shared with risk managers and other interested parties, including FAO and OIE. This classification should be reviewed on a regular basis. For new antimicrobial classes developed for humans or any new antimicrobial classes with cross-resistance to critically important antimicrobials in human medicine, in addition to management options for all antimicrobials, specific options include the following.

Options include:

- do not use these drugs at all.
- use only in individual animals based on culture results and lack of alternative agents.
- use only in individual animals.
- use in groups of animals after risk assessment demonstrates acceptable level of safety.

Implications:

These options are listed in the order that will minimize selective pressure and are therefore least likely to contribute to the development and spread of resistant bacteria in animals treated with these agents.

II. Contingency plans be developed to control or eradicate *Salmonella* and other zoonotic pathogenic bacteria resistant to two or more "critically important" antimicrobials when they appear in food production animals or in the food supply.

Options include:

- recall associated foods.
- restrict movement of infected or colonized animals.
- processing that guarantees removal of all resistant bacteria.
- destroy food items.
- destroy groups of animals infected or colonized.

Implications:

These options are listed in the reverse order that will minimize the spread and persistence of these multi-resistant bacteria and thus safeguard public and animal health.

6. Implement the risk assessment approaches that are needed to support selection of risk management options

I. Governments should see methods used for antimicrobial resistance risk assessment as a continuum from purely qualitative to quantitative assessment. Both qualitative and quantitative approaches may be appropriate. Risk assessments should, however, address the range of potential human health impacts and the cumulative effects of resistance. The following risk assessment strategies could be considered:

- A tiered approach would best address when to use qualitative or quantitative risk assessment.
- A qualitative approach for risk assessment should be used to make the pre-marketing or post-marketing decision. Depending on the outcome, the drug sponsor has the option to develop a quantitative risk assessment.
- If currently marketed antimicrobials used in food-producing animals have not been evaluated with respect to antimicrobial resistance, such an evaluation should be conducted.
- In addition, currently marketed antimicrobials should be regularly reexamined with respect to antimicrobial resistance.
- If a new antimicrobial is introduced for human therapy that has a related chemical structure to an antimicrobial approved for non-human uses, a qualitative risk assessment should be conducted to assess the potential that the human drug will be compromised due to non-human uses.
- There is a need for peer review of risk assessments by appropriately qualified scientists. OIE is invited to continue its work on risk analysis in coordination with FAO and WHO.

II. When dealing with a high level of uncertainty, precaution should be applied in risk management. There needs to be extensive communication between risk managers and risk assessors such that the goals and objectives of the risk assessment are clearly defined and understood. A mechanism should be developed for sharing the results of risk assessments by governments.

Implications:

- Facilitation of risk-based evaluations of antimicrobials by countries with limited resources.
- Enhancement of the methods and practices of risk assessment.
- Current barriers to sharing the results of risk assessments include confidentiality and harmonization issues.

III. Governments should regularly review the effectiveness and adequacy of risk management strategies related to antimicrobial resistance and share this information.

Implications:

- Regulatory authorities would need to regularly review all available data including experimental laboratory investigations, epidemiology studies or surveillance data.
- Ethical and economic considerations need to be included.

- When antimicrobial resistance reaches a level of concern for existing antimicrobials used for non-human purposes, then a risk assessment should be conducted.

7. Enhance the capacity of countries, particularly developing countries, to conduct surveillance of antimicrobial use and resistance, to implement intervention strategies to contain antimicrobial resistance and to implement risk assessment approaches to support selection of risk management options

Options include:

I. Increase participation in international meetings relevant to the issue

II. FAO, OIE and WHO should support the expansion of programmes in developing countries that address food hygiene issues throughout the food-chain to enable surveillance and susceptibility testing such as the WHO Global Salm-Surv.

III. FAO, OIE and WHO should facilitate that the needs of developing countries in implementing all of the above recommendations are addressed.

Implications:

- Reduced public health risk
- Reduction of direct selection pressure in animals
- Potential impact on animal health and welfare
- Potential economic impact, including access to international markets for foods from developing countries
- Overall reduction in use

8. Risk management of antimicrobial resistance on the international arena

Antimicrobial resistance issues crosses many disciplines, including microbiology, toxicology and pharmacology, and risk assessment approaches for chemical and microbial contamination are not currently adequate for risk assessment on antimicrobial resistance. Therefore, when issues pertaining to antimicrobial resistance arise in CRVDF, CCFH or CCPR, a coordinated approach between the committees is needed. CCFH should take a lead on such issues since antimicrobial resistance is mainly one of microbiological hazards. The questions may need to be referred to a FAO/WHO expert body for risk assessment, preferably JEMRA. OIE may also need to be consulted. This body shall undertake an appropriate risk assessment. For this to occur, appropriate sets of data (i.e. data dealing with antimicrobial usage and resistance) have to be routinely provided.

The assigned FAO/WHO expert group will need to have the expertise to assess the new and/or additional data requirements.

Data gaps and areas for improvement

Surveillance of non-human antimicrobial usage

- More comprehensive collection of data of non-human usage of antimicrobial agents at the national level, at a minimum overall usage data. This includes usage in aquaculture, companion animals and horticulture.
- Development and adoption the ATCvet system to uniformly classify antimicrobial agents according to antimicrobial activities.
- Quantities of "unaccounted antimicrobial agents" such as unreported imported drugs.
- Development of a unit of measurement, such as the DDD system used in human medicine, that will better take into account the potency of the drug rather than just weight.
- Development of epidemiological methods that will enable better understanding of the association between antimicrobial usage, antimicrobial resistance and animal health and production.
- More stratified usage data such as usage per species, at herd level, usage in relation to indications, administration schemes, and in various regions.
- Develop a better control system on product quality. Under such a system only good quality products preferably elaborated under GMP would reach the market.

Surveillance of antimicrobial resistance in animals and food

- National surveillance systems with quantitative susceptibility data of food and food animals for zoonotic pathogens and commensal bacteria. Such surveillance systems should include close collaboration between persons in public health, veterinary medicine, and food reference laboratories.
- The suitability of *E. coli* and enterococci as the optimal genera for surveillance resistance in commensal bacteria from terrestrial animals.
- Identifying suitable indicator bacteria in aquaculture and horticulture and developing optimal methods for susceptibility testing of these bacteria.
- Extent of cross-resistance and co-selection between antimicrobial agents and other agents such as disinfectants and heavy metals.
- Molecular characterization of resistance genes and mutations conferring resistance.
- Robust and internationally accepted subtyping methods.
- Susceptibility testing methods that are robust, cost-efficient and suitable for implementation in developing countries.
- Comparability of results from susceptibility testing in various countries.
- Internationally agreed upon breakpoints.
- Implementation of quality assurance including harmonization of control strains.
- Agreement of antimicrobial agents and classes to be included.

Association between non-human usage of antimicrobials and resistance in human pathogens

- Quantification of spread of resistance determinants by international trade of animals and food products.
- Research on the public health impact from usage of antimicrobials in aquaculture, companion animals and horticulture and the consequent development and spread of antimicrobial resistant bacteria and resistance determinants.
- Impact of different animal production systems with different usage patterns on development of resistance.
- Co-selection of resistance determinants by antimicrobials.
- Selection by other substances with antimicrobial activity.
- The flow of resistance determinants between humans and animals.
- The role of commensals as reservoirs of resistance.

Human health implications

- Association between "virulence" and resistance mechanisms. Are antimicrobial resistant organisms more virulent? Are resistance genes associated with virulence factors?
- Data on the effects of resistance to specific antimicrobials and possible human health consequences for resistant bacteria, other than *Salmonella*, (e.g. *Campylobacter*).
- Studies focusing on factors, related to drug usage and antimicrobial resistance, causing increased infections, morbidity and mortality.
- Supplementary data for risk assessments and further understanding of human health consequences in different countries.
- Data on the appearance and disappearance of multi-resistant clones?
- Data on the additional costs associated with infections caused by antimicrobial resistant bacteria.

Risk assessment

- Development of methodology for antimicrobial resistance risk assessment
- Data enabling impact analysis related to different risk management strategies
- Criteria for the prioritization of antimicrobials in human
- Data addressing economic aspects

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OIE

OIE Guideline on antimicrobial resistance 1: Harmonisation of National Antimicrobial Resistance Monitoring and Surveillance Programmes in Animals and in Animal –derived Food

OIE Guideline on antimicrobial resistance 2: Standardisation and Harmonisation of Laboratory Methodologies for the Detection and Quantification of Antimicrobial Resistance

OIE Guideline on antimicrobial resistance 3: Monitoring the quantities of antimicrobials used in animal husbandry.

OIE Guideline on antimicrobial resistance 4: Responsible and Prudent use of antimicrobial agents in veterinary medicine

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