



**World Health
Organization**



International Food Safety Authorities Network (INFOSAN)

7 March 2008

INFOSAN Information Note No. 2/2008 - Antimicrobial Resistance

Antimicrobial Resistance from Food Animals

SUMMARY NOTES

- Antimicrobial agents are important drugs for human and animal clinical medicine as well as for animal welfare. To a large extent, the same classes of antimicrobials are used in animals and humans.
- In some cases, antimicrobials are added to feed and water to promote growth and increase feed efficiency. This long-term, low dose exposure to antimicrobials is considered more likely to result in the development of antimicrobial resistance than treatment or prevention of infections with antimicrobials in food producing animals.
- An FAO/OIE/WHO workshop held in Geneva in 2003 concluded that there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials
- In the past decade some countries, including the European Commission (EC), have discontinued the use of certain antimicrobials for growth promotion purposes due to the risks to public health. Such policies are in accordance with the recommendations given by WHO and guidelines developed by the Codex Alimentarius Commission.
- The available evidence suggests that the risk related to toxicity and flora perturbation caused by residues of antimicrobials in food is very low, while the risk associated with development of antimicrobial resistance in bacteria can be significant.
- Infections with resistant pathogenic bacteria will result in more difficult and expensive therapy; antimicrobial resistance is therefore a public and animal health problem and an economic burden.
- Few new antimicrobials have been developed to replace those that have become ineffective through resistance. Therefore management measures are urgently needed to preserve the efficiency of all antimicrobials, particularly critically important antimicrobials.

Introduction

Antimicrobial agents are essential drugs for human and animal health. Severe bacterial infections may be associated with high morbidity and mortality if not treated promptly and efficiently. Antimicrobial resistance is associated with the use of antimicrobials in humans, animals (including aquaculture) and horticulture. This INFOSAN note focuses primarily on the public health impact of the use of antimicrobials in food producing animals.

In the animal production sector antimicrobials are used for the treatment of infections in single animals and in flocks of animals. Prophylactic and metaphylactic treatment are used to prevent the spread of infections from sick to healthy animals in the same production unit. In addition, antimicrobials are sometimes used for growth promotion purposes (in lower doses than used for disease treatment). Antimicrobial growth promoters (AGPs) are antimicrobials added to the feed of food animals to enhance their growth rate and production performance. It is likely that AGPs act by reducing the normal intestinal flora (which compete with the host for nutrients) and harmful gut bacteria (which may reduce performance by causing sub-clinical disease). This

long-term, low-dose exposure to antimicrobials is considered more likely to result in the development of antimicrobial resistance than treatment or prevention of infections with antimicrobials in food-producing animals.

There is a growing body of evidence of the link between extensive antimicrobial use in the food producing animal sector and appearance of resistant strains in human beings. Other non-human uses of antimicrobials (use in pet animals, aquaculture and horticulture) may also play a role in this transfer of antimicrobial resistance, even if less data are available. When resistant pathogenic bacteria are the cause of infections in humans (as well as in animals) this will often result in inappropriate and/or more protracted therapy to cure infections. Therefore antimicrobial resistance is a public and animal health problem and an economic burden.

The potential risk of emergence and spread of resistant microorganisms associated with such use has been the focus of scientific research and regulatory actions, in particular during the last decade; the public health concerns related to the use of antimicrobials in food producing animals have been addressed by the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and WHO. The fact that, to a large extent, the same classes of antimicrobials are used both in humans and animals, and few new antibiotics from existing classes and new classes have been developed to replace those that have become relatively ineffective through resistance, has led to an agreement on the necessity to develop management measures to prevent and/or contain antimicrobial resistance. These include prudent use of antimicrobials, monitoring of antimicrobial use in food producing animals, surveillance of emerging antimicrobial resistance in both the human and the veterinary sectors and appropriate education and training of farmers and prescribers. Regulatory measures, such as a restriction or ban of use of antimicrobials (or some classes of antimicrobials) for certain purposes and/or certain animal species, have also been established, i.e. the ban on use of antimicrobials in food producing animals as growth promoters in the EC.

Antimicrobial Resistance in Foodborne Pathogens: The Problem and its Magnitude

Salmonella and *Campylobacter* are two of the most common causes of foodborne diseases, and increasing antimicrobial resistance is reported in both bacteria. Most of the non-typhoid *Salmonella*, particularly in developed countries, is spread via food sources with the initial source being food animals. Outbreaks of multi-resistant non-typhoid *Salmonella* have occurred in both Europe and the United States of America. In some cases there has been no effective antibiotic therapy available.

Most cases of *Salmonella* associated diarrhoea do not require antibiotic therapy, since therapy may prolong excretion of the organism. However, there are also a large number of episodes where invasive disease occurs with *Salmonella* (i.e. bloodstream infections and/or signs of systemic reaction with fevers, rigors, etc). In these cases antibiotic therapy is needed and currently the most effective antibiotics are fluoroquinolones and third generation cephalosporins. Resistance is therefore a problem when it occurs. This is especially true for children as fluoroquinolones are contraindicated because of the potential for joint damage and thus in children 3rd generation cephalosporins are often the only effective therapy available.

Gastrointestinal infections caused by *Campylobacter* spp. can manifest as self-limited gastroenteritis or more severe diarrhoea. They can also cause secondary complications such as reactive arthritis and Guillian-Barré syndrome. In most cases *Campylobacter* spp infections do not need antibiotic therapy and are resolved spontaneously. However, in a reasonable percentage (likely 10% or more) antibiotic therapy is usually needed because there is evidence of invasive disease or prolonged symptomatic disease with some systemic reaction (i.e. fever). In these cases either macrolides (erythromycin) or a fluoroquinolone are the drugs of choice. Increasing resistance to this agent is seen, particularly to fluoroquinolones such as ciprofloxacin. Available evidence suggests that much of this fluoroquinolone resistance is related to the use of fluoroquinolones in food animals. Countries where fluoroquinolones are either banned in food animals (Australia) or else used fairly sparingly (Sweden) have very low levels of resistance to fluoroquinolones. On the contrary, in countries with much higher usage rates of fluoroquinolones in food animals (Spain, China, USA), fluoroquinolones resistance in *Campylobacter* spp is seen frequently in both animals and human isolates.

Macrolides are widely used in food animal production and are known to favour selection of macrolide resistant *Campylobacter* spp. in animals. Macrolides are one of few available therapies for serious *Campylobacter* infections, particularly in children in whom quinolones are not recommended. Given the high incidence of human disease due to *Campylobacter*, the absolute number of serious cases is substantial.

Recent development of antimicrobial resistance in foodborne pathogens are a matter of concern. These include: (i) transferable low-level resistance fluoroquinolone resistance in *Enterobacteriaceae*, (ii) Methicillin resistant *Staphylococcus aureus* (MRSA) in animals and, (iii) the emergence worldwide of *Escherichia coli* and *Salmonella* isolates from human and animals with extended spectrum beta-lactamases.

Reduction of the risk: Containment of antimicrobial resistance arising from use of antimicrobials in animals

Containment of antimicrobial resistance due to non-human use should be a multisectoral activity, involving all stakeholders concerned with non-human use of antimicrobials. Collaboration between international organizations and between all interested stakeholders is vital.

The following initiatives could contribute to the containment of antimicrobial resistance due to non-human use.

At the international level

- Promote implementation by countries of the *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* by building capacity for monitoring antimicrobial use and antimicrobial resistance (using existing training platforms such as Global Salm-Surv), identifying barriers for the implementation of the Global Principles, assist Member countries in implementing the different activities listed below.
- Promote implementation by countries of OIE International Standards for prevention of antimicrobial resistance.
- In collaboration with governments and non-government organizations, international agencies such as FAO and OIE are developing and promoting guidelines for veterinarians on the prudent use of antimicrobials in animals for protection of human health.
- Ensure active participation of countries in activities of the Codex Alimentarius Commission in relation to antimicrobial resistance (Codex Task force on Antimicrobial Resistance; Codex Committee on Residues of Veterinary Drugs and other Codex committees as necessary) and that public health issues are taken into account properly when developing recommendations/guidelines/standards.
- Promote and assist Member countries in undertaking integrated surveillance of antimicrobial resistance. This includes collection and analysis of data on antimicrobial use, data on antimicrobial resistance from animal isolates (at farm or slaughterhouse, as well as samples from diseased animals from veterinary clinics), food isolates at retail level and human isolates.
- Promote the establishment of surveillance networks for sharing information on antimicrobial resistance development.
- Encourage and fund educational and research activities.
- Encourage incentives for the development of new antimicrobial drugs.

At the country level:

- Make containment of antimicrobial resistance a national priority, as recommended in the WHO Global Strategy for the Containment of Antimicrobial Resistance and OIE International Standards for prevention of antimicrobial resistance.
- Create a national task force for containment of antimicrobial resistance caused by both human and non-human use, with representatives from Ministries of Health and Agriculture (and others as appropriate) and all interested stakeholders: the medical and veterinary professions, farmers,

patient and consumer organizations, farmers and livestock producers associations, food industry, and pharmaceutical industry etc.

- Take into account the potential development of antimicrobial resistance during pre-licensing safety evaluation of veterinary antimicrobial drugs, including the potential for cross-resistance to drugs used in human medicine.
- Post licensing surveillance should be undertaken to detect emergence of antimicrobial resistance in time in order to put in place appropriate corrective actions.
- Distribution and sale of antimicrobials should be controlled to prevent illicit manufacture, importation and sale of veterinary antimicrobial drugs. Special attention should be paid to counterfeit drugs and promotional activities from the pharmaceutical industry that may strongly influence prescribing habits.
- Prescription should be obligatory for antimicrobial use to control animal diseases.
- Monitoring antimicrobial use in animals, in terms of quantities of active ingredients and in terms of usage patterns.
- Surveillance of antimicrobial resistance in animals, humans and food, and use integrated data to identify emergence of antimicrobial resistance arising from non-human use and to implement timely measures for the containment of antimicrobial resistance.
- Develop guidelines for veterinarians and other responsible persons on the correct prescription and use of antimicrobials.
- Encourage good hygienic practices and farm management to ensure animal health (hence the possible reduction of the need for antimicrobials use), optimal housing, safe feeding stuffs, water, etc.

Overall, there are many effective options available to mitigate the risk of resistance in humans resulting from the use of antimicrobials in animals. Action is urgently needed to preserve the efficacy of all antimicrobials, particularly critically important antimicrobials. Efforts to reduce unnecessary use in all sectors are needed, as are efforts to contain infections and to stimulate the innovation of new antimicrobials and diagnostics.

Additional information on activities carried out at an international level and the way forward

WHO's involvement with the issue of foodborne antimicrobial resistance dates back to 1990, with increased interest from 1997, when medical problems arising from the use of antimicrobials in livestock production were identified and concern was raised that drug-resistant pathogens could be transmitted to humans via the food-chain. Two important milestones for WHO were the publications of the *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*, which provides a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health, and the development of a WHO list of critically important antimicrobials for human health. The full report of WHO Global Principles is available at:

http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf.

FAO's involvement with the issue of foodborne antimicrobial resistance includes normative and field activities, which are carried out by several units; mainly the Nutrition and Consumer Protection Division (AGN), the Fishery Industries Division (FII) and the Animal Production and Health Division (AGA). The activities consider the food-chain approach and have a primary focus on prevention. Some of the normative activities have been carried out jointly with WHO. The Codex Alimentarius Commission has developed guidelines for the responsible and prudent use of antimicrobials in food producing animals. These include: *Recommended International Code of Practice for control of the Use of Veterinary Drugs CAC/RCP 38-1993*

http://www.codexalimentarius.net/download/standards/46/CXP_038e.pdf and the *Codex Code of Practice to Minimize and Contain Antimicrobial Resistance CAC/RCP 61-2005*

http://www.codexalimentarius.net/download/standards/10213/CXP_061e.pdf.

Since 1997, due to the growing importance of antimicrobial resistance at a worldwide level, the OIE requested its Collaborating Centre for Veterinary Medicinal Products, in Fougères, France, to implement an

action plan in this field. The main achievement has been the publication of the OIE *Guidelines for Responsible and Prudent Use of Antimicrobials* . http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.3.htm and the OIE guidelines on *Risk Assessment for Antimicrobial Resistance Arising from the Use of Antimicrobials in Animals* http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.4.htm.

After a wide exchange of viewpoints and assessment of the challenges, the International Committee of OIE decided to create an ad hoc group of internationally recognized experts on antimicrobial resistance and to develop a list of critically important antimicrobials for veterinary medicine

During the last five years, the potential risk of emergence and spread of resistant microorganisms associated with use of antimicrobials in food producing animals has been addressed jointly by FAO, OIE and WHO following recommendations by the Executive Committee of the Codex Alimentarius in 2001. All the reports related to this consultative process are available at WHO website:

http://www.who.int/foodborne_disease/resistance/publications/en/index.html

The main outcome of this collaborative effort has been the development of two lists of critically important antimicrobials (a human list by WHO and a veterinary list by OIE www.who.int/foodborne_disease/resources/Report%20joint%20CIA%20Meeting.pdf) and the establishment of a Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance hosted by the Republic of Korea at the 29th session of the Codex Alimentarius Commission, held in Geneva in July 2006. The Task Force will develop science based guidance, taking full account of its risk analysis principles and the work and standards of relevant international organizations such as FAO, OIE and WHO. This guidance will assess the human health risks associated with the presence and transmission of antimicrobial resistant microorganisms and antimicrobial resistance genes in food and animal feed, including aquaculture. Appropriate risk management advice will also be developed.

The Task Force will submit to the Codex Commission, through the Executive Committee, the proposals for new work on the development of guidance documents on: (1) Science-based risk assessment of foodborne antimicrobial resistance; (2) Risk management options to contain foodborne antimicrobial resistance; and (3) Risk profiles for setting risk assessment and management priorities.

INFOSAN serves as a vehicle for food safety authorities and other relevant agencies to exchange food safety information and to improve collaboration among food safety authorities at both the national and international level.

INFOSAN Emergency, embedded in INFOSAN, links official national contact points to address outbreaks and emergencies of international importance and allows for the rapid exchange of information. INFOSAN Emergency is intended to complement and support the existing WHO Global Outbreak Alert and Response Network (GOARN).

INFOSAN is operated/managed by WHO, Geneva. It currently includes 166 Member States.

More information is available at: www.who.int/foodsafety