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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 11 **CX/FH 00/11**
August 2000

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD HYGIENE

Thirty-third Session
Washington, D.C., USA, October 23-28, 2000

RISK PROFILE ON ANTIMICROBIAL-RESISTANT BACTERIA IN FOOD

(Prepared by the Delegation of Denmark with assistance of Canada, Finland, France, Germany, Italy, Norway, Sweden, The Nederlands, United Kingdom, the United States of America, CI, COMISA, FAO, OIE, and WHO)

1. DESCRIPTION OF THE SITUATION

A. INTRODUCTION

In recent years, the number of foodborne infections in humans, which are caused by antimicrobial-resistant bacteria, has increased. Besides the presence of antimicrobial-resistant bacteria in food, other factors contribute to the occurrence of such infections. These include host factors including age and immune competence, food consumption patterns, international travel, and use of antimicrobials in humans for other infections.

Antimicrobial use leads to the selection of resistant bacteria in the ecosystem of use, and has consistently been identified as the major risk factor in the emergence and spread of antimicrobial-resistant bacteria. This resistance may include resistance to more than one antimicrobial with common mechanisms of action. Compared with susceptible bacteria, certain antimicrobial-resistant bacteria are more likely to acquire additional resistance determinants through horizontal gene transfer making them resistant to additional antimicrobials. Furthermore, resistance to different antimicrobials may be linked if the resistance is encoded by genes that reside on the same genetic element. If two resistance determinants are cross-linked, the use of either antimicrobial may select for resistance to both antimicrobials.

The extent to which antimicrobial use in food animals (including aquaculture), horticulture or humans contributes to antimicrobial-resistant bacteria in humans varies between the different bacteria and different regions. When humans ingest antimicrobial-resistant bacteria in food, some species of bacteria may cause illness. These and other species of bacteria may also serve as a source of transferable resistance determinants for other bacteria, including human pathogens.

B. ANTIBIOTIC RESISTANT BACTERIA – FOOD VEHICLES AND RESERVOIRS

Bacterial pathogens with food animal reservoirs

Foodborne bacterial pathogens with food animal reservoirs include *Salmonella*, *Campylobacter,* and verotoxigenic *Escherichia coli.* Infections caused by these bacteria occur worldwide. Currently, increasing antimicrobial resistance is a public health concern predominately with respect to *Salmonella* and *Campylobacter*. The increasing prevalence of resistance to antimicrobials which are commonly used to treat patients with serious *Salmonella* (e.g., third-generation cephalosporins and fluoroquinolones) or *Campylobacter* (e.g., fluoroquinolones and macrolides) infections are of particular concern. Food animals, including cattle, swine, chickens and turkeys, are the principal reservoir for *Salmonella* and *Campylobacter*. In the developed countries, humans usually acquire these bacteria through ingestion of foods that are contaminated with food animal fecal material. These foods are commonly of animal origin, but may include a wide variety of other foods including water, fruits and vegetables. There are regional differences in the most common food sources of these bacteria due to variations in the prevalence of these bacteria in the food chain and consumption patterns. When considering the additional possibility that foods of animal origin may cross-contaminate other food items during food preparation, almost any food item, particularly those eaten uncooked or without further cooking after handling, may, on occasion, serve as a vehicle for transmission of antimicrobial-resistant bacteria to humans.

Use of antimicrobials in food animals is the principal source of antimicrobial resistance in foodborne bacterial pathogens with food animal reservoirs. Several examples are available in the medical literature. For example, fluoroquinolone-resistant *Campylobacter* has emerged in several countries following the use of fluoroquinolones in food animals. In developing countries, antimicrobial use in humans is also an important source of antimicrobial resistance in these pathogens. For example, several hospital outbreaks of multidrug-resistant *Salmonella* associated with human antimicrobial use and person-to-person transmission have been reported.

Bacterial pathogens with a human reservoir

Foodborne bacterial pathogens that have a human reservoir include *Salmonella* Typhi, *Shigella* spp. and *Vibrio cholerae* although an environmental reservoir for *V. cholerae* also exists. Increasing antimicrobial resistance is a public health concern for each of these bacteria. For example, in some instances, multidrug-resistant *S.* Typhi, *Shigella dysenteriae*, and *Vibrio cholerae* have become resistant to all locally available antimicrobials. Human infections caused by *Shigella* spp. other than *S. dysenteriae* occur in many developed countries, but infections caused by *S.* Typhi, *Shigella* and *V. cholerae* are seen predominately among persons in the developing world. Humans usually acquire these bacteria through the ingestion of foods, including water, which are contaminated with human faeces. Use of antimicrobials in humans is the principal source of antimicrobial resistance among these foodborne bacteria.

Other bacteria and genes

Other bacteria that may be transmitted to humans through food include *Enterococcus* spp. and *Escherichia coli.* Enterococci are commonly isolated from the intestinal tract of humans and animals. Although enterococci exhibit low virulence, they may cause infection in patients with impaired immunity. In humans, the use of antimicrobials in hospitals has resulted in increased incidence of nosocomial transmission of multidrug-resistant enterococci in several countries. Increasing resistance among enterococci to clinically important antimicrobials, including glycopeptides and streptogramins are of particular concern. In food animals use of antimicrobials effective against Gram positive organisms, has resulted in the acquisition of resistance by enterococci Most of these antimicrobials are used for growth promotion in food animals and where

these drugs have been used, resistant enterococci have frequently been isolated from food animals and foods of animal origin. Once ingested by humans, enterococci may transfer resistance determinants to other bacteria, including other enterococci. *E. coli* also is commonly isolated from the intestinal tracts of humans and food animals. *E. coli* may be transmitted from animals to humans through ingestion of food and may, in some instances be pathogenic, or serve as a source of transferable resistance determinants for other bacteria.

Bacteria can harbour mobile genetic elements, called plasmids, transposons, and integrons, which commonly transfer resistance determinants to bacteria of the same or other species. Identical resistance genes or resistance transferring genetic elements in bacteria from humans and animals have been reported in several studies.

C. FACTORS CONTRIBUTING TO THE OCCURRENCE OF ANTIMICROBIAL- RESISTANT BACTERIA IN FOOD

The presence of antimicrobial-resistant bacteria in food is primarily the consequence of antimicrobial use and transmission of antimicrobial-resistant bacteria.

Pre-harvest

Antimicrobial use

Antimicrobials are used in food animals for growth promotion, prophylaxis, metaphylaxis, and therapy. This use is the principal contributing factor to the emergence and dissemination of antimicrobial resistance among bacterial pathogens and commensals that have food animal reservoirs. Growth promotion use, particularly of antimicrobials which are used in human medicine, is an area of particular public health concern. It involves giving antimicrobials to a large number of animals, over a long period of time, at lower than therapeutic doses; a usage pattern that can promote the development of antimicrobial resistance. Most prophylactic and metaphylactic use and some therapeutic use also involves giving antimicrobials to a large number of animals, but at a therapeutic dose and for a shorter duration period. In aquaculture, antimicrobials are commonly administered directly or via feed in the water, while those used in horticulture are commonly administered by aerosol. The public health risk of antimicrobial use in aquaculture and horticulture has not been well characterized but should be evaluated There is a specific need for generating data addressing such issues.

Transmission between food animals

Since antimicrobial-resistant bacteria with a food animal reservoir are transmitted between food animals through the fecal-oral route, spread of these bacteria between food animals is largely due to consumption of contaminated feed and water. Several factors contribute to an increased likelihood of transmission between food animals including crowding, mixing, and animal disease status.

Post-harvest

Antimicrobial use

Disinfectants and some food preservation additives have an antimicrobial effect. The contribution of these uses to the occurrence of antimicrobial-resistant bacteria in food should be evaluated.

Antimicrobials are also used in humans for therapy and for prophylaxis. Use of antimicrobials in humans is the principal contributing factor to the emergence and dissemination of antimicrobial resistance among bacterial pathogens with a human reservoir. In the developing world, use of antimicrobials in humans also contributes to antimicrobial resistance in *Salmonella*.

Transmission during slaughter, food processing and food handling

Food can become contaminated with antimicrobial-resistant bacteria from the faecal material of food animals or humans throughout the farm-to-table continuum. The primary point of dissemination of food animal fecal material is during slaughter. The primary point at which food becomes contaminated with human faeces is during food handling. Food handling is therefore a common means of introducing antimicrobial-resistant bacteria into food for bacterial pathogens with a human reservoir.

2. VALUES EXPECTED TO BE PLACED AT RISK

A. HUMAN HEALTH

Introduction

Antimicrobial-resistant bacteria in food may pose a risk to human health in several ways. This risk may relate to limiting therapeutic options, their selective advantage in certain environments where antimicrobials are used and, potentially, more virulent strains. The population at increased risk is characterized by immunocompromised indivduals. This population is increasing in many parts of the world, for different reasons. In addition, antimicrobial- resistant bacteria represent a reservoir for resistance genes that can be transferred to human pathogens. However, so far these potential adverse effects remain incompletely elucidated.

Limited treatment options for infections related to antimicrobial resistance in food-borne pathogens

Resistant food-borne pathogens are involved in an increasing number of reported disease cases in humans. Despite the fact that the majority of food-borne infections are self-limiting and antimicrobial therapy is not needed in most cases, antimicrobials are quite commonly prescribed, and are necessary in cases of severe gastroenteritis or extraintestinal infections

Some studies show increasing therapeutic failures, a higher morbidity and mortality related to infection with resistant food-borne bacteria. Such data exist for instance for *Salmonella, Shigella* and *Vibrio*. In some developing countries, no treatment is effective for some of these infections. In other instances, only more toxic or more expensive drugs than the ones usually prescribed remain effective.

Campylobacter infections rarely result in extraintestinal complications. However, infections with antimicrobial resistant *Campylobacter* may, in spite of treatment, run a prolonged clinical course, due to lack of efficacy of the antimicrobial.

The incidence of non-infectious immunological complications of enteric infections seems to be higher after prolonged acute illness. Thus, it is possible that infections caused by antimicrobial resistant strains may trigger more of these diseases, e.g. reactive arthritis.

Increased morbidity of infections caused by resistant pathogens relating to antimicrobial treatment

The resistance characteristics give the antimicrobial-resistant bacteria a selective advantage in environments where antimicrobials are used. In several studies antimicrobial therapy for reasons other than enteric disease has been identified as a general risk factor for the acquisition of food-borne diseases and this may be due to several reasons. Patients receiving antimicrobial treatment may already be vulnerable due to an underlying disease and, consequently, may be more susceptible to infection. This may be the underlying reason for an apparent difference in virulence between

antimicrobial-resistant and antimicrobial-sensitive strains. Furthermore, antimicrobial treatment can alter the composition of the normal intestinal flora, which may result in a lower infectious dose of a pathogen needed to establish an infection. It is also possible that antimicrobial therapy in a patient harbouring resistant opportunistic bacteria, or with a subclinical infection caused by a resistant food-borne pathogen, may trigger development of clinical disease.

Finally, as mentioned earlier, resistance genes in non-pathogenic bacteria may be transferred to pathogens in the gastrointestinal tract of food animals or man and thereby precipitate an infection caused by a resistant pathogen. Such reservoirs, as for example vancomycin-resistant enterococci, may cause opportunistic infections in humans.

Virulence of resistant bacteria

Current data do not indicate that antimicrobial resistant food-borne pathogens carry more virulence factors compared to their non-resistant counterparts.

B. ECONOMICS

Economic consequences of increasing infections with antimicrobial- resistant pathogens may relate to:

- Production losses due to the patients incapacity to work
- Hospital costs
- Increased medication costs and other treatment related expenses
- Increased costs in the food industry

3. POTENTIAL CONSEQUENCES

The potential consequences of increased antimicrobial resistance in food-borne bacteria may be:

- increased morbidity
- increased mortality
- increasing number of treatment failures and cases where no treatment options are available
- increased economic costs

4. CONSUMER PERCEPTION AND PERSPECTIVES ON THE RISKS OF ANTIMICROBIAL- RESISTANT BACTERIA IN FOOD

It is important to recognize that societies in different countries differ in attitudes and economics on issues related to food. Consumers in general have great concerns about the safety and healthfulness of the food supply as well as the means of food production, including issues related to animal welfare. The specific issue of antibiotic resistance and risks of infection related to the use of antibiotics in food production has been recognized in some countries by the general public. It is likely that as the problems of antimicrobial resistance are more widely publicized and recognized, the public will respond. Perception of other food risks has caused rapid and significant changes in consumer purchasing. Consumers in many countries have expressed willingness to pay for and a desire to be informed about the quality of food, including methods of food production. Economic developments in the food industry support this expressed preference.

Consumers have the following perspective:

(1) A holistic approach should apply to the development of a risk profile and to the assessment of the risk in order to include all sources of selective pressures and all reservoirs of resistant organisms that may affect food quality, human health, and animal health-welfare. International organizations are encouraged to cooperate and consult mutually in order to incorporate this understanding.

(2) The human health risks from antibiotic resistance related to food consumption involve potential contamination at all stages of the food chain, including transfers in or from the environment, drinking water, other reservoirs, recycling of animal wastes for feed, fomites, food production, handling and cooking practices.

(3) The animal health and welfare issues involve concerns that use and overuse of antibiotics may be substituted for good practice in animal husbandry. Improper use of antibiotics also puts animals at risk for infection by resistant organisms as a consequence of the development of microbial resistance, and jeopardizes the quality of animal-derived food intended for human consumption.

(4) The use of antibiotics for growth promotion should be prohibited. All other non-therapeutic veterinary uses should be clearly justified and carefully considered in the context of present and future requirements of clinical medicine. Management of wastes from animal production facilities, including aquaculture, must protect humans and the environment from exposures to antibiotics, resistant organisms, and resistance genes (including marker genes in genetically modified organisms).

5. DISTRIBUTION OF BENEFITS AND RISKS

The general benefits from the use of antimicrobials in food production derive from therapy, metaphylaxis, prophylaxis, and growth promotion. The benefits of antimicrobials in veterinary therapy, metaphylaxis and prophylaxis, include the protection of animal health and welfare, as well as contributing to the health of consumers through quality and safety of animal derived food. The benefits of antimicrobials in growth promotion are related to reduced costs of production, involving reduction in the time to achieving harvest weight and reductions in costs of animal husbandry. According to studies carried out on the impact on food production costs of a ban or restriction on such uses, the benefits of this use may be relatively small. These benefits are expected to vary in different countries and over time according to developments in the production of animal derived food products as well as shifts in consumer demand.

The general risks associated with the use of antibiotics in food production involve increases in risks of selection of antimicrobial resistance and infection, through impacts on nonpathogenic and pathogenic microbes and the diversity of microbial communities. These risks may have negative impacts on both human and animal health, with associated costs in health care and food production. The distribution of these risks among different groups and stakeholders is largely unknown. However, as noted above, the human health risks may be greater for persons who are immunocompromised, the elderly, and those undergoing invasive medical procedures.

The risks of antimicrobial use in food production increase with increasing amounts and frequency of antimicrobial use. The risks associated with metaphylaxis are relatively greater than those associated with therapeutic use because in general larger amounts of antimicrobial are used. The risks associated with prophylactic use have greater risks because larger amounts of antibiotics will be used and broad-spectrum drugs are often selected in the absence of specific diagnoses or index cases. The use of antibiotics in food production to enhance growth has greater risks than any therapeutic or prophylactic use in agriculture because antibiotics are used without veterinary oversight and for long duration in animal production. In addition, there may be increased costs associated with the management of wastes from food production facilities where antimicrobials are used.

Changes in the perceived societal benefits and risks could affect patterns of consumption of animal-derived food and economic interests in the use of antimicrobials.

6. RISK MANAGEMENT OPTIONS

General Introduction

The primary objective of assessing microbiological risk management options is to focus on the key interventions necessary to prevent and to control microbiological risks. It is aimed at selecting the option, or options that achieve the chosen level of public health protection for the microbiological hazard in the commodity of concern.

The management of antimicrobial-resistant bacteria in the food chain includes general hygiene measures to reduce the occurrence of undesirable bacteria in foods together with specific activities aimed at controlling the use of antimicrobial agents in animals, humans and horticulture.

Good hygienic practices (GHP) are critical to the control of pathogens in the food chain and will impact on these organisms irrespective of whether they are resistant or susceptible to antimicrobials.

Although risk management options assessment is not part of a risk profile, risk managers may find it helpful to have a list of possible areas for consideration. This will assist in identifying priority areas and in commissioning risk assessments. These areas should be considered as part of an integrated risk analysis process.

The following areas are not listed in any order of priority and do not have any particular weighting in terms of importance.

I. Hygienic measures

In order to address the issue of resistant bacteria in the food chain, risk managers may consider measures in particular in the following areas.

General Principles of Food Hygiene

Codex has developed general principles of food hygiene that are applicable throughout the food chain, including primary production through to the consumer, to achieve the goal of ensuring that food is safe and suitable for human consumption (Codex 1997a). Good hygienic practices are critical to the control of pathogens in the food chain and will, by their nature, address the occurrence of both resistant and susceptible bacteria in food. Such measures will also impact on some non-pathogenic bacteria that may be a reservoir of resistance genes.

A. HACCP

Implementation of Hazard Analysis and Critical Control Point (HACCP) programs will contribute to addressing the risk of antimicrobial-resistant bacteria in food and guidelines for the application of HACCP have been elaborated (Codex 1997b). HACCP can be applied throughout the food chain from primary production to final consumption and its implementation should be guided by scientific evidence of risks to human health. Implementation of good agricultural practices may reduce the problems of both resistant and susceptible pathogens/bacteria in the food chain.

B. Maintenance of animal health control programs and infection control

Maintenance of animal health involves biosecurity, feed and water quality, optimal nutrition, and good hygienic practices on the farm. The regular monitoring of antimicrobial susceptibility in bacteria should be conducted. Programs to reduce the incidence of disease in herds and flocks of animals (for example vaccination programs) should be implemented and maintained.

C. Waste management

Environmental considerations are important in containing the spread of antimicrobial resistance and preventing contamination of foodstuffs intended for human or animal consumption. Human, animal and plant waste may contain antimicrobial-resistant bacteria and residues of active compounds that continue to select for resistant bacterial populations. Human and animal waste of faecal origin may be used to fertilise crops intended for human and animal consumption, potentially propagating resistant bacteria widely onto plant materials. Risk management options to address the issue of waste management will vary depending on the sanitary infrastructure existing in an individual country or region.

D. Water as a vehicle for transmission

Depending on its microbiological quality, water may impact on contamination of food with antimicrobial-resistant bacteria throughout the food chain from primary production to consumption.

Additional Measures for Certain Pathogen/Resistance Pattern Combinations

In addition to the management options listed above, one may want to consider other measures with regard to certain resistant pathogens. Such measures could take many forms such as prevalence levels and/ or microbiological criteria addressing certain pathogen/resistance pattern combinations, for example, multiresistant *Salmonella* Typhimurium DT104. Such measures should be related to a "farm-to-table" approach beginning in primary production. Feasibility of such an approach would be contingent on many factors, including an adequate surveillance program.

II. REDUCING THE MISUSE AND OVERUSE OF ANTIMICROBIAL AGENTS

The work of other international organizations (WHO and others) should be taken into account when considering these issues.

Use of Antimicrobials in Animals and Horticulture

A. Approval, licensing and surveillance

As part of the approval process for an antimicrobial to be used in food animals, pet animals, aquaculture or horticulture, consideration should be given to the issue of antimicrobial resistance. High-risk uses identified, as part of a pre-approval assessment may be restricted. Consideration should be given to choosing those use conditions that will maximise the efficacy of the antimicrobial, while minimizing the development of antimicrobial resistance.

Other restrictions that countries might consider in order to limit the development of antimicrobial resistance include making all antimicrobials prescription only and restriction of “extra-label” use of certain antimicrobial products. Recommendations on the prudent use of antimicrobials may also be considered as part of product labelling. Other limited use strategies may involve use of an antimicrobial being contingent upon certain management interventions on the farm, or application of processing treatments of the food derived from the treated animals/crops to reduce the microbial load.

It is important that any use of antimicrobials that pose a potential human health concern be closely monitored with appropriate surveillance systems after approval. A monitoring program permits the identification of resistance trends and, if well designed, may be a useful tool for estimating the magnitude of the resistance concern and the need for any re-evaluation. Collection of data on antimicrobial use may also be helpful in interpreting resistance data from a surveillance program.

B. Prudent use of Antimicrobials

It is important to ensure prudent use of antimicrobials in food animals, aquaculture and horticulture. This should include reducing the overuse and misuse of antimicrobials in agriculture

Use of Antimicrobials in Humans (hospital/community)

The measures considered will differ depending on whether hospital or community settings are being addressed. The epidemiology of humans as a source of antimicrobial-resistant bacteria in the food chain may vary from country to country.

A. Human Health Infrastructure

General approaches to the prevention of infectious diseases in humans will influence the need for antimicrobial use. Good hygiene is important in the management of infections by health care workers and patients. Food handlers also need to be considered. Management of human waste will depend on the sanitary infrastructure existing in an individual country.

B. Prudent Use of Antimicrobials

As humans may be a source of antimicrobial-resistant bacteria for the food chain, it is important to ensure prudent use of antimicrobials. This should include reducing the overuse and misuse of antimicrobials in human medicine.

Food Preservatives/Biocides

If evidence exists that use of such antimicrobials is linked to the occurrence of resistant bacteria of human health concern, then risk management options to address this use may be considered.

7. CONCLUSIONS

The working group has revised the discussion paper CX/FH 99/12 in the form of a risk profile as requested. Based on this profile the following points can be highlighted:

- It is recognized that antimicrobial resistance contributes to the public health risk of pathogenic bacteria in food, because they result in an increase in the morbidity, mortality and costs associated with infection.

- Moreover, antimicrobial-resistant bacteria also represent a public health risk via food due to the potential dissemination of resistance genes.
- The presence of antimicrobial-resistant bacteria in food is related to the use of antimicrobials, including growth promoting antimicrobials, in food production and in humans, as well as the transmission of bacteria in the various steps of the food chain and environmental spread.
- A number of strategies are available to control antimicrobial- resistant bacteria in foods including hygienic measures, prudent use and other efforts to reduce overuse and misuse of antimicrobials.

8. RECOMMENDATIONS

- This risk profile acknowledges the public health risks associated with antimicrobial-resistant bacteria in the food chain, but the magnitude of the risk is not established. Therefore it is recommended to further address this problem in the various committees involved.

- Based on the current risk profile it is recommended that the CCFH should commission risk assessments for selected specific scenarios relating to antimicrobial-resistant bacteria in food (e.g., bacterium/antimicrobial/food combinations). It is suggested that member countries be requested for proposals for the bacterium/antimicrobial/food combinations that are a priority for risk assessment.

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