codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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DISCUSSION PAPER ON ANTIMICROBIAL RESISTANT BACTERIA IN FOOD[1]

(Prepared by the Delegation of Denmark with assistance of Brazil, Canada, France, Finland, Hungary, Iceland, Netherlands, Norway, Sweden, United Kingdom, and the United States of America)

Background Information

The 31st Session of the Codex Committee on Food Hygiene (CCFH) under the Agenda Item 13 *Other Business and Future Work* had considered the paper on Antibiotic Resistance Bacteria in Food (CRD 4) prepared by the Delegation of Denmark. The paper outlined the need to evaluate and address the risks associated with the development of drug resistance in bacteria following the use of antibiotics. There were various opinions expressed regarding the issue itself and on the way of proceeding (ALINORM 99/13A, paras 112-113).

Some delegations and the Observer from Consumers International supported this proposal as antibiotic resistance was a significant emerging public health problem. The Delegation of Switzerland expressed the view that antibiotic resistance was essentially related to medical use of antibiotics, and it did not appear relevant to address it as a food hygiene issue. Some delegations pointed out that matters concerning antibiotic resistance as related to their use in veterinary medicine was under the responsibility of the CCRVDF and should be addressed accordingly.

Some delegations indicated that scientific research was being conducted in their countries on antibiotic resistance and antibiotic use for different purposes, and it would be useful to consider this question in the perspective of food hygiene concerns. It was also proposed that the development of such work could be undertaken in conjunction with the CCRVDF and other interested committees. The Committee noted that the Executive Committee was responsible for the assignment of specific work to Codex Committees and that careful consideration should be given to the entire issue of antibiotic resistance in bacteria before deciding whether further action was required.

The Committee agreed that the delegation of Denmark, with the participation of Brazil, Canada, Denmark, France, Finland, Hungary, Iceland, Netherlands, Norway, Sweden, United Kingdom, and United States should prepare a discussion paper to clarify the issues involved and their relevance to the work of the Committee, for further consideration at the next session (see Annex).

While considering the "Designation of Host Governments for Codex Committees and *Ad Hoc* Intergovernmental Task Forces the 23rd Session of the Codex Alimentarius Commission (CAC)

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[1] To be discussed under the Agenda Item 12 “Discussion Paper on Antibiotic Resistance in Bacteria in Food”.

(ALINORM 99/37, para. 230) noted the recommendation of the 46th Session of the Executive Committee concerning the urgent need for the Commission to develop international guidelines or recommendations which addressed all the issues relating to animal feeding and that the new mechanism of an ad hoc Intergovernmental Codex Task Force would be an appropriate means of achieving this goal and therefore established *Ad Hoc* Intergovernmental Task Force on Good Animal Feeding and designated the Government of Denmark to be as the host country for the above Task Force. The Section (j) of Terms of Reference (see ALINORM 99/37, Appendix VI) *"To address other aspects which are important for food safety, such as problems related to toxic substances. pathogens, microbial resistance, new technologies, storage, control measures, tracebility etc."* is relevant to the issue under consideration of the current discussion paper (see Annex).

Annex

ANTIMICROBIAL RESISTANT BACTERIA IN FOOD

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1. INTRODUCTION

Discussion paper clarifies issues concerning antimicrobial[2] resistant bacteria in the food chain[3] (including primary production through to the final consumer). This paper considers these issues in the context of international responsibilities in this area.

The use of antibiotics in food animals and the emergence of resistant bacteria in the food chain are of considerable importance and have been the subject of numerous national and international consultations (1,2,3). The issues relating to antimicrobial resistant bacteria in live animals are discussed internationally by veterinary, microbiological and epidemiological expertise through the OIE (Office International des Epizooties), FAO (Food and Agriculture Organisation), VICH (Veterinary International Cooperation on Harmonisation) and the CCRVDF (Codex Committee for Residues of Veterinary Drugs in Foods). Aspects relating to the medical impact in humans of antimicrobial use in animals have been considered by the WHO (World Health Organisation). Antimicrobial resistant bacteria in relation to food hygiene, including aspects relating slaughter, processing, handling, distribution, and the retail level, have not been specifically addressed. This area falls within the terms of reference of the CCFH.

It is internationally agreed upon, that risk assessment should underpin all decisions relating to food hygiene and in this respect it should be noted that CCFH has already undertaken work in relation to the assessment of risks associated with microbiological contamination of food. In addition, CCFH has initiated the development of principles for the management of microbiological hazards associated with such risks. The CCFH risk assessment document was adopted by the Codex Alimentarius Commission

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[2] Antimicrobial agents or antimicrobial(s) refers to naturally occurring, semi-synthetic or synthetic substances which exhibit antimicrobial activity (destroy or inhibit the growth of other microorganisms). The term antimicrobial(s) comprises antibiotics which refer to substances produced by or derived from microorganisms.

[3] In this paper the term foods refers to any substance whether processed, semi-processed or raw, which is intended for human consumption, and includes drinks.

in July this year, whereas the CCFH risk management document has been drafted and is currently under consideration at step 3.

In view of the development in the area of risk analysis, work relating to antimicrobial resistance, which is proposed to CCFH, should focus on a risk analysis approach and follow the principles identified in relevant Codex documents. Work undertaken by the CCFH in relation to antimicrobial resistant bacteria in the food chain should take into consideration work being undertaken in other fora. Close co-ordination between CCFH and CCRVDF in this area may also be necessary.

This document is intended to clarify the public health issues relating to antimicrobial resistant bacteria in the food chain. It is suggested that Codex increases its activities on the area and outlines considerations that should be taken into account in a risk profile[4]. It has been noted by the drafting group, that certain aspects of the problem with antimicrobial resistant bacteria in the food chain are associated with the general problem of microbial food contamination.

1.1 SCOPE

This paper considers antimicrobial resistant microorganisms in the food chain in the context of international responsibilities in this area by using the principles of risk analysis. Further work on the subject is suggested, and a division of the work between the relevant Codex committees in this area, CCFH and CCRVDF, is recommended.

2 IDENTIFICATION OF THE PROBLEM OF ANTIMICROBIAL RESISTANCE

Antimicrobial agents are extensively used in human and veterinary medicine for treatment and control of infectious diseases. Without these drugs many infective diseases would be untreatable. Antimicrobials are also used in animal husbandry for growth promotion, in horticulture and for industrial purposes including food preservation.

Since the introduction of penicillins in the 1940s, the introduction of any new antimicrobial has been followed by the emergence of bacteria that are resistant to this drug. However, no truly novel antimicrobial drugs have been developed during the last decade. Today antimicrobial resistance is the cause of increasing concern world-wide.

In recent years the efficacy of human antimicrobial therapy has been challenged by the emergence of different resistant bacterial pathogens like vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, and multiresistant Mycobacterium tuberculosis, as well as different resistant zoonotic bacteria such as Salmonella and Campylobacter.

The primary impact of resistance to antimicrobials is failure of empirical therapy of bacterial infections. This may lead to an increase in morbidity and mortality and hence prolonged suffering of infected patients and subsequent increase in the costs for the public health sector.

2.2 AREAS OF ANTIMICROBIAL USES

2.2.1 Use of antimicrobials in humans

Antimicrobials are used both in the community and in hospitals, especially in intensive care units. Antimicrobial therapy is usually initiated on indications of a bacterial infection (empirical treatment) which preferably is followed by the establishment of a specific bacterial diagnosis.

Antimicrobial treatment is also commonly used for prophylactic purposes, e.g., in connection with surgery, in immunocompromised individuals, and as for example in malaria prophylactics.

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4 The use of the term 'Risk Profile' relates to the Risk management document [at step 3 of the Codex procedure]. It is realised that this document and the concepts defined herein are not yet considered part of the official Codex vocabulary.

2.2.2 Use of antimicrobials in animals

Antimicrobials are widely used to treat and control infectious diseases in food producing animals, including fish in aquaculture. Antimicrobials are also used therapeutically in pet animals. The therapeutic use of antimicrobials in animals includes both individual treatment as well as flock or herd medication.

Antimicrobials are also used for growth promotion in food animals, by adding feed low, sub-therapeutically levels of antimicrobials. This ultimately results in increased growth rates for the animals.

Generally, there is no difference between the classes of antimicrobials used for animals and humans. Animal use includes substances that currently are considered the most potent for human therapy, e.g., fluoroquinolones, 3rd generation cephalosporins, and glycopeptides.

Like in humans, resistant pathogenic bacteria are a major problem in food animals. Resistance among animal pathogens such as E. coli, Salmonella Typhimurium, staphylococci, and streptococci represents a problem for the treatment of different infectious diseases in animals.

2.2.3 Use of antimicrobials in horticulture

Antimicrobials are also used for plant protection (pesticides). The antimicrobials used on plants include important human therapeutic drugs such as gentamicin, chloramphenicol, streptomycin, and (oxy)tetracycline.

2.2.4 Use of antimicrobials in food preservation

Antimicrobials can act as preservatives in food preservation. Some countries have implemented a ban on such uses due to the potential risk of development of antimicrobial resistance. In Codex a limited number of antimicrobial substances, nisin (bacteriocin) and natamycin (antifungal agent), are proposed for inclusion in the Codex General Standard on Food Additives (GSFA) for the use in selected foodstuffs.

3 ANTIMICROBIAL RESISTANCE

The definition (clinical) of a resistant versus a sensitive microorganism is associated with the ability of a drug to be effective in the treatment of a specific infection. The susceptibility of a bacterium to an antimicrobial is a quantitative characteristic, usually expressed as the minimum inhibitory concentration (MIC), which denotes the lowest concentration of the specific antimicrobial that inhibits growth of the tested bacteria under standardised conditions in the laboratory. Different expert groups have suggested breakpoints for classification of different pathogenic bacteria as resistant or susceptible. These breakpoints support physicians and veterinarians in their choice of antimicrobials.

Many antimicrobials are derived from microorganisms, and consequently resistance is a naturally occurring phenomenon. Microorganisms that initially lack a target site for an antimicrobial drug are referred to as being naturally or intrinsically resistant.

Microorganisms can acquire antimicrobial resistance: Changes in the DNA (mutations) or uptake of foreign DNA can change the susceptibility of a microorganism to an antimicrobial agent.

Mutations, which are naturally occurring in the genome, are one mechanism for acquisition of resistance in a microorganism. Another important way of acquiring resistance is the uptake of foreign DNA mediating resistance. Nature has developed different systems for transfer of genes between bacteria (conjugation, transformation, transduction, and transposition) and these mechanisms have proven effective in the promotion of resistance genes. Thus, the different resistance genes are shared by a number of various bacteria. Mobile genetic elements often carry several resistance genes, and consequently the uptake of a single mobile genetic element may confer resistance towards several antimicrobials at the same time. Multiresistant bacteria represent a special problem because the use of

one antimicrobial can select for several resistance genes, a phenomenon referred to as co-selection of resistance.

Bacteria proliferate by division and this means, that most bacteria inherit their resistance from their ancestors. In environments with antibiotics, resistant bacteria can disseminate very quickly because of their selective advantage.

It is generally accepted that all antimicrobials selects for bacteria that are resistant, and it has furthermore been established, that there is an association, although complex, between the use of antimicrobials and the occurrence of resistant bacteria. Currently prudent use of antibiotics seems to be the main tool for preserving the effectiveness of antimicrobials.

4 PATHWAYS OF TRANSMISSION OF ANTIMICROBIAL RESISTANT BACTERIA

The widespread occurrence of resistant bacteria in humans, animals, foods, and the environment indicates that the pathways of transmission of resistant bacteria are complex. Transfer of bacteria between humans can occur by direct transfer from human to human, or indirectly via utensils or food.

4.1 HUMANS

Resistant bacteria represent a problem both in the community and in the hospitals.

Nosocomial infections represents a special problem. Because of the density of highly susceptible patients the rates of transmission of bacteria from patient to patient can be high in hospitals, and outbreaks of inter-human transferred resistant bacteria occur periodically. Factors predisposing to this transmission include the severity of underlying illness, length of stay in hospital, and intensity and duration of exposure to antimicrobials. Nosocomial infections with resistant bacteria can have severe outcome with treatment failure and possible fatality as the result. In hospitals, multiresistance in staphylococci, enterococci, Pseudomonas and a number of Enterobacteriaceae e.g., Klebsiella spp. and Enterobacter is the cause of serious problems.

Interhuman spread of resistant pathogenic bacteria is also a problem in the community and include bacterial pathogens like pneumococci, staphylococci, Haemophilus influenzae, gonococci, meningococci, and Mycobacterium tuberculosis.

4.2 FOODS

The food chain is considered to be an important route for transmission of resistant bacteria from man to man, from animal to man, and from the environment to man. Because of the use of antimicrobials in food animals, including fish, and horticulture, foods are often contaminated with resistant bacteria.

The widespread occurrence of resistant bacteria in the food chain include both zoonotic and commensal bacteria. The slaughter process represents a key step in the transfer of bacteria from animals to food, and E. coli and enterococci, which are considered to be indicators of faecal contamination, can readily be isolated from fresh meat products and unpasteurized milk. Indicator bacteria, like E. coli and enterococci are frequently resistant to antimicrobials and represent a source from which resistance genes can be further spread.

A number of resistant zoonotic pathogens can also be isolated from food animals and foods, e.g. Campylobacter and different serotypes of Salmonella. The spread of zoonotic bacteria from animals to foods can be partly prevented, but not completely interrupted, by good hygiene.

Foods, including water, can further act as a vehicle for transmission of bacteria from man to man, especially when the water or foods are contaminated with faecal material originating from humans. Food and water are major sources for transmission of non-zoonotic pathogenic bacteria such as typhoid Salmonella, Vibrio cholerae and Shigella spp..

Resistant bacteria can also be isolated from fresh fruits and vegetables. The resistant bacteria may originate from humans, animals or the environment. The use of untreated manure or infected irrigation water is an important risk factor for spread of resistant bacteria to fresh produce.

Food and water are also important reservoirs for resistant commensal or saprophytic bacteria, which generally are considered to be harmless to humans and animals. However, such bacteria represents a reservoir of resistance genes, which potentially can be spread to other bacteria including pathogenic bacteria.

5 PUBLIC HEALTH ISSUES AND IMPACT

Food- and water-borne resistant pathogenic bacteria constitute an important increasing health problem in many parts of the world.

Foodborne bacterial infections in humans do generally not require the use of antimicrobials since the disease pattern often is a self-limiting diarrhoea. However, there are cases where the bacterial disease progresses and becomes systemic, and in such cases the lack of an effective antimicrobial may be fatal. It is also commonly seen that physicians prescribe antimicrobials to patients suffering from unspecific gastro- and extraintestinal diseases. Thus, antimicrobials are frequently used for treatment of food-borne bacterial diseases.

There is an association between routine use of antimicrobials for various diseases, including extraintestinal infections, and antimicrobial therapy is identified as a risk factor for contracting foodborne zoonotic diseases in case-control studies. This finding is supported by studies that have shown that resistant bacteria may cause more serious disease than susceptible bacteria. In a retrospective study of 52 Salmonella outbreaks in USA it was found, that the case mortality rate was higher for patients infected with resistant Salmonella (4,2%) than for those with sensitive infections (0,2%).

Fluoroquinolone resistant bacteria represent a special challenge due to its importance in human medicine. Following the introduction of fluoroquinolones in animal livestock in the early nineties, resistant strains of zoonotic bacteria such as Campylobacter and Salmonella have emerged.

Antimicrobial resistance in commensal and other non-clinical bacteria can also affect human health. It is well known that resistant commensal sometimes cause opportunistic infections, e.g. during surgery, when for instance immunocompromised patients are treated with an antimicrobial agent.

The knowledge on antimicrobial resistance gene transfer in natural environments like food matrixes and the digestive tract is relatively limited and it is difficult to estimate the significance of this problem for human health. However, transfer of resistance-genes between different genera has been documented in foods as well as the gastrointestinal tract of animals and humans.

The use of antimicrobials for growth promoting purposes in animal livestock represents a special problem when it includes classes of antimicrobials that are used or potentially can be used for treatment of humans or is known to select for cross-resistance to antimicrobials used in human medicine. Examples of cross-resistance between different classes of antimicrobials used for both growth promotion and human treatment include tylosin/erythromycin (macrolides), virginiamycin/pristinamycin (streptogramins) and avoparcin/vancomycin (glycopeptides) and avilamycin/ everninomycin.

6 CONSIDERATIONS FOR A RISK PROFILE

For items to be considered in a risk profile see Appendix 1.

7 RISK ASSESSMENT POLICY CONSIDERATIONS

The general principles and guidelines on risk assessment as established by Codex should be followed in risk assessment policy considerations. In particular risk assessors should give due consideration to the

identification of areas, where there is a lack of data. Where data exists, their variation, comparability and uniformity needs careful consideration.

Risk assessments in the area could be performed using two different approaches: Antimicrobial resistance could be considered in relation to the pathogen under consideration, e.g. when considering *Salmonella* in a food context the resistance trait could be considered as one of the properties of the organism in question. Resistance could also be looked at from a specific, carefully chosen, antimicrobial/bacteria combination concept. This could be from the perspective of a specific antimicrobial, a specific antimicrobial/bacteria combination or a specific antimicrobial/bacteria/food combination.

8 SUGGESTIONS FOR FURTHER WORK IN CODEX

The problem of antimicrobial resistance is a multifactorial problem, which most efficiently is handled by a multidisciplinary approach. In Codex, the CCRVDF and the CCFH should have the mandate to deal with these problems according to the terms of reference of these committees[5].

The CCFH is a committee dealing with horizontal approaches to microbiological problems in food using a risk analysis approach. In the future, the CCFH is likely to be assisted by scientific expertise for microbiological risk assessment. The CCFH will then be able to consider the risk related to the occurrence of resistant bacteria in food by addressing the question to the scientific expertise.

The CCRVDF considers issues concerning drug residues in food. In the process the committee receives scientific advice from Joint Expert Committee on Food Additives (JECFA), dealing with risk assessment of certain chemical substances in food. In the process of determining maximum limits of drug residues in food, the CCRVDF could also include considerations of the problems concerning the spread of resistant bacteria. The committee could also consider these problems in the relevant existing codes of practice concerning the use of veterinary medicines. In both frames, the CCRVDF should work in a close co-operation with the OIE.

It is recommended, that CCFH, if appropriate in co-operation with CCRVDF, develop a discussion paper placing the problem of resistant bacteria in food chain into a more formal risk analysis context and prioritise relevant questions to be commissioned by these committees to the relevant scientific expert group(s) as part of a formal risk assessment procedure.

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[5] Secretariat's Note: See also the last Section of the Background Information on the *Ad Hoc* Intergovernmental Codex Task Force on Good Animal Feeding on page 2.

APPENDIX 1: ITEMS TO BE CONSIDERED IN A RISK PROFILE

In analysis of an identified problem a risk profile can be made. The following issues could be considered in a risk profile. It should be noted that the lists, concepts and descriptions are neither final nor exhaustive.

Microbiological hazards causing the problem

- Antimicrobial-resistant pathogens
- Antimicrobial-resistant commensal bacteria

Sources of the hazard

- Human medicine
- Veterinary medicine
- Animal feed as growth promotors
- Aquaculture
- Horticulture
- Food preservation

Mechanisms for the development of antimicrobial resistance

- Acquisition of resistance genes
- Pathogenic bacteria
- Commensal microorganisms
- Antimicrobial resistance marker genes in genetically modified foods including microorganisms

Reservoirs for resistant bacteria

- Humans (hospitals and community)
- Animals
- Plants
- Soil
- Water

Factors that may contribute to the spread of antimicrobial resistant bacteria in the food chain

- Harvesting
- Processing and handling stages of food production, including transport
- Preservation of foods
- Retail sale/handling of foods
- Hygiene practices
- International trade and distribution of foods
- International trade with live animals

- International travelling

Types and severity of the adverse effects

1) Resistant pathogenic bacteria present in food which cause infection

- Severity (mortality/morbidity)
- Available therapy/relative to the resistance pattern
- Capacity to colonise the gastrointestinal tract may be influenced

2) Resistant commensal bacteria present in food which transfer resistance genes to pathogenic- or other commensal bacteria in the food or in the intestinal tract

- Bacteria may acquire the resistance genes
- Available therapy/relative to the resistance pattern
- Capacity to colonise the human gastrointestinal tract
- Probability of transfer of genes to pathogenic bacteria
- Probability for resistant commensal bacteria causing opportunistic infections

Populations affected

Effect most severe in:

- patients on antimicrobial therapy (systemic and oral use)
- high risk groups including immunocompromised persons, the very old, the very young, and pregnant women

How stakeholders (people concerned) perceive the problem

There is a general public concern about resistance to antimicrobials and Codex should consider the interests of interested parts and involve the key players.

Examples of interested parts could be:

- farmers
- food producers
- producers of feed and additives
- producers of pharmaceuticals
- retail/distributors
- shops/vendors
- consumers
- consumer organisations
- environmental organisations
- governmental bodies
- unions

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