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MEETING REPORT

Risk analysis according to the Federal Institute for Risk Assessment international symposium “Towards a Risk Analysis of Antibiotic Resistance”

Abstract

In the following, the conclusion reached by four expert working groups as regarding the aspect of risk assessment in the risk analysis process on antimicrobial resistance is outlined. Playing a central role is the procedure, which was endorsed by the FAO/WHO CODEX Alimentarius Commission in 1999, entailing hazard identification, hazard characterization, exposure assessment and risk characterization. Scientific observations in these four areas are subjected to evaluation. In essence, risk assessment decisions in this context are fundamental as they form the basis for risk management options, which in turn should reduce health risks posed by resistant microorganisms.

Keywords: Antimicrobial resistance; Risk assessment

Introduction

Initiated by the Federal Ministry for Consumer Protection, Food and Agriculture (BMVEL) and the Federal Institute for Risk Assessment (BfR) and supported by the Federal Office for Consumer Protection and Food Safety (BVL) and the Federal Agriculture Research Center (FAL), the international symposium “Towards a Risk Analysis of Antibiotic Resistance” was staged on November 9–11, 2003 at the BfR in Berlin.

Target of the symposium was the documentation of state-of-the-art knowledge of development and transmission of antibiotic resistance in microorganisms. Conclusions reached through analyses done in the working groups, should serve as a basis for risk assessment discussions and recommendations for risk management concepts elaborated at the national follow-up conference entitled “Risk Management for the Limitation of Antibiotic Resistance” held at the BVL in November 2004.

The BfR symposium on risk assessment was directed foremost at national and international experts in antibiotic-resistance research and consumer health safety. During the four sessions on the first day of the symposium attended by approximately 200 scientists from 16 countries, papers relating to the work plan on risk analysis adopted by the FAO/WHO CODEX Alimentarius Commission in 1999 were submitted, entailing the sub-division of the microbiological risk assessment process in hazard characterization, exposure assessment and risk characterization (CODEX Alimentarius Commission, 1999). On the second day, the working groups, which were set up to examine the individual components of risk analyses, formulated their conclusions and recommendations based on an assessment of their main findings and current knowledge.

This report entails the summary of the conclusions reached by the working groups. Further details have been published by Helmuth and Hensel (2004).

Working Group 1: Hazard identification

This working group was assigned the task of identifying known and potential health risks from a specific pathogen or agent.

The conclusions relevant to risk assessment of BfR are as follows:

1. Antimicrobial resistance is transmitted by bacteria of animal origin.
2. Humans can be directly or indirectly infected by resistant bacteria from animals.
3. The resistant genes in animal bacteria are transmitted to bacteria, which play a significant role in human medicine.
4. Due to transmission, the spread of resistant bacteria in food-animals and humans can be observed.

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Reasons for the lack of success in the treatment of severe infection in humans are emphasized in these conclusions. Factors inducing the selection and spread of resistant bacteria in animals were elucidated by the working group; which include sub-therapeutic doses, mass medication, and the use of broad-spectrum antibiotics for long-term treatment as opposed to the use of narrow-spectrum antibiotics. Further risk factors mentioned were the indiscriminate prophylactic and metaphylactic use without prior and appropriate microbiological diagnosis, which should include an antibiogram.

The following observations were made regarding the selection and transmission of resistant bacteria in animals:

For therapeutic, metaphylactic and prophylactic purposes, domestic food animals are generally administered antimicrobial substances. In Germany only a small percentage of animals receive these substances to promote growth. However, it is an acknowledged fact that antimicrobial substances destroy or prevent the reproduction of sensitive bacteria. Resistant bacteria survive and multiply. This demonstrates the selection process, which favors the accumulation of resistant bacteria and the subsequent transfer of both resistance genes and bacteria between individual animals as well as between herds.

Transmission of resistant bacteria from domestic animal to humans can occur via the food chain or from animals directly. Transfer of resistant bacteria can occur through contamination of meat of food-animals during the slaughtering process or during food production. In the case of direct transmission, contamination occurs via human contact with affected animals or their excrement. Farmers, veterinarians and slaughter-house workers are therefore particularly at risk. The effect of resistant, animal pathogenic bacteria on humans depends on several bacterial and host factors. Experts distinguish between long- and short-term colonizing pathogens. However, a horizontal bacterial gene-transfer from animal to human commensal flora or human pathogenic bacteria may occur in both groups.

Both cases result in transmission of resistant genes present in the bacteria of domestic animals to the bacteria present in humans. A subsequent colonization can lead to disease in the human body. Resistant pathogens deter effective treatment of disease and result in prolonged illness. The course of the disease may also incline to an increase in severity. Resistance resulting in unsuccessful treatment of the illness could ultimately lead to the death of the patient. In the experts' discussions focus was placed on situations involving *Salmonella*, *Campylobacter*, *Escherichia coli* and *Enterococcus*. The working group endeavored to find answers to the following questions on pathogens:

1. Does the administration of antimicrobial substances to animals lead to the emergence and spread of resistant bacteria?
   - *In the case of Salmonella*: Fluoroquinolone resistance, apramycin-gentamicin resistance and multi-resistance were considered to be particularly worrying.
   - *In the case of Campylobacter*: Fluoroquinolone resistance and macrolide resistance are prominent.
   - *In the case of E. coli*: Fluoroqinolone, apramycin-gentamicin and streptothricine resistance.
   - *In the case of Enterococcus*: Glycopeptide, macrolide and streptogramine resistances are especially worrying.

2. Which resistances are transmitted from animals to humans?
   - *In the case of Salmonella*: Fluoroquinolone resistance by the spread of strains exhibiting resistance to this antimicrobial; and apramycin-gentamicin resistance by the spread of plasmids/genes and resistant strains.
   - *In the case of Campylobacter*: Fluoroquinolone resistance. Macrolide resistance was deemed questionable.
   - *In the case of E. coli*: Apramycin-gentamicin resistance and streptothricine resistance. Fluoroquinolone resistance was deemed questionable.
   - *In the case of Enterococcus*: Glycopeptide, macrolide and streptogramine resistance.

3. Which resistance determinants of these bacteria can be transmitted to other human pathogenic bacteria? The experts quoted the following examples
   - *In the case of Salmonella*: Apramycin-gentamicin and multi-resistance.
   - *In the case of Campylobacter*: Macrolide resistance.
   - *In the case of E. coli*: Apramycin-gentamicin and streptothricine resistance.
   - *In the case of Enterococcus*: Glycopeptide, macrolide and streptogramine resistance.

   The general consensus of the working group was that no definite statement can be made regarding the transmissibility of other resistance genes, due to the fact that these genes are present in bacteria of both animal and human origin. Consequently, at present the origin of widespread resistance genes cannot be clearly identified. Undisputed however, is the fact that the use of antimicrobial substances in humans, in veterinary medicine, in agriculture and aquaculture has frequently lead to the transfer of genes among human pathogenic, plant and animal pathogenic organisms and among bacteria which live in the environment.