Situation analysis – abridged version

”Antibiotic resistance of bacteria in human and veterinary medicine and in foodstuffs”

Drafted by the "Co-ordination group for antibiotic-resistant microorganisms" comprising representatives of the management of the following institutions: Swiss Federal Office of Public Health, Federal Veterinary Office, Federal Office for Agriculture, Swiss Federal Dairy Research Station of Liebefeld-Bern, Swiss Federal Research Station for Animal Production of Posieux, Swiss Farmers Union, "Istituto Cantonale Batteriosierologico" of Lugano, Bern University, Zürich University and the Swiss Federal Institute of Technology, Zurich

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Background

The discovery of antibiotics constituted an enormous medical advance. Very soon after the introduction of these active substances into clinical practice, however, a certain disillusionment spread. It was found, namely, that bacteria could develop resistance to antibiotics. In 1944, the year when penicillin was first used, almost all strains of *Staphylococcus aureus* were sensitive to this new medicine. By 1950, on the other hand, only 30% of the clinically isolated strains of this infectious disease pathogen still responded to penicillin, and now the corresponding rate is 15%. Over time, bacteria also developed multiple resistances. Thus, for example, gram-negative pathogens which are resistant to 15 active substances are known. Fortunately, these multiple resistances are mostly limited to locally occurring strains of a type of bacteria.

Since antibiotics are very important tools in modern medicine, a great deal of attention is being paid to the phenomenon of the bacterial resistance in scientific circles. A large number of papers have therefore been published in the past decades on the mechanisms, transmission and spread of bacterial resistance to antibiotics. In addition, the measures for limiting the development and transmission of resistance have been known for a long time and are described in many standard medical textbooks on microbiology. There are, however, justified doubts as to whether these preventive measures really are put into practice consistently.

Until now, the general public has hardly been aware of the intensive research into antibiotic resistance. This has changed now that the media have focused on this problem of resistance. A vast campaign was conducted at the end of 1997 in this respect, in which specific foodstuffs were labelled as sources of risk for the spread of resistant bacteria. Unfortunately, this was done by giving the issue a veneer of sensationalism and without sufficient reference to its complex context. Thus, for instance, in the “Blick” edition of 24th October 1997, one could read that eating Appenzeller cheese could mean that pneumonia would no longer respond to treatment in future.
It is absolutely unclear what this type of statement is based on. Neither the intestines nor cheese are habitats of the most important human pneumonia pathogens, and although penicillin has been administered for over 50 years, this antibiotic is currently still very effective in Switzerland against pneumococci (1.1% resistant strains and 6% with a lowered sensitivity).

Health authorities found that this undifferentiated reporting led to fears among readers, and also gave rise to the belief that antibiotic resistance of bacteria was something completely new. There was plainly a need for objective and comprehensive information. In view of these facts, the BAG (Federal Health Department) set up a committee of experts comprising representatives from various federal departments, research institutes, universities and the farmers’ association. The first task of this forum was to look into pressing issues and to provide answers. This reinforced the standpoint taken by the BAG that, among other things, there was no direct danger for consumers due to antibiotic-resistant bacteria in foodstuffs and there was no urgent need for action. The importance of bacterial resistance to antibiotics was however also highlighted and it was resolved to shed light on this issue with reference to Switzerland in a complete manner. This task was assigned to three working groups covering the fields of “Human Medicine”, “Veterinary Medicine” and “Technology and Foodstuffs”. The activity of these expert committees was steered and monitored by a core team comprising the following members: Dr. C. Steffen, FAM Director (Chairman until June 1998), Dr. U. Klemm, Deputy Director of the BAG (Chairman as from June 1998), Dr. P. Heimann of BAG (Minutes), Dr. A. Baumgartner of BAG, Prof. Dr. Morel, acting Director of BLW, Dr. A.-F. Piguet, Deputy Director of BVET, Prof. Dr. J.-C. Piffaretti of ICB Lugano, Dr. P.-A. Raeber, BAG Department Head, Dr. H. Schwab, BAG Department Head. By the end of 1998 the individual working groups had completed and documented their investigations and laboratory work to a degree which made this draft report possible. It provides an overview of the overall situation of resistance and in particular, its proportions in Switzerland. The problems relating to vancomycin-resistant enterococci in foodstuffs are also extensively illustrated. The available data highlights the gaps in research that exist and the need for preventative action with regard to antibiotic resistance in Switzerland.
Overview of current global and national resistances

Ever since antibiotics were first administered in human medicine, experience has shown that within a few years after the introduction of a new class of substances, organisms which had developed a resistance were found, making treatment increasingly ineffective. The increase in the resistant strains that has been observed is a consequence of the selective pressure exerted on bacteria by antibiotics, which is at its strongest in hospital environments. The greatest problem is caused by multi-resistant organisms. Increasing resistance, accompanied by a dearth of new or further developments of antibiotic substances, is a serious problem.

Generally speaking, lower proportions of resistant strains are found in highly developed countries than in less developed countries. In Europe, the proportions of multi-resistant strains of *Staphylococcus aureus* are higher in the southern part of the continent than in the north. Many studies have indicated that the use of antibiotics in human medicine is the most important risk factor for the development of resistance. For most pathogens, a close relationship between dose and effect can be demonstrated. The greatest differences in sensitivity of pneumococci (*Streptococcus pneumoniae*) to penicillin between the various European countries are closely correlated to the consumption of antibiotics in these countries, but also to treatment compliance.

Compared globally, in Switzerland the situation is relatively favourable. The numbers of multi-resistant *S. aurens* and resistant pneumococci are among the lowest observed in Europe. Concerning other important pathogens, some of which demonstrate a higher resistance, it must be pointed out that a large proportion of these or even most of these were contracted whilst travelling outside Europe (above all *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., gonococci). The most worrying problem now in Switzerland beyond hospital medicine is the decreasing sensitivity of various types of bacteria to fluoroquinolones, as these are the medicines of first choice for treating various diseases.
The use of antibiotics in the rearing of productive animals (therapeutic, prophylactic, performance-enhancing) also leads to the selection of resistant bacteria. Here, some of the same substance classes (glycopeptides, fluoroquinolones) found in human medicine are used. There is no doubt that the resistance pattern in human medicine is influenced by this.

It is increasingly acknowledged that the, in some cases, drastic increase in resistant organisms observed in many countries is due to the improper use of antibiotics. The best way to lower the selection pressure exerted on bacteria by antibiotics is to cut down their use (in veterinary medicine the ban on antimicrobial performance-stimulators was a step in this direction). The best scope for improvements lies in prescription practice. The spread of nosocomial pathogens can be stopped primarily by measures in the field of hygiene. Alongside these immediate steps, the risks relating to several unanswered questions still need to be investigated, in order to permit the targeted use of antibiotics to continue.
The situation in food and technology

Facts

• The entry of resistant bacterial into foodstuffs has been increasingly lowered since the introduction in 1995 of the compulsory systems for good manufacturing practices and food safety.

• For foodstuffs produced in open systems (e.g. cheese), pasteurisation is not a safe method for eliminating enterococci.

• Vancomycin-resistant enterococci are found very seldom in ready-to-eat foods (<1%). The increase of these bacterial strains in human medicine does not appear to have been caused by the consumption of foods.

• The antibiotic content of ordinary milk does not constitute a problem in Switzerland. In 1997 only 0.04% of the over 500,000 samples tested reacted positively to the inhibitor test.

• With reference to mastitis pathogens in cattle, there was no worsening of resistance between 1980 and 1992. Indeed, as far as staphylococci is concerned, a decrease in resistance to penicillin was even found.

• Starter cultures from FAM and similar international distributors are being tested for resistance to antibiotics and do not pose any problems.

• Technological approaches for reducing the enterococcus content in hard cheeses are available.

• Ampicillin-resistance marker genes in genetically modified crop plants have no significance in terms of the spread of resistance.

• Klebsiellas and *E. coli* strains found in ready-to-eat foods are markedly less frequently resistant than clinically isolated strains of the same bacterial types.

Further work and need for action

• The role of foodstuffs in the transmission of antibiotic resistance to human beings must be clarified in detail, and quantified.

• Screening of ready-to-eat foods for vancomycin-resistant enterococci should be continued in order to enable even better probability forecasts to be made.
• Monitoring of ready-to-eat foods for the occurrence of resistant indicator organisms should be introduced.
• In future, the manufacturers of probiotic products must be required to prove that the active organisms have no resistances, which are not naturally intrinsic
• The use of natamycin for the surface treatment of cheese needs to be further researched in the light of the resistance issue.

Conclusions
Ready-to-eat foods may contain bacterial flora by way of organisms that are necessary for technological purposes (starter cultures, probiotics), saprophytic bacteria from the environment, as well as pathogenic agents. The occurrence of the latter entails a direct health risk for human beings. The risk is even higher when these pathogens are of a multi-resistant type (e.g. *Salmonella typhimurium* DT104). Limiting the risk that these pathogens entail is implemented by means of legally-binding food safety systems for food manufacturers (Hazard Analysis Critical Control Point-System). Some types of saprophytic organisms that can be found in foodstuffs – enterococci, *E. coli* and klebsiellas, for example - can cause diseases (e.g. urinogenital infections). The presence of the bacteria referred to above in foodstuffs is however quite harmless, since they occur naturally in large numbers in the intestines of human beings and animals. In addition, some enquiries have shown that, for example, enterococci with transmissible vancomycin resistance, which were considered critical, occur only extremely infrequently in ready-to-eat foods, including cheese. The question concerning the extent to which foodstuffs contribute towards the spread of resistance genes in nature is, however, justified. In view of the complex ecology of resistance, it is hardly likely that a conclusive answer will be found to this question. It must however be assumed that ready-to-eat foods play only a marginal role. In this respect it has been shown that *E. coli* and klebsiellas in foodstuffs are markedly less frequently resistant than clinically isolated strains of the same type of microorganism, which indicates that different "cycles" are involved. Other facts indicate that the main cause of the resistance problems lies in the field of medicine. Several resistant pathogens that are not related to foodstuffs cause serious problems (e.g. *M. tuberculosis*). All this, however, does not exclude the need to prevent
resistant bacteria from entering foodstuffs to the greatest possible extent. In this respect, it is important that starter cultures should have no non-intrinsic resistances. This is guaranteed in Switzerland. The same requirement must also be applied to probiotically active bacteria cultures. Furthermore, the introduction of unnecessary bacteria into foodstuffs must be minimised generally. The means of choice for doing this are the methods underlying good manufacturing practices and personal hygiene, which foodstuff manufacturers are obliged to comply with since 1995. Lastly, the use of antibiotics in foodstuff production should only be permitted when no alternative procedures are available and following reliable risk assessments. Applying the measures indicate above in the field of foodstuffs will ensure a sufficient contribution towards decreasing the spread of resistance properties in bacteria.
The situation in veterinary medicine

The use of antibiotics in veterinary medicine and in animal production has now led to certain fears among the public at large. It is obvious that using antibiotics for any purpose (medical, veterinary or phytosanitary) brings selection pressures to bear on the bacteria concerned and leads, therefore, to a growing problem of resistance to antibiotics and in the long term, to a threat.

Recent scientific papers have demonstrated the presence of resistance-carrying bacteria in certain diary and meat products, and suggest that the antibiotics used in animal food or for veterinary treatments could be the underlying cause.

In Switzerland, the ban on using antibiotics in animal food (as antimicrobial growth stimulants) came into force on 1\(^{st}\) January 1999, with a provisional deadline extending until 30\(^{th}\) June 1999. Its purpose is to decrease the use of antibiotics in animal breeding. This ban, contained in the new law on agriculture (PA 2002), entails stricter regulation of the use of antibiotics in veterinary medicine and the obligation to keep a record of the treatments administered to productive animals. Indeed, keeping a « treatment book » does make it possible to monitor better and improve the health of these animals and avoid the abuse of antibiotics, thus contributing towards bringing the problem of resistance towards these substances under control.

A large-scale information campaign targeting all the parties concerned has been prepared jointly with the Swiss Federal Agricultural Department, the cantonal veterinary authorities, the associations of Swiss veterinary surgeons, the agency for rural popularisation and the Swiss "Union des Paysans" (Farmers' Union). The information campaign is due to start in January 1999. Every livestock owner will receive a loose-leaf file containing specimen forms and all the explanations needed for keeping the treatment book.

Other steps are also envisaged for the years to come. The setting up of a system for monitoring resistance to antibiotics in veterinary medicine should make it possible to follow up the situation on a regular basis. Co-ordination of this programme with the human medicine programme and the programmes implemented in other countries is
also planned. Several working groups are currently drafting a programme of long-
term measures concerning the steps to be taken with reference to the problems con-
cerning the health, production, breeding, keeping and management of animals. The 
aim of these measures is to lower the general use of antibiotics in animal production 
without resorting to other substances to make up for the loss of beneficial effects.

In the field of training, it is planned to include the subject in courses provided by agri-
cultural schools. On its part, the Association of Swiss Veterinary Surgeons organises 
in-service training of its members and runs local courses ("On the proper use of 
medicines " ) that will place an emphasis on antibiotics and resistance to them.
The situation in human medicine

The progressive resistance to antibiotics is the result, in the first place, of the selec-
tion pressure caused by their use in medicine. The transference of resistance of
animal origin into human ecology has been demonstrated, but not studied in depth. It
is a matter of preventing the transmission of resistance, whether of human, foodstuff
or animal origin.

Medical monitoring is incomplete and covers a limited number of community or hos-
pital organisms. National reference laboratories contribute towards this monitoring
activity. The shortcomings that have been identified and reported include the need to
broaden the range and the possible ways of intervention, the absence of systematic
monitoring in hospital practice, the insufficiency of rapid microbiological diagnostic
tests that would make it possible to avoid "blind" treatment, the lack of data on ac-
ceptance and compliance in out-patient treatment, the lack of knowledge on the
overall consumption of antibiotics in Switzerland, the absence of human risk analysis
based on the consumption of antibiotics by animals, the lack of knowledge concern-
ing the importance of pseudo-parasitic organisms and the lack of new families of an-
tibiotics over the last quarter of a century.

The European conference held in Copenhagen on the 9th and 10th September 1988
on ‘The Microbial Threat’ drafted a list of recommendations known as the ‘The Co-
penhagen Recommendations’. To the same end, three sets of measures must be
undertaken in order to control any increase in resistance to antimicrobials in Swit-
zerland.

1. The monitoring possibilities must be stepped up by means of the ruling on the
revised declaration that comes into force on 1st March 1999 ; the information from
the national reference centres must be completed; our country must participate in
the existing international monitoring programmes (WHO, EU) ; arrangements
must be made for chemists and manufacturers of medicines to take part in the
monitoring of antibiotics; prescribing physicians, distributors and consumers of
antibiotics must be better informed with a view to increasing their awareness of
the problems of resistance and instructing them accordingly.
2. The monitoring of hospital organisms must be stepped up in the context of the prevention of nosocomial infections, in a lasting manner and in the quality assurance framework; recommendations must be published (Swiss-NOSO), competent hospital committees must be set up; the correct use of antibiotics and protection of the most important ones must be encouraged.

3. A national research programme must be set up under the auspices of the Swiss Microbiology Society. This multidisciplinary programme proposes: to achieve a complete overview of resistance in all the sectors concerned, to establish the extent of mobility of resistant bacteria or resistance genes, and to stimulate studies on the resistance of bacteria for the purpose of helping to develop new antibiotics.
Proposal for a national research project

Following the discussions which took place in Switzerland on the problem of resistance to antibiotics and the involvement of certain foodstuffs in its propagation, a Promoting Committee was set up which proposed an NRP (National Research Project) with the title "Resistance to Antibiotics". Indeed, it seemed that this was the only way in which it would be possible to study this problem in a complete manner considering all the sectors concerned (man, the animal world, agriculture, the environment, foodstuffs), and to fill the gaps that currently exist in Switzerland in this field.

The following members comprise the Promoting Committee: Professors J. C. Piffaretti (Committee Chairman, Istituto Cantonale Batteriosierologico, Lugano), R. Auckenthaler (Hôpital Cantonal Universitaire, Geneva), Patrick Francioli (Centre Hospitalier Universitaire Vaudois, Lausanne), J. Frey (Institut für Veterinär-Bakteriologie, Bern), F. Kayser (Institut für Medizinische Mikrobiologie, Zurich), J. Nicolet (Institut für Veterinär-Bakteriologie, Bern), M. Teuber (Institut für Lebensmittelwissenschaften, Zurich), F. Untermann (Institut für Lebensmittelsicherheit und – Hygiene, Zurich).

The NRP on "Resistance to Antibiotics ", as formulated by the Promoting Committee, proposes: i) to acquire rapidly an overall view of resistance in Switzerland in all the sectors concerned (human and animal populations, agriculture, foodstuffs, the environment) and to assist in setting up a continuous dynamic system for monitoring resistance; ii) to determine the extent of mobility of resistant bacteria or resistance genes, in particular in the transmission chain from animals to foodstuffs, and then to human beings; iii) to stimulate molecular studies on bacterial resistance in order to help develop new antibiotic molecules. The results obtained, thanks to the research activities conducted in the framework of this NRP, will have an impact in the following fields: public health, agronomy, food-processing technology, basic research on bacteria, the pharmaceutical industry and the economy.

In order to accomplish this multi-disciplinary programme, the amount of 12 million francs has been requested for a period of 5 years.
The project is supported by the Société Suisse de Microbiologie (Swiss Microbiology Society), the Société Suisse d'Infectiologie (Swiss Infectivology Society), the Office fédéral de la santé publique (Federal Public Health Department), the Office vétérinaire fédéral (Federal Veterinary Department) and the Office fédéral des affaires économiques extérieures (Federal Department for External Economic Affairs).

Early in 1998, the proposal was submitted to the service of the Office fédéral de l’éducation et de la science (Federal Department for Education and Science) which has the remit of setting up new NRPs. The proposal was considered with great interest. It was subsequently discussed by the group responsible for the 8th series of NRPs, and here again it was very favourably received. The proposal is currently in the stage of consultation between the Federal Administration, the Swiss Science Council and the FNSRS and, according to preliminary opinions expressed, it should be submitted to the Federal Council for a final decision in the summer of 1999.
Overall picture: facts, knowledge gaps, research requirement and necessary actions

The field of foodstuffs and technology

Vancomycin-resistant enterococci

- Enterococci are found in many ready-to-eat foods. The bacterial counts vary considerably and are in the region of $10 - 10^7$ organisms per gram. The highest bacterial counts are found in soft cheeses. The enterococci content of hard cheeses made from ordinary milk is generally low.

- In the manufacture of hard cheeses, the enterococci content can be influenced and minimised in a targeted manner using technical means. Should it be found necessary in future, the existing possibilities could be further developed. It must be mentioned here, however, that enterococci also have useful properties from a technological viewpoint, and are currently used in several products as starter cultures, flavourings or probiotics.

- Tests on ready-to-eat foods carried out by the Bundesamt für Gesundheit (Federal Health Department), the Kantonalen Laboratoriums (Cantonal Laboratory) in Lugano, the Forschungsanstalt für Milchwirtschaft (Dairy Farming Research Institute) and the University of Zurich indicate that vancomycin-resistant enterococci are infrequent in ready-to-eat foods (<1%). To date, only one strain of this type been isolated in the very extensive investigations.

Action required: The number of samples of ready-to-eat foods for examination should be enlarged, so that probability forecasts for an occurrence vancomycin-resistant enterococci can be improved!
Elimination of enterococci by pasteurisation

- Investigations by the (Forschungsanstalt für Milchwirtschaft) Diary Farming Research Institute and the Bundesamt für Gesundheit (Federal Health Department) have shown that in open systems (e.g. cheese-making) pasteurising is not a safe method for producing enterococci-free products.

Starter cultures

- The FAM cultures frequently used in Swiss hard cheese production reveal nothing particular in terms of resistance to antibiotics that would indicate the introduction of any measures.

- The large European culture manufacturers are aware of the resistance problem. The bacteria strains in their ranges have either been tested or are undergoing testing. To date, no observations relating to problematical resistance properties have been made.

**Action required:** So-called intrinsic (natural) resistances have been found in organisms in starter cultures (mainly lactic acid bacteria). It is accepted that this type of resistance is not transferable. In this respect, however, there are still gaps in our knowledge that must be filled by basic research. In particular, more detailed knowledge about the mechanisms of intrinsic resistance would be useful.

Antibiotic residues in milk

- At the moment the antibiotic content of ordinary milk does not present any food-related hygiene problem in Switzerland. Additional measures over and above the existing control mechanisms are not required.

Antibiotic resistance of mastitis pathogens

- In spite of the extensive therapeutic and prophylactic use of antibiotics in fighting udder inflammations in dairy cattle, the resistance of the prime mastitis pathogens to the antibiotics used in veterinary medicine did not worsen in the years
from 1980 to 1992. There was even found to be a sharp drop in the resistance of Staphylococci to beta-lactam antibiotics (penicillin).

Resistances of *E. coli* and Klebsiella – Strains found in clinical practice and in foods

- *E. coli* and Klebsiellas in ready-to-eat foods are significantly less frequently antibiotic-resistant than clinically isolated strains. This is an indication that resistant strains circulate first and foremost in the medical environment and from one human being to another, rather than via foodstuffs.

**Action required:** The investigations should be continued and in particular the resistances enterococci originating from foodstuffs should be compared with those originating from clinical practice.

Use of antibiotics in foodstuff production

**Action required:** Certain cheeses are surface-treated with the antibiotic "natamycin" in order to prevent mould from growing on them. This controversial technology has not been authorised in Switzerland yet. It would therefore be desirable to clarify in depth any possible adverse effects stemming from the use of "natamycin".

Probiotics

**Action required:** A growing number of foodstuffs containing probiotically-active organisms are reaching the market. In future, when official approval for these products is obtained, the manufacturers must be required to produce resistance data for the micro-organisms employed.

Resistance genes as markers in genetically modified organisms

- Certain genetically modified commercial crops contain the ampicillin-resistance gene as a marker. These genes have no effect on the resistance status of bacterial pathogens. Moreover, future plant varieties will, moreover, contain different marker systems.
The field of veterinary medicine

Antimicrobial performance stimulants

- The use of antimicrobial performance stimulants (antibiotic substances that are not used for therapeutic purposes) has been banned as from 1st January 1999.

**Action required:** This ban was a political measure from the viewpoint of preventive protection of consumers. Whether the chosen procedure was really justified should be investigated in greater depth. The appropriate question could be included in a resistance monitoring programme in this area. Among other things, it should be clarified whether larger quantities of antibiotics are being administered as therapeutic doses as a consequence of the ban.

Treatment book

- The obligation to maintain a treatment book recording the administration of antibiotics has been introduced.

**Action required:** Binding specifications must exist as to how checks are to take place and what safeguards are to be used to ensure their effectiveness. The canton veterinary surgeons are currently working on the appropriate concepts.

The state of knowledge concerning resistances of pathogens important in veterinary medicine

- Data are available, however they have not been collected systematically.

**Action required:** Systematic resistance monitoring should be established. This system should be harmonised with the corresponding structures in human medicine.
State of knowledge concerning the quantities of antibiotics used.

- Evaluations concerning the quantities of antibiotics introduced do exist. There are, however, gaps in the available data and it is not sufficiently differentiated. The same applies for human medicine!

**Action required:** A study providing information concerning the quantities of antibiotic substances used in human and in veterinary medicine should be initiated. Experiences abroad indicate that obtaining the relevant data is not a simple matter. In spite of this, an attempt in this respect must be started. Attempts should also be made to shed light on black market practices in farming.

Spectrum of used antibiotics

- For therapeutic purposes the same substances which are used in human medicine, are administered.

**Action required:** The question arises as to whether certain medicines should only be restricted to human medicine. This discussion should be continued in further depth. The appropriate decisions should be preceded by risk assessments. These, in turn, must be preceded by meaningful resistance monitoring.

Good practices in antibiotic use

- The rules of good practices for using antibiotics are known. There are however no legal regulations whatsoever for enforcing these. The same problem also applies to human medicine.

**Action required:** With regard to the global resistance problem, it should be discussed and investigated whether certain rules concerning the use of antibiotics need be established compulsorily by law.
Probiotics

*Action required:* Organisms with a probiotic effect are increasingly being used with productive animals. The same requirements relating to antibiotic resistance of starter cultures in the food industry should be applied to the antibiotic resistance of these micro-organisms.
The field of human medicine

Resistances of clinically significant organisms

- A relatively large quantity of data, originating from a variety of sources, is available. The real problem organisms as far as resistance is concerned, are known. The greatest attention must be paid to resistant pathogens from the hospital environment (hospital organisms).

- With regard to resistance, Switzerland occupies a good position by international comparison. The status in certain developing countries and in countries in the southern hemisphere is worse (North-South gradient).

**Action required:** Systematic resistance monitoring should be established. The field of out-patient medicine should also be covered by this activity. This resistance monitoring must, as already stressed, be co-ordinated with the corresponding activities in veterinary medicine.

Volumes of antibiotics used / selection of medicines for therapeutic use / good practices in antibiotic use

**Action required:** The considerations expressed for the field of veterinary medicine apply to a great extent also to human medicine, and both to out-patient care and to hospitals.

**Economic considerations**

Certain measures for limiting resistance called for in this report, which, in the main, have been known for some time, may meet with resistance when put into practice. Legal regulation of good practices for antibiotic use, for instance, would impinge on the freedom of practising physicians and a more limited use of antibiotics would affect the interests of the pharmaceutical industry. For these reasons, it is necessary to conduct cost-benefit analyses with reference to various issues. The following aspects should be clarified in greater depth in this regard:
• Evaluation of costs incurred by health authorities due to the unnecessary or improper administration of antibiotics.

• Evaluation of costs due to pathogens that can no longer, or only with difficulty, be treated with antibiotics.

• Evaluation of the extent to which the known preventive measures contribute towards limiting the resistance problem. Ecological considerations are partially necessary here.
Summary

The starting point of this report was the question as to whether vancomycin-resistant enterococci in foodstuffs represented a health hazard for human beings. The evaluation of facts already to hand and the results of Swiss experimental studies have led to the following assessment of the situation:

With the exception of sterile products, ready-to-eat foods contain a multitude of bacteria in different quantities. With reference to the bacteria in food, these may be intentionally added organisms (starter cultures, probiotics, flavourings), saprophytic organisms from the environment, or pathogens. With reference to health risks for humans, the bacteria categories mentioned above can be evaluated as follows:

Starter cultures contain micro-organisms that are completely harmless from a health point of view. The same applies to probiotically active cultures. It is true that some organisms in this field are in a position to produce infections in human beings (e.g. Lactobacillus rhamnosus, Lactobacillus acidophilus), however these events are extremely rare and necessitate certain pre-conditions in the patients, such as immunosuppression or underlying diseases. It should be mentioned here that L. rhamnosus is resistant to vancomycin without exception. This resistance is, however, intrinsic (natural, and not transferable) and is not to be compared with the transferable vancomycin-resistance of enterococci.

Foodstuffs may also contain pathogens that can cause infections, and toxin-forming bacteria. If infective agents, with an alimentary transmission route, are multi-resistant or resistant to the antibiotics of choice, their risk potential is increased (e.g. Salmonella Typhimurium DT 104). Several regulations have been passed however with the objective of preventing pathogenic and toxigenic organisms from reaching food, as far as is possible. Thus, foodstuff manufacturers must work in accordance with the principles of good manufacturing practices, set up food safety systems and train their personnel in personal hygiene. Thanks to tools such as inspections and analyses for control purposes, a properly structured food control system ensures that legal requirements are complied with and put into practice. All sorts of regulations and con-
trolling authorities also exist in the agricultural and veterinary medicine fields that strives to make food of vegetable origin and above all of animal origin as free as possible from harmful micro-organisms. Considered as a whole, Switzerland has a food control system, the standards of which are leading edge by international comparison. In our country, therefore, the risk of falling ill with salmonellosis or with campylobacteriosis is significantly lower than when travelling abroad.

Lastly, saprophytic bacteria are present in nearly all foods in different compositions and quantities. Most of these are completely harmless and are significant only in that they are capable of making food perish. Some of these, however, such as enterococci, *E. coli* and klebsiellas, for example, can also produce infections in human beings, above all of the urinogenital system. Since the organisms referred to, however, are a part of normal intestinal flora, and occur there in large quantities, foodstuffs are totally insignificant as sources of infection. The question must be asked, however, whether opportunistic pathogenic bacteria in foodstuffs entail a risk for human beings if they are antibiotic-resistant. In a hospital environment, a certain direct health risk could exist for foodstuffs contaminated with multi-resistant, opportunistic pathogenic organisms. There are several papers on this subject in the specialist literature. Of course, multi-resistant or omni-resistant strains can also reach foods which are transferred outside the hospital environment. It should, however, be assumed that this is not frequently the case. Some enquiries have shown that *Klebsiella* strains from foodstuffs have far less multiple resistances than strains of the same bacteria genus isolated in clinical practice. The corresponding comparisons for enterococci are still to be received. It may, however, be assumed that they will give rise to similar findings. The available results indicate that human beings themselves are far more significant as reservoirs of resistance than foodstuffs. Foods, however, undoubtedly do contribute towards spreading resistance genes in nature. It is not possible to say clearly how great this effect is in the framework of the whole process. It would be difficult to make a quantitative statement on this subject, in view of the extremely complex ecology of resistance. In a study by the Bundesamt für Veterinärwesen (Federal Veterinary Department) (P. Mani), an attempt is being made to develop mathematical approaches for evaluating risk. With reference to vancomycin-resistant enterococci, that are considered a significant medical problem and were the main
reason for drafting this report, it can however be stressed that they only occurred extremely infrequently in ready-to-eat foods. In the light of these facts, but also on consideration of the fact that various pathogens which can be problematical in terms of resistance (tuberculosis pathogens, gonococci, pneumococci) have no links with food, it can be concluded that bacterial resistance to antibiotics is not a problem stemming from food hygiene. This opinion was held by the Swiss Delegation on the occasion of the last session of the Codex Alimentarius Hygiene Committee and was not seriously disputed. There is hardly any doubt that, with reference to selection and transference of resistance properties, human beings and animals rank highest, together with the hospital environment. For this reason it would be natural to institute preventive measures in this field as a priority. This does not exclude, however, a reduction in the number of resistant organisms introduced into foods. A sufficient contribution in this respect will, however, be provided by good manufacturing practices and personal hygiene, which foodstuff manufacturers have been under an obligation to comply with since 1995. Lastly, it must also be ensured that technologically employed bacteria or probiotics show no resistance properties, that are not of a transferable nature.

Due to the central importance which resistance has assumed in medicine, this report would have been incomplete, had it concentrated only on food. For this reason an overall picture was drafted with the title "Overview of global and national resistance", which includes two chapters in which a situation assessment in the areas of human and veterinary medicine is undertaken. These contributions have brought certain recent nightmarish scenarios, conveyed in the media, into context. Thus, there is no therapeutic emergency to report in veterinary medicine. With reference to S. aureus, an important bovine mastitis pathogen, it has even been possible, in recent years, to ascertain an improvement in terms of penicillin-resistance. Methicillin-resistant S.aureus has not been isolated as yet in Swiss veterinary diagnostics. As far as human medicine is concerned, the problems relate first and foremost to some nosocomial pathogens (multi-resistant S.aurens, enterococci, gram-negative bacteria). In addition, there are various organisms that are acquired outside the hospital environment (community acquired) for which an increase in the frequency of resistance to
important medicines has been recorded. It must also be stressed that the occurrence of resistant strains is characterised by a marked north/south gradient as well as an industrialised / developing country gradient. In this respect, Switzerland is one of the countries with the lowest occurrence of resistant strains. In this country, 1.8% of pneumococci are resistant to penicillin, but in some other countries the corresponding value even reaches even 40%. In the U.S.A. 52% of the strains of enterococci isolated in clinical practice are vancomycin resistant, while in this country on the other hand, the corresponding rate is 4.2%. *S. aureus* isolated from hospital environments is up to >30% methicillin-resistant in certain southern countries. The corresponding rate for our country is only 1.8%. In strains isolated from the University Hospital in Geneva, however, a rate of 19% was ascertained. This shows on the one hand that resistant strains often occur locally and do not spread evenly. On the other hand it must be assumed that due to the extremely large number of people from every part of the world who work in Geneva, resistant bacteria strains are imported. This brings up the international dimension of the resistance problem and it is pointed out that certain aspects must be discussed from this point of view. Although Switzerland now has a good international ranking with reference to the antibiotic resistance in antibiotics, several measures of a prophylactic nature in the field of medicine, and thanks to which further improvements could be achieved, have been suggested. This also makes sense because the problem of antibiotic resistance in bacteria is taking on increasing global dimensions and will not solve itself. The introduction of resistance monitoring has been identified as imperative for future activities. Sufficient epidemiological knowledge is a fundamental prerequisite for clarifying the action that is required and the introduction of whatever measures are needed. A monitoring programme would also very probably make it possible to show whether the ban on anti-microbial growth stimulants, which was declared by way of a preventive measure, really could produce the hoped-for effects. Filling the knowledge gaps that have been highlighted in this report and listed above entails additional financial and human resources. Then, there is the further question as to which organisational framework this would assume in practice. The most sensible thing would undoubtedly be for the whole range of activities found to be necessary, to be developed in the framework of the planned "National Research Project on
Resistance to Antibiotics”. This project, a description of which is provided in an appendix to this report, already covers some aspects of the required action which have been listed here (resistance monitoring). In addition, the emphasis of planned activities lies primarily in the field of basic research into resistance mechanisms. In this report, however, it has been shown that several gaps also need to be filled also in the field of applied research. For example, a better quantification of existing risks, uncovering the volumes of antibiotic used, etc. If the planned national research proposal is accepted politically and is able to be implemented, then the questions raised in this report as important should be fully addressed and investigated.

Federal Health Department

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