

## Joint antibiotics and resistance action plan

### SUMMARY

In international terms, Denmark has relatively low consumption of antibiotics and a low rate of development of resistance to antibiotics. This is due, in part, to close cooperation between relevant authorities and an ability and willingness to respond to new knowledge and new challenges.

However, if this position is to be maintained there is a need for a continuous and persistent effort. Uncritical use of antibiotics may mean that several antibiotics become ineffective, and antibiotic-resistant bacteria pose a threat to human health.

It must be acknowledged that we face challenges in the area of antibiotics. The consumption of antibiotics is rising, and increasing problems with resistance in certain areas are becoming apparent at the same time. In particular, complex and very extensive problems with resistance have arisen with regard to MRSA and ESBL (extended spectrum beta-lactamase producing) bacteria and antibiotic-associated diarrhoea caused by *Clostridium difficile*. These complex resistance problems have primarily been observed in other countries, including in Europe, but have now also started to appear in Denmark.

It must be acknowledged at the same time that problems with resistance and treatment failure are often due to increased travel and food imports. Resistant bacteria do not respect national boundaries, and a greater European and international effort is therefore needed. Denmark must use its favourable starting position in this regard to influence other countries. It must be ensured at the same time that our strategies and surveillance in relation to minimising the importing of resistant bacteria are up-to-date and continuously strengthened.

There is a particular challenge in livestock production in relation to large increases in consumption of antibiotics, particularly in pig production. More routine consumption of antibiotics cannot be ruled out with the economic crisis in livestock production. This challenge thus has to be addressed.

The Ministry of Health and the Ministry of Food have therefore taken the initiative to draw up a joint antibiotics and resistance action plan, which is to safeguard Denmark's favourable position in the area of antibiotics into the future. The purpose of the plan is to ensure that Denmark maintains the effectiveness of antibiotics for the treatment of infections in humans. At the same time it must be possible to continue to treat infections in livestock.

The plan is to ensure an organisational and decision-making structure that can respond quickly and effectively to a new development in the area, and that at the same time ensures effective communication of risk based on the latest research and knowledge.

The following initiatives have specially been or will be taken:

- National cross-sectoral antibiotics council
- New research projects focused on cross-sectoral relationships
- Strengthened surveillance of resistance
- Revision of the reporting system for infectious diseases in humans
- Strengthened coordination in relation to MRSA
- Adoption of national principles for use of antibiotics
- Strengthened advice and incentive structure in herds
- "Yellow card" scheme in pig herds with high consumption of antibiotics
- Increased focus on reporting of resistance
- Increased participation in international cooperation

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## **1. INTRODUCTION**

### **1.1. SAFEGUARDING OF THE FAVOURABLE DANISH POSITION**

Treatment with antibiotics may, in many situations, be crucial to human and animal health.

In international terms, Denmark has relatively low consumption of antibiotics and incidence of resistance. The health authorities and food authorities have taken this joint initiative for a Danish policy on antibiotics to ensure that the favourable Danish position of rational consumption of antibiotics and low incidence of resistance is maintained.

Antibiotic-resistant bacteria may be a significant threat to human health, and uncritical use of antibiotics may lead to several antibiotics becoming ineffective. As antibiotic resistance can be transferred between bacteria, regardless of whether

the bacteria are pathogenic or not, increased incidence of resistance in all kinds of bacteria may, in principle, pose a problem.

Initiatives have regularly been taken in Denmark regarding the development of resistance when a need to do so has been ascertained. This applies in both veterinary and human medicine.

In particular, the health authorities and food authorities in 1995 set up the DANMAP cooperation (Danish integrated ANti-microbial resistance Monitoring and reseArch Programme), which ensures good surveillance of the consumption of antibiotics and the development of resistance in Denmark. This helps to ensure that Denmark knows the incidence of resistance.

Both the health authorities and the food authorities have regularly responded to the results contained in the DANMAP reports, and in several areas Denmark has led the way in international contexts.

This is the case, for example, with regard to the use of antibiotic growth promoters in animal feeds, where Denmark had a relatively high level of consumption in the 1990s. This was problematic as it was demonstrated that consumption was leading to the development and accumulation of resistant bacteria with transmission from animals to humans. On the basis of data from DANMAP and the discussion that followed, a gradual scaling-down of the use of antibiotic growth promoters took place in cooperation with the food industry, and from 2000 a voluntary halt to the use of antibiotic growth promoters was established by agreement with relevant agricultural organisations. Denmark has since worked towards introducing a ban on the use of antibiotic growth promoters at EU level, which has proved successful. A ban on using antibiotic growth promoters in the whole of the EU was introduced on the initiative of Denmark from 1 January 2006.

In the veterinary area, the food authorities have been working on a multi-annual strategy to optimise antibiotic consumption and reduce the development of antibiotic resistance among animals in Denmark. The preparation of treatment guidelines and supervision of veterinary surgeons in large-animal practice have ensured that the consumption of critically important antibiotics for the treatment of humans has fallen sharply in recent years. This has led to the related development of resistance in veterinary medicine having been limited. New figures from the EFSA (European Food Safety Authority) show that the level of resistance to critically important antibiotics for the treatment of humans is low in Denmark: cephalosporins, fluoroquinolones and macrolides. Resistance to these substances is low in both *Salmonella* and *Campylobacter* bacteria, which are the most significant types of zoonosis (communication of infection between animals and humans).

Measures have also been taken regularly in human medicine to retain both rational consumption of antibiotics and low incidence of resistance. The Danish National Board of Health, in the light of increasing incidence of MRSA (multiresistant staphylococci/methicillin-resistant *Staphylococcus aureus*) in humans, issued guidance on the prevention and spread of MRSA in 2006. The DANMAP reports from 2007 onwards show that there has been a substantial decline in the incidence of MRSA in hospitals and nursing homes, emphasising that a targeted effort is both

necessary and effective. At the same time, however, increasing incidence of MRSA has been observed outside hospitals and nursing homes.

In 2009, intensified surveillance of the bacterium *Clostridium difficile* 027 was launched when a major outbreak of this bacterium, which is causing significant problems in several European countries, was identified for the first time.

In the same year, the new DANCARD centre (Centre for Antibiotic Research and Development) at Statens Serum Institut received a six-year grant of DKK 31 million from the Danish Agency for Science, Technology and Innovation, Programme Committee for Health, Foods and Welfare.

The Centre's research activities will focus on developing new activities and on increasing the effectiveness of existing antibiotics. Research will be conducted into ways of bypassing resistance, for instance by inhibiting the resistance mechanisms in bacteria. In addition, new methods will be developed to study the efficacy of antibiotics, with a view to optimising the use of antibiotics in the individual patient.

DANCARD is an interdisciplinary research cooperation between 11 research institutions and companies including the Copenhagen University, Aalborg University, Roskilde University, DTU, Novozymes, DHI and Statens Serum Institut.

Finally, in 2010, the Danish Government established an Antibiotics Council with the aim of contributing to promoting appropriate use of antibiotics in Denmark, including ensuring that antibiotics can continue to be used to treat infections. This council is an interdisciplinary, coordinating body and contains representatives of relevant bodies in the areas of human medicine (including regionally) and veterinary medicine. The council has a key role in the implementation of the joint antibiotics and resistance action plan.

## **1.2. CHALLENGES FOR THE DANISH SITUATION**

Denmark has a favourable starting position in order to retain low incidence of antibiotic resistance, as explained in section 1.1. It is, however, crucial that the effort is continuously adapted to relevant developments, and that as far as possible it is proactive. A number of trends are evident at present that make it appropriate to describe the future effort and structure of a joint antibiotics and resistance action plan for both the human and veterinary areas.

There is, in general, increasing activity in the health sector and livestock production, which naturally leads to increasing consumption of antibiotics and consequent antibiotic resistance.

In veterinary medicine in particular, however, there has for a number of years, and especially in 2009, been a sharp rise in the consumption of antibiotics, which cannot be explained solely by increasing production. This consumption is related in particular to pig production and the use of tetracyclines. Tetracyclines are not critically important for treatment of humans, but continuous and uncritical use should be limited. This is related to Denmark having a relatively high level of resistance to tetracyclines. There are also fears of more routine consumption of

antibiotics in the light of the economic crisis in livestock production, and this challenge will therefore have to be addressed in the future.

Rising consumption of antibiotics in many European countries has led to complex and very extensive problems of resistance. In addition to familiar problems with resistance in food-borne bacteria, salmonella and campylobacter, new problems have also arisen such as MRSA and ESBL (extended spectrum beta-lactamase producing) bacteria and antibiotic-associated diarrhoea caused by the bacterium *Clostridium difficile*. These complex resistance problems have now started to become apparent in Denmark.

Overall, the latest statement from DANMAP shows that the total consumption of antibiotics for humans has fallen. However, there has been increasing consumption in particular of the broad-spectrum antibiotics in the hospital sector and in general practice. This has contributed in the Danish context to increasing incidence of resistance in some areas. Danish outbreaks of the gut bacterium *Clostridium difficile* 027 have been observed in the past year. This bacterium represents a particularly extensive problem abroad, and the aim is to avoid the same trend happening in Denmark through a rapid and targeted effort. Use of the broad-spectrum antibiotics also contributes to a rise in the incidence of ESBL-resistant bacteria. This poses a challenge to human and veterinary treatment options and food safety. Finally it has been noted that MRSA can be transmitted between animals and humans (zoonosis), and this leads to a need for an expanded effort between the areas of human and veterinary medicine.

In addition to national consumption being of significance to the development of resistance, many of the problems that Denmark will face in the future come from abroad as a result of imports of meat and travel activity. There is consequently a need to work in an international context to a far greater extent than previously.

A joint human and veterinary coordinated effort reflects caution at the right time with regard to risk assessment, risk management and risk communication in relevant focal areas.

### **1.3. TERMINOLOGY**

#### *Risk assessment*

Risk assessment means assessing the extent and nature of the risk of resistance. Risk assessment covers the following:

- 1) Surveillance, where the aim is to obtain information that can shed light on current incidence, including changes over time in the risk (resistance) and in relevant risk factors, for example the consumption of antibiotics. Surveillance is characterised by being a systematic collection of relevant data over a long period.
- 2) Research and development, where the aim is to obtain information that may shed light on relevant mechanisms for occurrence, spread and methods for the prevention of resistance. Research is generally managed on a sectoral basis, but also has its own overarching legislation and

management. This action plan focuses primarily on cross-sectoral research.

### *Risk management*

Risk management signifies implementing preventive efforts and outbreak management, which is aimed at bringing down the number of infections with microorganisms resistant to antibiotics. With regard to resistance, measures that optimise consumption of antibiotics and the use of appropriate hygiene precautions are mainly concerned. Risk assessment is essential in enabling risk-management activities to be targeted and adapted.

### *Risk communication*

Risk communication means that the management measures decided upon, as well as the background to them in the risk assessment, are communicated to those who have to implement the measures in practice. The aim is to make it clear to the parties concerned, for example doctors and practising veterinary surgeons, why these measures are being taken, and how they should act for example in order to lower the risk of antibiotic resistance. The likelihood of the risk-management measures working in practice depends to a great extent on effective and targeted risk communication.

## **2. A JOINT ANTIBIOTICS AND RESISTANCE ACTION PLAN**

### **2.1. OBJECTIVES**

The antibiotics and resistance action plan is intended to ensure that Denmark preserves the effectiveness of antibiotics for the treatment of human infections. At the same time, it has to continue to be possible to treat serious infections in livestock.

Continued status as a country of low resistance for Denmark necessitates rational use of antibiotics and known and minimal incidence of antibiotic resistance.

The focus in order to attain rational consumption of antibiotics is on rules or guidelines so that the individual infection is treated with the product that provides the best treatment in consideration of the risk of the development of resistance.

In addition, work is required to strengthen the effort so that relevant hygiene precautions are taken at all levels in Denmark. This must be done to ensure that the risk of infection of people who are already debilitated is minimised. At the same time, measures to protect people who work with livestock against infection should be intensified in relation to bacteria with critical resistance characteristics. This will primarily involve general hygiene rules.

At the same time, there is a need for an increased international focus. Only by creating high international standards and working towards greater international focus in the area can problems relating to the importing of resistance problems be limited. In this connection, priority must be given to work in existing international cooperative frameworks, and there must be an endeavour to ensure that this area gains renewed focus.

A joint antibiotics and resistance action plan thus has to identify areas where there is a need for greater effort to maintain the favourable Danish position. It is important that new problems are addressed promptly, and that they are addressed in such a way that all relevant areas of risk assessment, management and communication are covered. The effort made also has to be covered and coordinated across the fields of human and veterinary medicine. In addition, cooperation and coordination between the human and veterinary sectors have to be enhanced in the areas of risk assessment, risk management and risk communication. This has to be done with a view to ensuring that new problems continue to be addressed with due diligence.

The three elements – risk assessment, risk management and risk communication – thus constitute the basis of a joint national antibiotics and resistance action plan.

A description is first given below of the area of risk assessment, with the focus on surveillance, with an introductory review of the present-day structure, followed by proposals for improvements, after which risk management is discussed, again first with a description of the present-day structure followed by proposals for improvements. Finally risk communication is discussed.

## **2.2. SURVEILLANCE AND RISK ASSESSMENT**

### **2.2.1. The present-day organisational structure in the area of surveillance and risk assessment**

#### *Parties involved in the area*

Statens Serum Institut is the country's central laboratory in human diagnostic analyses and, on behalf of the Danish National Board of Health, undertakes national surveillance of a number of infectious diseases and provides advice to authorities and institutions concerning the Institute's tasks, which are to prevent and control infectious diseases. Statens Serum Institut is responsible for collecting and processing data relating to antibiotic resistance among bacteria isolated in humans in Denmark. These data are contained in the DANMAP report, but are also forwarded directly to the National Board of Health when a trend that causes concern is observed. In addition, Statens Serum Institut is responsible for research in the area of antibiotics. These data are generated by, and primarily collected from, the country's departments of clinical microbiology, which consequently represent a crucial factor in the surveillance of antibiotic resistance.

The Danish Medicines Agency monitors the consumption of antibiotics in a number of forums (including monthly statements, [www.medstat.dk](http://www.medstat.dk) and analyses of consumption). The Danish Medicines Agency continuously monitors the consumption of antibiotics in the primary healthcare sector and the hospital sector. These data are included in the DANMAP report. Detailed statistics are published monthly on consumption, presented for each individual region.

The National Food Institute at DTU is the Danish, EU and World Health Organisation reference laboratory in antibiotic resistance in food-borne and zoonotic bacteria, and DTU (the Technical University of Denmark) undertakes

national surveillance of antibiotic resistance in livestock, as well as providing advice within the Institute's tasks, which are to:

- Promote the production of safe and healthy foods
- Prevent food-related and environment-related diseases in humans
- Maintain laboratory-based food safety preparedness
- Supply training and instruction at a high level

The National Food Institute performs risk assessments for the Danish Veterinary and Food Administration, and is responsible for the collection and processing of data relating to antibiotic resistance among animals and foods in Denmark. These data are included in the DANMAP report. The National Food Institute is also responsible for research in the area of antibiotics.

#### *Cooperation between authorities*

DANMAP (Danish integrated ANti-microbial resistance Monitoring and reseArch Programme) is a formalised cooperation on the surveillance of antibiotic consumption and antibiotic resistance, which the health authorities and food authorities jointly established in 1995.

The surveillance data for DANMAP are produced by Statens Serum Institut, the National Food Institute, the Danish Veterinary and Food Authority Veterinary Institute at DTU, the Danish Veterinary and Food Administration and the Danish Medicines Agency.

Funding is provided by the Ministry of Health and Prevention to Statens Serum Institut for the DANMAP cooperation, while the Ministry of Food's funding goes to the National Food Institute at DTU, the Veterinary Institute at DTU and the Danish Veterinary and Food Administration through the CO2 funds of the agricultural industry.

The objective of the DANMAP programme is to:

- Monitor consumption of antibiotics
- Monitor the incidence of antibiotic-resistant microorganisms in livestock, foods and humans
- Examine the relationship between the consumption of antibiotics for animals and humans and the incidence of antibiotic-resistant microorganisms among bacteria from livestock, foods and humans
- Be responsible for research in the area

The results of DANMAP are published in the individual DANMAP report. The DANMAP report provides an essential basis of data for advice and risk assessment, which the authorities receive from DTU and Statens Serum Institut, in the use of antibiotics and the incidence and significance of antibiotic resistance. Data from the DANMAP cooperation have been of great significance, for instance for the Danish effort on the use of growth promoters in agriculture and for the effort in relation to MRSA.

Data from DANMAP also provides the basis for the reporting by DTU and Statens Serum Institut of surveillance data on antibiotic resistance to the EFSA (European Food Safety Authority) and the ECDC (European Centre for Disease Prevention and Control).

The consumption of antibiotics, primarily human, is also followed in the Forum for the Assessment of Consumption of Medicines. This Forum includes representatives of the Danish Medicines Agency, the Institute for Rational Pharmacotherapy (IRF), the Danish National Board of Health, the regional pharmaceutical consultants and a number of medical associations. The Forum's remit is to assess the consumption of medicines based on specific problems, for example abuse or excessive consumption of a medicine or a group of medicines. The Forum can make recommendations for measures, which the Danish National Board of Health, IRF and the Danish Medicines Agency can put into effect.

In addition, the Danish Medicines Agency runs the ORDIPRAX system, which presents statistics in graph form on prescriptions for medicines in regions and general medical practice. The Danish Medicines Agency also takes part in a working group with the participation of Statens Serum Institut, in which discussions are held on the basis of consumption statements, and work is done on communicating the message. In addition, work takes place on making it possible to prepare the statistical reporting, for instance better use of indication codes.

There is also the DANRES cooperation, which is a loosely based cooperation between representatives of the individual clinical microbiology departments and Statens Serum Institut.

To obtain an overview of the consumption of antibiotics and other medicines for Danish livestock, the Danish Government decided in 1998 that a central register of medicines should be set up, VetStat. All consumption and sale of prescription medicines for livestock is reported by veterinary surgeons, dealers, including pharmacists, and food companies. The objective of VetStat is to minimise the consumption and optimise the use of antibiotics in Danish livestock herds in order to consequently reduce the risk to human health.

VetStat registers the use of prescription medicines for veterinary use, as well as foods containing coccidiostats at herd level. VetStat was primarily established with a view to strengthening knowledge of the correlation between consumption and resistance, and consequently to achieving better opportunities for risk-based advice. VetStat is therefore closely integrated into DTU's surveillance of antibiotic resistance in livestock. In addition, the Danish Veterinary and Food Administration has gained an opportunity to effectively monitor consumption of medicines, both for the individual farm and for the individual veterinary surgeon. The veterinary surgeon has also acquired a good tool for use in advising clients.

The Danish Veterinary and Food Administration continuously extracts data from VetStat and prepares statements of consumption for the individual veterinary surgeon. This is used as a check in the supervision of veterinary surgeons. All veterinary surgeons who work with pigs and cattle are supervised with regard to their consumption and choice of antibiotics. In addition, statements are drawn up

on consumption by herds for other specific checks carried out by the Veterinary Task Force of the Danish Veterinary and Food Administration.

VetStat is organisationally located at the National Veterinary Institute and is funded by the Ministry of Food through the Finance Act. The Danish Medicines Agency forwards information on veterinary sales by the pharmacies to VetStat.

In addition, the authorities take part in international cooperation concerning surveillance and risk assessment. Among other things, Statens Serum Institut takes part in a Scandinavian cooperation, and in a number of cooperations at European level<sup>1</sup>. The Danish Veterinary and Food Administration and the National Food Institute take part in Codex cooperation concerning risk assessment and management of antibiotic resistance in foods. Both the health authorities and the food authorities also take part in WHO cooperation.

### **2.2.2. Needs for surveillance, research and international cooperation, which are to be met, and tasks to be accomplished in order to ensure that risk assessment continues to work well in Denmark**

Good surveillance is essential for good preparedness. It is therefore important that data of adequate and uniform quality continues to be ensured with a view to effective surveillance of antibiotic consumption and development of resistance in Denmark. It must be continuously ensured at the same time that the surveillance is up-to-date and makes optimum use of the technological opportunities, for example real-time surveillance, that could contribute to quicker and more effective intervention to deal with relevant problems.

This applies to both the human and veterinary areas, where a number of focal areas are reviewed below, and in the interdisciplinary surveillance cooperation in DANMAP, where an assessment will be made of what opportunities there are for development.

A targeted approach to the most pressing problems is required. A targeted effort has been launched, through the MRSA action plan in 2006, tighter surveillance of *Clostridium difficile* 027 in the health service in 2009 and by earmarking funds for the Food Research Council in 2009 to look into the transfer of MRSA and ESBL producing intestinal bacteria from livestock to humans.

However, there is a need to follow development closely and continuously adapt the effort to the latest developments. An effective effort requires updated and comprehensive knowledge of spread (for example through the reporting of laboratory data and central typing of isolates), infection routes and what conditions

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<sup>1</sup> The Scandinavian cooperation takes place in RAF-M, the Reference Group on Antibiotics and, Methodology Subgroup, which works on optimising laboratory methods to detect resistant bacteria. The European cooperation takes place in ECDC, EARSS (European Antimicrobial Resistance Surveillance System - monitors the incidence of resistance in Europe), ESAC (European Surveillance of Antimicrobial Consumption - monitors use of antibiotics), and EUCAST (European Committee on Antimicrobial Susceptibility Testing - establishment of criteria for when bacteria and fungi are resistant - advisory body to EMEA).

promote incidence (selection, transmission) in relevant areas. A targeted research effort supplemented by scientific risk assessment is thus an important basis for effective strategies.

### **2.2.3 Initiatives for strengthening surveillance**

#### *New research projects focused on intersectoral relationships*

Research projects have to be continuously adapted to current problems. Major initial areas for efforts in connection with the antibiotic and resistance strategy are judged to be ESBL, MRSA in animals and *Clostridium difficile*, where the long-term planning of the effort, including a review of human alert systems, requires more detailed knowledge of spread, types, infection routes etc.

On this basis, a decision has been taken to allocate funds to the National Food Institute for an MRSA and ESBL research project that is concerned with incidence, infection routes and the factors that are significant for the spread of MRSA and ESBL in livestock in Denmark.

With this knowledge it is difficult to propose effective intervention strategies. The project studies the incidence and spread of MRSA and ESBL in Danish pig production, and which primarily herd-related risk factors promote incidence and spread in the herds, between herds and to humans. The results of the project, in the form of a risk assessment, are to be used to advise the Danish Veterinary and Food Administration, which is then to draw up an actual risk management strategy.

At the same time, the National Veterinary institute has received funding for a project aimed at developing a generally usable and quantifiable method for assessing resistance at herd level. It is expected that the project will be able to provide a methodological basis that can be used for rapid and cost-effective documentation of resistance in herds, for the certification of a low level of resistance and elimination of freedom for particular resistance genes. At the same time, it is expected that the project can result in targeted recommendations concerning the use of antibiotics for livestock.

The Danish Veterinary and Food Administration, in cooperation with the National Food Institute, is in the process of studying the incidence of MRSA and ESBL in livestock. Pigs for slaughter at abattoirs were tested for MRSA and ESBL in 2009.

In 2010, a study was carried out on MRSA, ESBL and *Clostridium difficile* in cattle and poultry for slaughter at abattoirs and pigs for slaughter in herds. It is expected that this study will be completed in December 2010. The projects are being performed as Central Coordinated Laboratory (CKL) projects.

#### *Strengthened resistance surveillance*

An important part of the prevention and control of diseases related to resistant bacteria takes place by continuous surveillance of the area. An important input to this is the resistance surveillance of fresh meat and foods. It has to be ensured at the same time that surveillance is updated at all times and follows the latest trend in the development of resistant bacteria.

A decision has therefore been taken to revise the rules on resistance, which means that the previous provisions on multiresistance, including zero tolerance of multiresistant *Salmonella typhimurium* DT 104 (MRDT104), are omitted, in favour of surveillance of resistance to critically important types of antibiotics. This will mean that all salmonella isolates from livestock and animal-based foods in future will be tested for resistance, in contrast to previously, where resistance has only been determined for *Salmonella typhimurium* isolates from pigs. The surveillance will at the same time be extended to poultry and cattle.

It has also been decided that a strengthened effort is to be made in relation to imported foods, as a rising proportion of the foods eaten in Denmark come from abroad. At the same time, it has been found in recent years that a rising proportion of human salmonella infections come from imported foods. The DANMAP surveillance has also shown that both the zoonotic bacteria such as *Campylobacter* and *Salmonella* and the indicator bacteria (*E. coli* and *Enterococci*) from the imported meat types are significantly more resistant to a number of antibiotics than bacteria from the corresponding Danish products.

Surveillance of both Danish and imported foods is taking place at present in connection with DANMAP projects and the case-by-case study. The case-by-case control is focused on imported foods, with samples taken from both Danish and foreign foods, with the aim of being able to reject consignments deemed to be dangerous for consumers to eat.

There is a need to strengthen this effort, which can be done for instance by combining the existing programmes with a focused effort targeted at particular food categories and/or product types. In addition, cooperation should be established with the primary countries of origin for foods on the establishment of programmes for surveillance and control of antibiotic resistance.

It is planned that the case-by-case control will be strengthened by being more risk-based, which is to be done on the basis of an evaluation of the results from the last four years of case-by-case control. In addition, it should be examined whether there is a need to extend the control for example to also cover resistance in *Campylobacter*. Figures from the EFSA on resistance in animals and foods for 2004-2007 show that there is a high incidence of resistance in *Campylobacter* from many countries.

#### Reporting system for infectious diseases in humans

In 2010, Statens Serum Institut launched the Danish microbiology database (MiBa), which automatically collects all electronic Danish microbiological laboratory test results. Reporting was previously a manual and time-consuming process. With the electronic registration of test results, it is possible to identify outbreaks of disease more quickly and with greater reliability to the benefit of the work of the health service and of national and international surveillance.

The statutory basis for the reporting system for infectious diseases is to undergo a review. In this connection, the surveillance of resistant microorganisms, including, to the relevant extent, hospital-acquired infections caused by resistant bacteria, will be assessed.

An important initial task will be to describe the objectives of such surveillance. The objective may extend from a preventive effort in relation to the individual patient, for example with regard to MRSA, to a wish to be able to monitor level, discover outbreaks and match for example with diagnostic (indication) and antibiotic product information.

The starting point for surveillance of resistance is a microbiological analysis, which is often performed locally. Any additional analysis often takes place at Statens Serum Institut, which also attends to central data collection. There are already several "prototypes" for different systems in the existing statutory basis, which will be used as a starting point.

In addition, coordination will continuously take place between the different registers in the development processes by improving the various surveillance registers.

#### **2.2.4. International situation**

A steadily rising proportion of the infections seen with antibiotic-resistant bacteria are due to the use of antibiotics in other countries. Most of the food-borne infections with antibiotic-resistant bacteria seen in Denmark are thus due to foods produced in other countries. But hospital infections and, to some extent, infections outside of hospitals, increasingly have an international spread.

As the development and spread of antibiotic resistance is thus becoming a global matter to a steadily increasing extent, it is essential that Denmark actively takes part in international forums, committees and research projects, including with developing countries, with a view to spreading best practice and receiving early warning of new problems. International network building with the participation of developing countries cannot be financed through traditional research programmes, nor through DANIDA, which is primarily focused on bilateral projects.

It should be noted that at EU level the aim of the Commission is that the collective EU statutory basis in connection with infectious diseases, including surveillance, the ECDC, the Networking Committee and the Health Security Committee will be reviewed in 2010.

The Commission has also been tasked with drawing up an action plan in this area. The action plan is to result in specific proposals to ensure rational use of antibiotics in the EU.

While European surveillance through the EU/ECDC/EFSA is increasingly working, work should be done, with Danish support, on upgrading surveillance outside Europe, for example through WHO, where Denmark already has great influence. Increased participation in international surveillance programmes, risk-based detection of infections and work on international committees may be assumed to have a favourable impact for Denmark.

Finally it may be mentioned that the EU is involved in a newly established cooperation with the United States on the control of antibiotic resistance. This cooperation has been named the EU-US Task Force.

## **2.3. RISK MANAGEMENT AND RISK COMMUNICATION**

### **2.3.1. The present-day organisational structure in the area of risk management**

The task of the Danish National Board of Health is to monitor health conditions and keep itself informed about specialist knowledge in the area and provide guidance on carrying out health-related tasks.

Antibiotics for human use in Denmark are prescribed by doctors, and to a lesser extent by dentists. Which antibiotics the doctors prescribe, and on what indications, thus depend on the general medical knowledge acquired through study and continuing training and in regular specialist reports in the area, and to an unknown extent on other factors such as pricing, information from manufacturers, news media, demands from patients etc.

In 2008, the Danish National Board of Health set up a permanent hygiene committee, which is concerned with all infectious diseases (i.e. also diseases due to non-resistant microorganisms) focused on breaking routes of infection. The Hygiene Committee thus discusses issues relating to problems of resistance, such as MRSA, ESBL and *Clostridium difficile*. In 2008, the Hygiene Committee appointed a working group, with the remit to review the MRSA guidance from 2006 and study whether the guidance can be expanded to also cover other resistant bacteria.

Risk management in relation to the use of antibiotics and development of resistance concerning the veterinary sector takes place under the auspices of the Danish Veterinary and Food Administration. In 2003, the Medicines Task Force was set up following several cases in connection with the use of antibiotics in agriculture. The primary task of this task force is to supervise the prescribing of medicines by veterinary surgeons and the handling of medicines by farmers. The Medicines Task Force is now part of the Danish Veterinary and Food Administration's Veterinary Task Force.

As part of the liberalisation of the distribution of veterinary medicines in 2006, a political decision was taken to expand the Medicines Task Force by adding a special supervision team. The supervision team was established in 2007 and undertakes supervision of practising veterinary surgeons with a view to guidance and advice, so that the prescriptions issued by the veterinary surgeons can ensure the health of the livestock and minimise the risk of resistance development. As part of the effort, treatment guidelines for the treatment of cattle and pigs have been drawn up, so that both the efficacy and risk of resistance development are taken into account in the connection with the individual veterinary surgeon's prescribing of antibiotics. Since the turn of the millennium, restrictions have been introduced in connection the prescribing of critically important antibiotics such as fluoroquinolones and cephalosporins by veterinary surgeons from 2007.

The sale of illegally imported veterinary medicines represents an increasing international problem, and in 2007 a Task Force was established between the

Danish Medicines Agency and the Danish Veterinary and Food Administration with a view to producing a strengthened and coordinated effort to tackle illegal imports and the sale of illegal veterinary medicines.

In the autumn of 2009, the Danish Veterinary and Food Administration appointed a warning committee on the veterinary use of antibiotics (the Warning Committee) with the purpose of strengthening surveillance and drawing up proposals for initiatives for optimum use of antibiotics in agriculture. The Warning Committee consists of representatives of the Danish Agriculture and Food Council, the Danish Veterinary Association and the Danish Veterinary and Food Administration.

One of the committee's tasks is to test a 'best practice' manual for pig producers, which the agricultural industry is drawing up. The manual is to be written by the Pig Research Centre of the Danish Agriculture and Food Council. The manual is expected to be implemented before the end of 2010.

In addition, cooperation is also taking place between several institutions and authorities in the area of antibiotic consumption and resistance.

The coordination group of the Danish Zoonosis Centre, appointed by the Ministry of Food, contains representatives from DTU, Statens Serum Institut, the Danish Veterinary and Food Administration, the Danish Environmental Protection Agency, the Danish National Board of Health and Copenhagen University. Interdisciplinary discussions take place here on all circumstances relating to zoonoses and microbiological food safety, including antibiotic resistance. The regular surveillance results from DANMAP and zoonosis surveillance are presented in this group. The purpose of the group is to ensure the best possible coordination.

In addition, the Danish National Board of Health established a coordination group for zoonotic MRSA in 2006. The purpose of the group is to closely monitor how the particular type of MRSA in pigs spreads, and how the situation is best managed. The coordination group consists of representatives of the Danish Working Environment Authority, the National Food Institute, the Danish Veterinary and Food Administration, Statens Serum Institut and the Danish National Board of Health, who monitor the development of MRSA in livestock and infection of humans.

The cross-sectoral coordination group prepared information for doctors and households with contact with pig herds infected with MRSA.

The coordination group has also appointed a project group consisting of Statens Serum Institute and the National Food Institute. This group carries out relevant scientific studies for use in the work of the coordination group.

DANMAP also has the option of recommending areas requiring particular attention and possible action to the Danish National Board of Health.

### **2.3.2. Needs to be met in order to ensure that risk management continues to work well in Denmark**

1. Reduce the number of cases of “self-created” antibiotic resistance in Denmark by influencing consumption of antibiotics in humans and animals in a more favourable direction
2. Prevent the spread of antibiotic resistance through hygiene precautions
3. Reduce the spread of antibiotic resistance via humans, animals and foods as a consequence of international trade and travel
4. Ensure that the individual infection is treated with the right product taking account of the potential of the product to select for resistance
5. Ensure an organisational and decision-making structure in the area that can quickly and effectively deal with a trend causing concern in the area of resistance
6. Ensure an incentive structure throughout the "antibiotic chain" (pharmaceutical manufacturers, pharmacies, doctors/veterinary surgeons, authorities) that meets the concern for optimum treatment efficacy with minimal development of resistance

It is judged that a targeted effort on the risk-management front against the most pressing problems is required, while work must also be done on broader initiatives, as described below.

### **2.3.3. Initiatives to ensure risk management that works well in the future**

#### Drafting of national technical principles concerning use of antibiotics

It is proposed that national health-related principles concerning the use of antibiotics should be drawn up in order to ensure the optimum use of antibiotics.

The goal is to limit unnecessary use, i.e. avoid the use of antibiotics that do not work or are not necessary (for example in mild infections of short duration) and to provide guidance on the need for certain critically important antibiotics to be preserved for specially defined situations. An important area of focus for the strategy is to continue to optimise the consumption of critically important antibiotics such as fluoroquinolones and cephalosporins in humans with a view to avoiding the development of resistance. In veterinary medicine there is, moreover, a special challenge in reversing the rise that has taken place in recent years in the consumption of antibiotics in pig production.

The principles may contain suitable checks to ensure that the doctors and veterinary surgeons comply with the principles. The principles must be continuously adjusted in accordance with information from the surveillance systems, the Antibiotics Council and other new knowledge in the area.

#### Hygiene precautions

Sets of rules and guidelines must be adjusted so that account is taken of the new problems regarding resistance, including MRSA in pigs, ESBL and *Clostridium difficile* etc. Beyond the hospital hygiene measures, it is important that the hygiene effort in the municipalities is strengthened, as resistant bacteria are increasingly being spread outside the hospitals, including in nursing homes and special institutions.

There has long been a tradition in agriculture of operational regulations aimed at reducing the incidence of disease. An example of these is the establishment of the

SPF system, the establishment of fixed trading patterns, sectioning of livestock facilities and the creation of classification systems for description of the individual herd's disease status. A number of hygiene-related precautions are also taken in this connection, for instance in relation to hygiene measures relating to visits to livestock facilities.

There is, however, particularly in the light of the MRSA situation, a need for a strengthened research and development effort to investigate risk factors for the transmission of bacteria from animals to humans in livestock facilities. Such studies are to cover all forms of contact, both professional contact and visits of various kinds. The research is to form the basis for the establishment of infection-reducing measures for staff and visitors at herd level.

#### Strengthened advice and incentive structure in the herds

As part of the Veterinary Settlement from August 2008, a decision was taken to introduce mandatory visits by veterinary surgeons to all large pig and cattle herds from the summer of 2010. An essential aim of the veterinary settlement is to shift the focus from treatment of animals to prevention, in part to avoid medication of livestock. Under this agreement, consumption of antibiotics is monitored at herd level, and problem herds will in future receive more visits and be at greater risk of public inspection.

In relation to strengthening the advisory effort, it is also important that advice is provided on the basis of the latest research and knowledge. It is important in this connection that the Danish Veterinary and Food Administration's treatment guidelines in relation to livestock are relevant, accessible and up-to-date.

In this connection, evidence-based treatment guidance for use by veterinary surgeons attending to pigs will shortly be published. The guidance has been prepared by a working group consisting of representatives of KU LIFE (the Faculty of Life Sciences at Copenhagen University), DTU, Veterinær Medicinsk Industriforening (the veterinary pharmaceutical industry association), the Danish Veterinary Association and the Danish Agriculture and Food Council. The guidance differs from previous guidance in being based on evidence and documentation – particularly with regard to safeguarding future human treatment options. The guidance is also focused on where and how well the individual antibiotics work at the registered dose at which they have been approved.

Similar guidance is being drawn up for poultry, and in the longer term the guidance for cattle will be revised in accordance with similar guidelines.

#### "Yellow card" scheme

With a view to reducing the rising consumption of antibiotics in pig production, a decision has been taken to implement a targeted effort in relation to those herds and veterinary surgeons who account for most of the consumption and who differ from other, comparable herds in having disproportionately high consumption. Against this background, a decision has been taken to issue a "yellow card" to the farmer when consumption of antibiotics in the herd exceeds a particular level. The yellow card is followed by the imposition of an action plan with a view to reducing the consumption of antibiotics. A "yellow card" also means that the herd owner can only be prescribed the precise quantity of medication that is to be used until the

veterinary surgeon's next advisory visit. The veterinary surgeon thus must not prescribe large quantities of antibiotics at once and has to re-prescribe on each advisory visit on the basis of the stock of medication in the herd.

In addition, the "yellow card" means that the herd is included in a pool for "50% inspection". Herds in this category are at a 50% risk of public inspection, so that official focus on the situation in the herd is substantially increased.

As far as veterinary surgeons are concerned, the inspection by the Danish Veterinary and Food Authority will be focused more closely on practising veterinary surgeons who have a high proportion of herds with "yellow cards".

If the consumption of antibiotics has not been reduced to an acceptable level in 9 months, the Danish Veterinary and Food Authority will impose a tightened action plan on the farmer and veterinary surgeon. A tightened action plan means an inspection visit to the farmer for which a fee must be paid. The inspection visit has to form the basis for the preparation of imposition of one or more practical measures, which may for example be requirements for diagnostics, management in the herd, advice and official inspections. The measures will thus be targeted at the individual herd.

As an increased focus on unacceptable consumption of antibiotics can prompt the unscrupulous to obtain antibiotics through illegal routes, it has been decided that the Danish Veterinary and Food Administration and the Danish Medicines Agency will have to increase checks to prevent illegal importation of veterinary medicines.

#### Reporting in connection with reports of side-effects

The inadequate efficacy of antibiotics as a consequence of resistance problems is not a "side-effect" that doctors and pharmaceutical companies have to report to the Danish Medicines Agency under the rules on the reporting of side-effects.<sup>2</sup>

It is evident from the Commission's guidance on surveillance of pharmaceutical safety that this type of information is not to be reported according to the rules on side-effects reports. However, the Commission recommends that the marketing authorisation holder should report on a life-threatening infection if inadequate efficacy may be caused by a new resistant bacterium which it has previously been possible to treat.

It is proposed that the Danish Medicines Agency should draw the attention of marketing authorisation holders to the Commission's recommendation, and that the Agency should otherwise urge marketing authorisation holders to submit reports to the Agency if such a situation might arise in Denmark.

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<sup>2</sup> A "side-effect" is understood to mean a harmful and unintended reaction induced by a medicine that occurs at doses that are normally used for humans or animals with a view to preventing, diagnosing or treating disease or modifying, restoring, correcting or influencing physiological function. The definition does not cover problems associated with inadequate efficacy of a medicine.

In the longer term it must be assessed whether there is a need for a discussion with the Commission concerning the Commission's recommendation as referred to above.

Reporting in connection with the periodic safety update report on an antibiotic

A marketing authorisation holder has to submit a periodic safety update report (PSUR) at regular intervals to the Danish Medicines Agency on the safety of the medicine.

A PSUR has to contain a list and review of all suspected side-effects and exposure reactions registered in the period concerned. There is generally not a requirement for a PSUR to contain a report on inadequate efficacy.

The Commission guidance on drug surveillance states, however, that information concerning inadequate efficacy should be mentioned in connection with products for the treatment of serious or life-threatening diseases, for example antibiotics, if it poses a significant danger/risk. In this situation, reports on inadequate efficacy are described and explained in the periodic safety update report.

The PSUR has to contain a scientific assessment of benefits and drawbacks of the drug in the evaluation of safety data for the current period in relation to the summary of product characteristics, and an overall assessment of the drug's safety profile. It is relevant to address problems with resistance and inadequate efficacy of antibiotics to be used in the treatment of serious diseases in a PSUR, as this can constitute a major safety problem.

It is proposed that the Danish Medicines Agency should in future request marketing authorisation holders for antibiotics to state any resistance problems in connection with review of periodic safety update reports, if the issue is not addressed in the reports. If the Agency receives new information on resistance problems in connection with the processing of individual reports or periodic safety update reports, this information may, if appropriate, be included in the Danish National Board of Health and Danish Veterinary and Food Administration guidance on the use of antibiotics and the prevention of resistance.

Reporting pursuant to Section 25 of the Medicines Act on new essential information

The holder of a marketing authorisation for a medicine has to inform the Danish Medicines Agency of any essential new information concerning the ratio between the benefits and risks of the medicine that does not come to the knowledge of the Agency under the procedure for the approval of changes to marketing authorisations or in the form of periodic safety update reports, cf. Section 25(1) of the Medicines Act. Information on resistant problems and inadequate efficacy of an antibiotic is essential new information on the ratio between the benefits and risks of the medicine, which the marketing authorisation holder has to report to the Danish Medicines Agency.

It is therefore proposed that the Danish Medicines Agency should forward information on this to the Danish National Board of Health and the Danish Veterinary and Food Administration, so that this information can, if necessary, be

included in guidance on the use of antibiotics and prevention of resistance problems.

It is also proposed that the Danish Medicines Agency makes marketing authorisation holders for antibiotics aware in particular that they must keep the Agency continuously informed of inadequate efficacy due to resistance problems. This can, for example, take place in connection with the approval of antibiotics, extension of marketing authorisations, review of periodic safety update reports or in the case of information on the Agency's website.

#### Consultation procedure

It is proposed that the Danish Medicines Agency should consult the Antibiotics Council concerning issues relating to general reimbursement and re-assessments of reimbursement status for antibiotics. The consultation procedures are to be conducted taking account of the requirements of case processing times to which the Danish Medicines Agency is subject. The Antibiotics Council can accordingly refer to the Danish Agency in the event of inappropriate consumption of human or veterinary antibiotics.

### **2.3.4. Initiatives concerning joint organisation in the area of risk management**

#### National level

In 2010, the Danish Government appointed an Antibiotics Council with the aim of contributing to promoting appropriate use of antibiotics in Denmark, including ensuring that antibiotics can continue to be used to treat infections. The Council is an interdisciplinary, coordinating body and has representatives of relevant bodies in the areas of human and veterinary medicine. The Council has a key role in the implementation of the joint antibiotics and resistance action plan.

#### Regional and municipal level

It is proposed that there should be a focus on the established regional pharmaceutical consultants, as these can gain an insight through ORDIPRAX into the individual doctors' patterns of prescribing, and can therefore identify those doctors who directly prescribe less appropriately. A dedicated effort in relation to the doctors concerned has proved capable of modifying the pattern of prescribing in a more appropriate direction in several groups of medicines, including antibiotics. The APO (Audit Project Odense) method has also proved capable of moving consumption of antibiotics in a more appropriate direction, in both the short and longer terms.

As far as the municipal level is concerned, it should be examined more closely whether representation on the Danish National Board of Health's Hygiene Committee is sufficient, or whether further strengthening can also advantageously be done at this level. The effort should initially be focused on the development of hygiene expertise in the municipalities.

### **2.3.5 International situation**

It is of great importance that all countries in the world work in a targeted and coordinated manner on the introduction of antibiotic policies aimed at minimising

the development of antibiotic resistance. It is therefore also important that the Danish authorities continue to focus on the international initiatives that can limit the spread of antibiotic resistance. Both the health authorities and the food authorities are thus involved in cooperation at EU level to ensure cross-sectoral cooperation between the human health sector, the veterinary sector and the pharmaceutical sector.

In the area of health there are Council conclusions from 2001, 2008 and 2009 concerning antibiotic resistance, in which both the individual Member States and the European Commission are urged to take a number of preventive measures.

At the European level, the EU institution the European Centre of Disease Prevention and Control (ECDC) was also established in 2005. The ECDC works on strengthening the common European effort against infectious diseases.

An annual European Antibiotic Awareness Day is also held in all the EU Member States, in which the focus is on a number of problems concerning consumption of antibiotics and development of resistance.

At EU level consequences have also been drawn from consumption of antibiotics and development of resistance being of international relevance, and the whole area of medicines has been brought under SANCO, the Directorate General for Health and Consumer Affairs. In the veterinary area, this means that diseases of livestock, and the medication used to control them, are now dealt with by the same organisation. On the Danish side, work must be done to exploit the benefits offered by having a collective EU authority in the area.

In the area of food, the various UN organisations such as the World Health Organisation (WHO), the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation (FAO), brought together under the Codex Alimentarius, have drawn up various guidelines with a view to effective management of the problem. The intention is not to eliminate resistance - an impossible task - but to ensure that the problem does not become so extensive that the treatment of bacterial infections in animals and humans is compromised or, in the worst case, made impossible. It is therefore recommended that those antibiotics that are critically important for the treatment of humans should be risk-assessed first. International attention has been drawn here to fluoroquinolones, macrolides and 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins. It should be noted that work is in progress at present in the Codex Alimentarius on drawing up guidance on risk assessment and risk management of antimicrobial resistance, work in which Denmark, through the Danish Veterinary and Food Administration and DTU, and France hold the presidency of the risk-management working group.

The Danish Veterinary and Food Administration is also taking place in an international cooperation known as "Small Bull" with other EU Member States with a view to uncovering illegal international sale of medicines, including growth hormones.

As the international organisations do not issue rules or set specific requirements, but draw up guidelines and recommendations, their direct effect on the handling of

antibiotics may be limited, but it is judged that results can be obtained in the areas of surveillance, risk assessment and risk management by setting the agenda for antibiotic consumption and resistance development. Cooperation with WHO and the EU in particular is therefore important. It should be noted in this connection that the 18-month programme of the Council of Ministers in the area of health (1 June 2008 to the end of 2009) chose to focus on antibiotic resistance.

### **2.3.6. Risk communication today**

Risk is communicated to many different parties with different backgrounds. It is thus possible to work advantageously in a more targeted manner on communication to professionals such as doctors, veterinary surgeons and dentists, but communication to stakeholder organisations, the media, citizens and international cooperating partners can also be strengthened.

Regular technical reports on human use of antibiotics are provided on the website of the Danish Medicines Agency, through the Institute for Rational Pharmacotherapy (IRF), which publishes the information sheet *Rationel Farmakoterapi* and operates the website [www.irf.dk](http://www.irf.dk), Statens Serum Institut (for example EPI-NYT) and [www.medicin.dk](http://www.medicin.dk).

The steering group of DANMAP is responsible for the annual report and the press releases related to the annual report. There is always great attention from the press, the agricultural organisations and the Danish Veterinary Association when the report and the press releases are issued, as these sum up and highlight the most important trends in the year in the consumption of both veterinary and human medicines and the development of resistance. These trends also set a natural framework for risk management and the risk communication derived from it.

The stakeholder group of the Danish Zoonosis Centre, which is appointed by the Ministry of Food, contains participants from industry organisations and stakeholder organisations (consumers, trade unions etc.). The same topics are presented and discussed here as in the Danish Zoonosis Centre's coordination group.

The Danish Veterinary and Food Administration's supervisory team and medicines task force publish an annual report on the number of fines and sanctions imposed in connection with the checking of medicines used by veterinary surgeons and herds, describing the actions of the medicines task force and major legislative changes as well as the results of the Danish Medicine Agency and Danish Veterinary and Food Authority Task Force. The report attracts some interest in agricultural organisations, the Danish Veterinary Association and the press.

In addition, the supervisory team and the medication task force regularly speak to veterinary surgeons, the pharmaceutical industry and other stakeholders around the country on rules and understanding of legislation and the content and results of the supervision of veterinary surgeons.

However, it is the direct risk communication concerning the individual veterinary surgeon's consumption and prescribing patterns on the supervisory team's visit that represents the most effective risk communication measure, as the direct dialogue is decisive for the change of behaviour that ensures future optimal use of

antibiotics and consequently the least risk of the development of resistance. Compliance with rules and of treatment guidelines etc. for the optimisation of veterinary consumption of antibiotics and the development of resistance is also ensured.

Rules, guidelines etc. in the area of antibiotics are also stated on the website of the Danish Veterinary and Food Administration.

### **2.3.7. Joint communication in the area of risk communication**

A joint communication based on the national Antibiotics Council is proposed. If deemed necessary, the Antibiotics Council can appoint a subcommittee - a joint risk communication committee

It is of great importance that all the countries of the world work in a targeted and coordinated manner for the introduction of antibiotic policies that are aimed at minimising the development of antibiotic resistance.

Denmark has a good opportunity to influence international development with the use of documentation that can show that the "Danish principles" for responsible use of antibiotics and cooperation across sectors can minimise the development of resistance, without this being at the expense of treatment efficacy in human and animals. It is therefore proposed that there should be greater international promotion of Danish experience in the area of risk communication with antibiotic consumption and resistance.

This can be done, for example, by the results of the Danish initiatives being evaluated and published scientifically. It can also be done by targeted lobbying of WHO. Increased international communication of favourable Danish experience in interdisciplinary cooperation in the area of antibiotics may, in the longer term, also provide Denmark with feedback and international discussion in this area.