The Microbial Threat

Progress Report on

Antimicrobial Resistance

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Contents

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EXECUTIVE SUMMARY

An invitational EU conference on antimicrobial resistance was arranged by the Swedish National Board of Health and Welfare. The conference was endorsed by the Swedish Government and the EU Commission. The aim of the conference was to follow up the present situation in relation to the recommendations from the Copenhagen meeting on the Microbial Threat 1998.

The conference gathered approximately 150 policy makers and experts from 29 countries representing both the human and animal health sectors.

Data presented at the Visby conference clearly illustrated that antimicrobial resistance remains a major problem in public health. Since the Copenhagen conference in 1998, the problem has become increasingly important as illustrated by more frequent clinical findings of resistant pneumococci, staphylococci, enterococci, and salmonellae. There are now several reports of high scientific quality, which show that antibiotic resistance is correlated to health care costs and clinical therapeutic failure. The impact of antimicrobial resistance on animal health is less well documented. Although the evidence for transmission of resistance from animals to man has increased during recent years the impact of such transfer on human health has not yet been fully clarified.

A theme of the Visby conference was to assess how much of the Copenhagen recommendations had been turned to action. Four key areas were covered by working groups – 1) Coordinated multidisciplinary actions; 2) Surveillance/registration of resistance to antimicrobials; 3) Monitoring the use of antimicrobials; 4) Implementing prudent use of resistance to antimicrobials-from guidelines to practice.

It was pleasing to see that all parties involved have realised the severity of the situation and have taken a series of initiatives. This was shown by submitted national reports, as well as from reports of international organisations such as ESCMID, OIE, WHO and manufacturers of antimicrobial agents. Notable was also a very positive attitude towards cooperation between organisations, both non-governmental and commercial ones, to seek new avenues for solutions of the problems associated with antimicrobial resistance.

Coordinated multidisciplinary actions

The Copenhagen report emphasised that future efforts should be “coordinated” and “multi-disciplinary”. The lack of clarity on where responsibilities lie in relation to the action areas was identified as one major obstacle. The working groups in Visby dealing with this part of the problem arrived at the conclusion that governments should support formal structures to underpin activities and ensure sustainability. Strategies defining targets for future projects must be formulated. Such projects should be sustainable, and transparent, at least to avoid duplications of projects and optimise use of available funds. The Visby meeting recognised

the lack shortage of experts in clinical microbiology as a major problem both in human and veterinary medicine.

Surveillance/registration of resistance to antimicrobials

An important basis for future activities in the field of antimicrobial resistance is reliable surveillance data. In this context it is embarrassing that after more than 50 years, no consensus has been reached on how to define breakpoints for antibiotic susceptibilities, nor is there an agreement on the methods to be used. The time has come for decions on international standards t for these measurements and it is clear that this target must be be met without delay. All countries should be urged to join the EARSS surveillance program as a minimum requirement national national surveillance program. In the veterinary sector, all European countries are encouraged to follow the ARBAO recommendations.

Monitoring the use of antimicrobials

In the discussion of monitoring of use of antimicrobials, it became apparent that even though national systems are running in most countries especially in the human field, the data are often not generally accessible for the purpose of antimicrobial monitoring. A common tool should be developed for easy collection and retrieval of data from the different countries. Research programs should be set up on the issue of correlating quantitative antimicrobial use with antimicrobial resistance.

Implementing prudent use of resistance to antimicrobials-from guidelines to practice.

The final part of the Visby conference working groups was on prudent use of antibiotics. Highly commendable educational activities on national levels were reported. For example, media campaigns directed towards the general population, including children, have been successful in increasing the public's awareness that antibiotics are not always necessary for the treatment of mild infections. However, improved education at medical and veterinary schools as well as more post-graduate training on the diagnosis,treatment and control of infectious diseases. It was stressed that improved animal husbandry is the most efficient way to reduce the risk of infections and, subsequently, the need for prophylactic or therapeutic veterinary use of antimicrobials.

In the context of prudent use of antimicrobials it is highly disturbing that there are still European countries, including some EU Member States where antimicrobial agents intended for prescription only are sold over-the-counter at pharmacies. Development of treatment guidelines should be drawn up locally by a multidisciplinary body, including the prescribers, to achieve a broad acceptance.

Conclusions

The end result of this conference is clear: we are heading towards effective counter-measures to contain the problem of antimicrobial resistance. However, the fact that resistance rates among common bacteria are still increasing, emphasises the urgent need for further efforts .

BACKGROUND

An invitational EU conference on antimicrobial resistance was arranged by the Swedish National Board of Health and Welfare. The conference was endorsed by the Swedish Government and the EU Commission. The aim of the conference was to follow up the present situation in relation to the recommendations from the EU conference in Copenhagen in 1998 on the Microbial Threat.

The meeting in Copenhagen resulted in "The Copenhagen recommendations" on strategies to prevent and control the emergence and spread of antimicrobial resistance. These recommendations focused on the following points:

- The EU and Member States must recognise that antimicrobial resistance is a serious European and global problem.
- Pharmaceutical companies should be encouraged to develop new antimicrobial agents, but these will not solve the problem in the near future.
- The European Union and member states should set up a European surveillance system of antimicrobial resistance.
- The European Union and member states need to collect data on the supply and consumption of antimicrobial agents.
- The European Union and member states should encourage the adoption of a wide range of measures to promote prudent use of antimicrobials.
- The European Union and member states and National Research Councils should make coordinated research on antimicrobial resistance a high priority.
- A way should be found to review progress with these recommendations and proposals.

The Visby meeting gathered approximately 150 policy makers and experts from 29 countries representing both the human and animal health sectors.

The meeting began with plenary lectures summarising state-of-the-art within the field of antibiotic resistance and reports from the following organisations on progress made since the Copenhagen meeting:

- EFPIA (Dr Anthony White)
- EMEA (Dr Bo Aronsson)
- FEDESA (Dr Johan Vanhemelrijck)
- FEFANA (Dr Robin Bywater)
- OIE (Dr Barbara Röstel**)**
- WHO (Dr Rosamund Williams)
  Written reports had been submitted by the afore-mentioned organisations and are available at:http://www.sos.se

Four key areas were subject for a detailed review and discussion in working groups:

- Coordinated multidisciplinary actions
- Surveillance/registration of resistance to antimicrobials
- Monitoring the use of antimicrobials
- Implementing prudent use—from guidelines to practice

The draft reports from the working groups were discussed in plenary. Finally, Professor Ragnar Norrby, Director of the Swedish Institute of Infectious Disease Control concluded the meeting.

PLENARY LECTURES

Professor Javier Garau from Spain highlighted trends and clinical consequences of resistance to antibiotics in the human field. Professor Garau gave several examples of rapidly increasing frequencies of resistance to commonly used antibiotics in important pathogens, eg, *Streptococcus pneumoniae* and *Staphylcoccus aureus*. Importantly he pointed out that there is now clear evidence of a correlation between *in vitro* resistance and clinical failure. The medical and economical consequences of antibiotic resistance in human medicine are thus obvious.

Professor Fritz Ungemach from Germany commented on the different Copenhagen Recommendations from a veterinary perspective. He pointed out that all antimicrobials used in veterinary medicine belong to groups of antibiotics used in human medicine or which may cause cross-resistance. Strategies to control of the spread of antimicrobial resistance must include improvement of animal husbandry conditions, control of infectious diseases, judicious use of antimicrobials and phasing out of antimicrobial growth promoters.

Professor Patrice Courvalain from France gave a general review of the genetic basis and epidemiology of resistance to antimicrobial agents. Knowledge and understanding of the mechanisms behind emergence and spread of resistance is rapidly increasing. Bacteria have a high degree of genetic flexibility. Exchange between bacteria of resistance genes take place rapidly in natural environments. This is true even for bacteria that are not closely related. For certain transfer genes, the presence of a specific antibiotic actually increase the frequency of transfer.

Initiatives by EU and different international organisations

The plenary lectures were followed by reports from the following organisations:

- **EU** Commission (DG SANCO, DG Research, EMEA)
- **WHO** (World Health Organization)
- **OIE** (Office International des Epizooties)
- **EFPIA** (European Federation of Pharmaceutical Industries and Associations)
- **FEDESA** (European Federation of Animal Health)
- **FEFANA** (European Feed Additives Manufacturers Association) manufacturers and Nutrition Animal)

The reports of these organisations are available at the website of the Swedish Board of Health and Welfare: http://www.sos.se.

RESULTS OF THE WORKING GROUP DISCUSSIONS

Group 1: Coordinated multidisciplinary action

Chairmen: John Devlin and Aase Tronstad
Rapporteurs: Johan Carlson and Henrik Wegener

Extracts from the Copenhagen recommendations

This area was not specifically included in the topics that were were discussed at the Copenhagen meeting .However, the words" co-ordinated", "multidisciplinary" and "collaborative"appears rapidly in the document..For the Visby working group the following definitions were used.
Coordination: "Bringing the respective parts of the system into proper relation with each other".
Multidisciplinary action: "Operates across different sectors (e.g., human health, animal health, agriculture, etc.) and includes the various stakeholder interests including professionals, organisations, industry, and consumers".

Current status

Many countries provided good examples of coordinated multidisciplinary activities (these are provided in detail in the country reports). These activities were perceived as crucial for the development and implementation of integrated national strategies. Because of the global nature of the problem, the delegates recognised the need for international collaboration.

The development and implementation of national strategies requires a common recognition and understanding of the problem. It is important that governments take action on this issue. The importance and value of informal structures was illustrated through several good examples. The meeting also recognised the need for government supported formal structures to underpin activities and ensure sustainability.

The meeting recognised the need for leadership (for example to take initiative and ensure coordination). Where strategies have been developed and implemented, the initiative and initial coordination has been provided by the health sector (Ministry of Health), but in close collaboration with the Ministry of Agriculture and other relevant stakeholders.

Elements of a national strategy

The following elements were identified as essential in the development of integrated national strategies:

- Surveillance of AMR and antimicrobial use, using harmonised methods, and feedback to those that need the information for action
- The development of prudent use guidelines, that may include formularies for prescribers
- Infection control and other preventative actions
- Multidisciplinary research
- Education, training, and continued professional development
- Information to the patients, farmers, and the general public.

In addition the participants agreed that national strategies should address:
- The current problems of resistance in human and animal health
- Look towards the future
- Include specific targets
- Define responsibility for each area
- Have systems to monitor and review progress
- Involve all relevant stakeholders.

There is no need to wait for all parts in the national strategy to be in place before actions are taken.

Obstacles

The following obstacles for successful strategy development and implementation have been identified:
- Lack of clarity on where responsibilities lie in relation to the action areas
- Lack of information or information sharing
- Lack of clarity on goals and targets
- Lack of manpower
- Inadequate recognition of the value of good practice in relation to antimicrobial usage in the human and animal sector. Examples of negative incentives include counterproductive reimbursement policies in human medicine, and profits from drug sales by the veterinarians in the veterinary field.
- Funding was not seen as a major obstacle, but the following areas needed for additional funding were identified: surveillance to measure the effect of the efforts, research in veterinary public health, education of professionals in the area of research and clinical microbiology and information for the general public, and modern information technology,

Considerations for future actions

- Countries should develop and implement national strategies to prevent and reduce antimicrobial resistance in human and animal populations.
- Governments should support formal structures to underpin activities and ensure sustainability.
- The initiative and initial coordination should be provided by the Ministry of Health, but in close collaboration with the Ministry of Agriculture and other relevant stakeholders.

- National strategies should contain the following elements:
  - surveillance of antimicrobial resistance and antimicrobial use
  - development of prudent use guidelines
  - preventative medicinal and veterinary actions, multidisciplinary research, education, training, and continued professional development
  - information for patients, farmers, and the general public.
- The strategy should specify where the responsibilities lie in relation to these action areas and take into account future manpower requirements. It should have specific goals and measurable targets and have systems to monitor and review progress. Strategies should be costed so that adequate funds are available.

Group 2: Surveillance/Registration of resistance to antimicrobials

Chairmen: Niels Frimodt-Möller and Preben Willeberg
Rapporteurs: Gunnar Kahlmeter and Catarina Wallén

Extracts from the Copenhagen recommendations

- A European surveillance system,based on national systems,should be set up
- Natonal systems must collect data on antmicrobial resistance in bacteria of animal and human origin and should be co-ordinated within the EU. Colllaboration between human and verterinary medicine should be established.
- Data to be included in the surveillance systems must fulfil the following crirteria:
  - antimicrobial susceptibility data must be quantitative and comparable,
  - representative sample,
  - priority organisms,
  - priority antimicrobials,
  - relevant data analysis and interpretation, and
  - information exchange and feed back (interactive)

Current status

EARSS (European Anrimicrobial Resistance Surveillance System) represents a minimum requirement national surveillance programme. However, all EU countries do yet not participate. The Danish monitoring programme, DANMAP, was considered an example of good coordination between surveillance of resistance in bacteria of human, food, and veterinary origin. The Swedish system (SRGA) was considered an example of good coordination between surveillance and quality control. Minimum criteria for surveillance of resistance in bacteria of animal origin have been agreed within a concerted action group (ARBAO). Most European countries still lack surveillance systems for bacteria of veterinary and food origin; one country has a system coordinated with human medicine.European resistance surveillance activities in human medicine are listed in Annex 2. Ongoing systems for collecting data on antimicrobial resistance in animal bacteria are listed in Annex 3.

Obstacles

There is an obvious lack of resources (funds, infrastructure, know-how, IT-support, manpower) on local, national and European level. The know-how required for producing good quality susceptibility testing and hence surveillance is often underestimated. The statistical and epidemiological knowledge is often lacking as well as coordination between political and/or administrative levels

within health authorities and between health authorities and the medical and veterinary profession. Further, a centralized European initiative to establish, fund and coordinate a pan-European surveillance program in the food and veterinary sector is needed. Last, but not least, national and European standardization of antimicrobial susceptibility testing and a common European definition of antimicrobial resistance are lacking.

There is a need for increased involvement of personnel trained in medical/ veterinary sciences at all levels of microbiological laboratory services. For the EARSS program in human medicine user-friendly methods for export of data to EARSS coordinators are needed. Systems linking routine microbiological databases with surveillance databases are needed. It was pointed out that an unclear status regarding ownership of surveillance data may be a problem in some situations.

Considerations for future actions

During the implementation of standardised methods and a common European definition of resistance, surveillance should be based on quantitative data (MIC or zone diameter distributions) or when possible on the detection of resistance mechanisms or genes ..A common European definition of resistance is required for meaningful comparisons, qualitative results from breakpoint-operated systems.

The need for resources (infrastructure, know-how, IT-support, manpower) for surveillance of antimicrobial resistance locally and centrally and the need for networks (human and veterinary) within and between countries must be acknowledged at the administrative level. In the sector of human medicine, all European countries should be urged to join the EARSS surveillance program as a minimum requirement national surveillance program. In the veterinary sector, all European countries are encouraged to follow the ARBAO recommendations. The latter would be in line with the OIE proposed guidelines.

Ownership of surveillance data must not stand in the way of national antimicrobial resistance surveillance. If necessary, agreements between the relevant authority and the participants in the surveillance program should be made.

Increased educational efforts regarding antibiotic susceptibility testing and resistance surveillance should be encouraged.

For future comparisons antimicrobial resistance frequencies in humans and animals should include zoonotic bacteria and indicator bacteria from food, healthy animals and healthy humans. Surveillance programs should generate data for intervention, risk analysis, early warning and should form a basis for antibiotic policies and guidelines for therapy. Surveillance programs should ideally contain defined action levels such as:

- notifiable findings (rare or yet not discovered resistance)
- epidemiological intervention
- change in empirical therapy
- regulation or legislation

Surveillance systems require continuous evaluation and development and the cost-benefit of ongoing surveillance must be considered. The close collaboration with the scientific community including microbiologists, epidemiologists, statisticians and specialists in information technology is called for. The analysis and presentation of surveillance data must be linked and correlated to the presentation and analysis of data on antimicrobial consumption, guidelines of prudent antimicrobial use and made available in the open domain to the scientific community, regulatory bodies and industry.

Group 3: Monitoring the use of antimicrobials

Chairmen: Herman Goosens and Michael Gunn.
Rapporteurs: Karl Ekdahl and Kari Grave

Extracts from the Copenhagen recommendations

- Every Member State should be able to collect national data on the supply and consumption of antimicrobial agents.
- Data should be collected on dispensing of antimicrobial agents by community and hospital pharmacists and on antimicrobial agents used to treat animals (by species) and for growth promotion.
- An EU strategy for ensuring transparency and comparability between national databases should be established.
- Research information should be collected about the consumption of antimicrobial agents by diagnoses.

Current status

Most of the countries participating in the conference collect national data on antimicrobial drug use, both in the human and the animal field. In the workshop, 19 countries were reviewed for use of antimicrobial drugs in human medicine and 13 countries for use in veterinary medicine.

Human field

All the 19 countries reviewed have ongoing, national systems, monitoring the use of antimicrobials. In two of these countries the systems were initiated after the Copenhagen meeting. In 17 countries the data were collected on community level, and in 15 countries the system covered hospitals. The ATC code was used in 13 countries. The unit of measurement was cost in 14 countries, DDD in 13 countries and prescriptions in 11 of the countries. In many of the countries reviewed, data systems are also available on antimicrobial resistance, demography, and socio-economic factors. Data from these different systems are not routinely pooled in a meaningful way.

In accordance with the Copenhagen recommendations, commercially available data are not used as a part of the routine data collection in any country. In several countries commercial data, e.g. IMS data have been evaluated. It seems that these data are more reliable for the community than for hospital consumption

Animal field

Eight of the 13 countries participating in the group were able to collect overall national data on antimicrobials used for therapeutic use in food producing animals (including farmed fish) and companion animals as well as feed additives. The

responsibility, including financial support, for data collection was not clearly defined for every country present at the workshop.

The use of antimicrobials (both those licensed for animal and human use) in companion animals, was recognized to have increased in recent years. The monitoring of antimicrobials used for horticultural purposes was not reviewed as data on antimicrobials used in this area are regulated, and recorded, as pesticides.

Use of data

Data on antimicrobial drug use, both for humans and animals, are being used in a number of ways:

- To follow trends and make comparisons between different geographical areas.
- To affect prescription patterns.
- To correlate antimicrobial use and morbidity.
- To correlate antimicrobial use and resistance.
- To function as a quality indicator for antimicrobial use

In the human field some additional uses of data were identified:

- To evaluate public awareness campaigns.
- To assess compliance with policy – for that you need indications on prescriptions. Important issues being raised in this context is confidentiality and the risk of doctors "altering" the diagnosis to fit the prescription.
- To form a basis for interventions on community and hospital level.
- To form a basis for cost driven systems.

Determinants of use

Available data clearly highlight the vast differences in antimicrobial consumption between different countries, as well as between different communities and regions within single countries. There are numerous determinants for these variations. These determinants will be further discussed and evaluated at the upcoming conference in Brussels in November.

Obstacles

Data collection

In countries with less comprehensive and well-functioning systems for antimicrobial drug use, manpower and funding were considered to be main obstacles. Other problems were difficulties in obtaining data, coordination of data collection, lack of legislative support, ownership and confidentiality.

Accessibility of data

Even though national systems are running in most countries the data are often not generally accessible for the purpose of antimicrobial monitoring. There are many reasons for this, one being that the collection of data is not made for monitoring purposes, rather as a basis for reimbursement and other economical reasons.

Another problem is that the availability of the data often is hampered for technical reasons, e.g. the computer systems are not designed for easy retrieval of these data.

At present, only two of 13 countries reported that they have methods to assess and publish data on animal use collected at species/herd level and fish farms. However, farmers in most countries are obliged to record data on antimicrobial use on their farms due to legislative requirements associated with residue monitoring.

Considerations for the future

Human and animal field:

- A cost effective system supported by national legislation is needed in some countries to facilitate the collection of valid data on an on-going basis.
- Initiatives should be taken by the EU to establish concerted action on a methodology for antimicrobial drug use monitoring.
- A common tool should be developed for easy collation and retrieval of data from the different countries.
- Harmonised reports at the national level should be presented annually and compiled into an EU report. These reports should form the basis for concerted actions.
- Research programs should be set up on the issue of correlating quantitative antimicrobial use with genotypic and phenotypic selection of resistance.
- The validity of monitoring data should be evaluated regularly.
- Data on antimicrobial use should be evaluated in the context of demographic, socioeconomic and other data.
- Projects should be initiated which could be used for a therapeutic audit.

Human field only:

- Optimal volume of use for treatment of infections on a community level should be defined.
- For the purpose of affecting prescription patterns, data on antimicrobial use should be local, broken down for different medical specialities, and be fed back to the individual prescribers in support of improved quality prescribing.

Animal field only:

- Targeted surveys at farm level rather than use of data from all farms would give valuable information. Analysis of data on drug use should be related to resistance patterns.
- Data of use of antimicrobials in companion animals, including horses, should be recorded.
- The group recommended that data on the usage of antimicrobials for horticultural purposes should be considered when reviewing the effects of antimicrobial use in general.

- The possibility that there is illegal dispensing of antimicrobials for animals was a concern of members of the working group.
- There is a necessity for countries to agree on a comparable drug classification system and unit of measurement in veterinary medicine in order to ensure comparability between national databases.

Group 4: Implementing prudent use – from guidelines to practice

Chairmen: Agnes Wechsler-Fördös and Matti Aho
Rapporteurs: Inga Odenholt and Per Wallgren

Extract from the Copenhagen recommendations

- Educational initiatives for health professionals(human and animal) and the general public are of major importanace for improving the use of antimicrobial agents.
- Antibiotics for therapeutic use should be prescription-only medicines and should not be advertised to the public.
- Antimicrobial treams,includingf clinical m icrobiologists,infectious disease specialists and other appropriate specialists,should be introduced in every hospital. The teams should also cover nursing homes and other residential institutions and the primary/seconday care inrterface.
- Guidelines for appropriate antimicrobial usage should be introduced in all aspects of both medical and veterinary practices
- Access to diagnostic testing must be increased

Three years later, there is still a consensus that the Copenhagen recommendations are still valid and should be implemented broadly.

For both human and veterinary medicine, it is a fact that there is no shortage of guidelines. The overall major gaps are merely in the implementation and follow up on adherence to these recommendations. As the structure and needs of human and veterinary medicine differ substantially, different strategies must be applied in order to overcome these gaps. Therefore, the sectors have been dealt with separately. However, many of the points raised in the respective sectors could be adapted to the other field.

Human medicine

Educational initiatives for health professionals and the general public

Current status
Many countries have agreed on national or local guidelines as an educational tool for the prescribing physicians. Many agreed that inappropriate prescribing had decreased after the introduction of the guidelines. For the European Community, a common curriculum for the postgraduate training of infectious disease physicians is being defined. Two countries have also conducted campaigns for raising awareness of the problem of antibiotic resistance in the general public.

Obstacles
There are still major gaps in some countries, in respect to the education of undergraduates and in continuing medical education, concerning appropriate antibiotic prescription. Another important issue is the lack of infectious disease specialists in most of the countries. It has not yet been defined how to measure the knowledge of the general public concerning antimicrobial resistance.

Considerations for future actions
Health care workers (physicians, pharmacists, nurses) must be educated.
The general public should also be educated to take responsibility by complying with treatment advice.

This education must be provided without creating anxiety but in order to increase their awareness for prudent antibiotic use.

Antibiotics should be available by prescription only

Current status
Although in most of the countries, antibiotics are available by prescription only, there was consensus that in some countries, antibiotics are still are sold over the counter (OTC). It is also common knowledge that in some countries, pharmacists substitute prescriptions of antibiotics from one compound to another and not only for generic products.

Obstacles
There are no scientific data to define the amount of the non-prescription use of antimicrobials in the EU. There is also lack of scientific evidence if and to what extent such use drive antibiotic resistance.

Considerations for future actions
Sales of antimicrobials should be restricted r to prescription only in all countries. Ongoing practices of non-prescription use should be investigated. The existing laws regulating the dispensing of antimicrobial agents should be enforced. The general public should not be exposed to direct advertisements for antimicrobial agents from the pharmaceutical industry.

Antimicrobial teams should be introduced in every hospital. The teams should also cover other institutions and primary/secondary care

Current status
Almost every country has an infection control team in major hospitals and many of those are also in charge of counselling in the management of infectious diseases and antimicrobial usage. Additionally some of the countries also have community-based teams working on the management of communicable diseases.

Obstacles
Although it was agreed upon that antimicrobial teams can make a substantial contribution to the proper usage of antimicrobials by reinforcing antibiotic policies and linking antibiotic usage to local resistance surveillance data, there is in general a lack of human resources and funding for these activities. In most countries, it is also impossible to trace antibiotic usage to the individual patient and prescribing physicians due to the lack of proper information technology. None of the countries is covering the needs of nursing homes, which are known to host a lot of inhabitants colonized with multiresistant bacteria ("Nobody cares").

Consideration for future action
Ideally the team should consist of an infectious disease physician and /or a clinical microbiologist, a pharmacist with special expertise in antimicrobial agents and a senior nurse. There is an urgent need for antimicrobial teams working across hospital boundaries. The consultation in hospitals and in primary care should be done by specially trained physicians preferably infectious disease physicians. There is also an urgent need to implement professional consulting in nursing homes.

Guidelines for appropriate antimicrobial usage should be introduced in all aspects of both medical and veterinary practices

Current status
Most countries have generated national or local guidelines dealing with the diagnosis and treatment of infectious diseases.

Obstacles
Nobody knows the best way to implement the guidelines. Lack of simplicity, credibility and easy availability of the guidelines could be major obstacles for broad acceptance. In order not to counteract the guidelines by marketing activities, it is important to inform the pharmaceutical industries of the existing guidelines.

Considerations
Supranational guidelines are needed e.g. concerning the duration of antimicrobial therapy in defined diseases, and in antimicrobial prophylaxis in surgery and also dealing with appropriate dosing based on pharmacodynamic/pharmacokinetic parameters. Guidelines must be based on scientific evidence, should be simple, easily accessible and should be generated locally based on local surveillance and consumption data.

The guidelines should be drawn up by a multidisciplinary body including the prescribers to achieve high credibility in order to ensure broad acceptance.

Access to diagnostic testing must be increased

Current status
In the Nordic Countries, rapid tests are widely available and used in primary care.

Obstacles
In most countries, there is no reimbursement of these tests. Additionally, in some countries there is also a conflict of interest between microbiological laboratories performing profound testing and primary care interested in rapid results to guide prescription.

Considerations
Rapid testing should be encouraged to be widely available in all countries. Rapid testing must be reimbursed.

Veterinary medicine

The use of antimicrobial agents in animal husbandry should be an integrated part of quality assurance systems. Furthermore, prudent use guidelines should also include the use of antimicrobial agents to pets and horses.

Educational initiatives

Current status
Many countries have started campaigns to improve the education of those involved in usage of antimicrobial agents in animals. Education is aimed both at the veterinarian, the public and the end user.

Considerations for future actions
Education of veterinary students concerning antibiotic resistance and pharmacotherapy of infectious diseases should be improved. Continuous education in relevant areas should be available to all practitioners. Farmers and other end users should be educated in adequate usage and handling of prescribed antimicrobial agents

Antibiotics should be available by prescription only

Current status
No consensus was reached on the potential effect of depriving the veterinarian in certain countries the right to make a profit from selling drugs. Although in Denmark this intervention had a limiting effect on the amount of antibiotics prescribed, it was disputed whether the same effect would occur in other countries where conditions differ.

Considerations for future actions
Antimicrobial agents should not be advertised to farmers and pet owners. Steps should be taken to harmonise the European legislation with regard to distribution and sales of veterinary drugs.

Guidelines

Current status

General guidelines on prudent use of antimicrobial agents are developed in most countries. Specific guidance on antibiotic choices ("formularia") is only implemented in a few countries, e.g. Denmark and The Netherlands. In addition, The Federation of European Veterinarians (FVE) recommends the use of specific guidelines for the choice of antimicrobial agents. In other countries more general guidelines and guidelines where antimicrobial agents are included as an integrated part of a control program for certain infectious diseases are favoured.

Obstacles

It is desirable that specific guidelines adhere to the dosage regimens authorised by licensing authorities for a given animal species. However, for currently licensed products the dosage regimen is not always optimised with respect to efficacy and undesirable side effects, such as selection of antibiotic resistance using pharmacodynamic/pharmacokinetic principles. Further, for some animal species only a limited number of antibiotics are licensed (varies by country).

It is difficult to implement prudent use guidelines drawn up by central bodies or other organisations into the everyday work of practitioners. Such guidelines are not efficiently communicated to the veterinarians or the end user. The usefulness of detailed guidelines is still questioned by many veterinarians. By some, very prescriptive formularia-type of guidelines was considered as inappropriate because it would limit the opportunities for a veterinarian to use his common sense and knowledge in pharmaco-therapy. Others claimed that making recommended choices of 1st, 2nd and 3rd line antimicrobial agents by expert veterinarians and veterinary pharmacists is the best way to promote rational therapy. Consensus on this matter was not reached.

The effect of the usage of guidelines cannot be assessed unless very specific consumption data of antimicrobial agents are available. Such data are mostly lacking.

Considerations for future actions

Pharmacodynamic/pharmacokinetic principles should be included in the application for licensing of new veterinary medicinal products.

Consensus within the veterinary profession should form the basis for guidelines for therapy, whether "formularia-type" or more general. Guidelines should be developed for food animals, aquaculture, pets and horses and should be presented and discussed in post-graduate courses for veterinarians. Guidelines should be linked to infectious disease prevention strategies (incl. vaccination programs) and herd or flock health management.

Guidelines should include discussion support systems for treatments of groups of animals e.g. when group treatment is rational. Preventive use of antimicrobial agents should be limited to indications such as pre-surgery treatment.

Optimal use of laboratory diagnostics and availability and use of on-site diagnostics is needed to improve the rational choice of antimicrobials. Updated data obtained on use of antimicrobials and on resistance should be available to prescribers.

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Last but not least - thanks to all participants for listening, discussing and actively participating including preparing papers for the meeting.

Peet J. Tüll

ANNEXES

Annex 1. Abbreviations used

AMR = Antimicrobial Resistance
AR = Antimicrobial Resistance
ARBAO = Antimicrobial Resistance of Animal Origin
ATC = Anatomic Therapeutic Classification
DDD = Defined Daily Dose
DG = Directorate General
EARSS = European Antibiotic Resistance Surveillance System
EASSA = European Antimicrobial Sensitivity Survey in Animals
EEA = European Environment Agency???
EFTA = European Free Trade Association
EFPIA = European Federation of Pharmaceutical Industries and Associations
EMEA = European Agency for the Evaluation of Medicinal Products
ERGAS = Erythromycin Resistant Group A beta-hemolytic streptococci
ESBL = extended spectrum beta-lactamase
ESCMID = European Society of Clinical Microbiology and Infectious Diseases
EU = European Union
DANMAP = Danish program for surveillance of resistance
FEDESA = European Federation for Animal Health
FEFANA = European Feed Additive Manufacturers Association
GISA = Glycopeptide Intermediate *Staphylococcus aureus*
IMS =
MDRTB = Multiresistant Mycobacterium tuberculosis
MIC = Minimal Inhibitory Concentration
MRSA = Methicillin Resistant *Staphylococcus aureus*
NORM = Norwegian Organization for Surveillance of Antibiotic Resistant Microorganisms
NORMVET = Coordinated veterinary program
OIE = Office International des Epizooties
OTC = Over The Counter
PHLS = Public Health Laboratory Services
SARI = Strategy for Antimicrobial Resistance in Ireland
SRGA = Swedish Reference Group for Antibiotics
UK = United Kingdom
VLA = Veterinary Laboratory Agencies
VRE = Vancomycin (glycopeptide) Resistant Enterococci
WHO = World Health Organization

Annex 2. Antimicrobial Resistance Surveillance in Human Medicine

The following country summary describes the surveillance activities in the European countries 2001 as reported by the countries in Eurosurveillance (human) and in the "Background papers" (Human and Veterinary: "The Microbial Threat Progress Report on Antimicrobial Resistance", Visby, Sweden, June 2001) and corrected in plenum during the workshop.

Abbreviations used:
EASSA = European antimicrobial sensitivity survey in animals
ERGAS = erythromycin resistant group A beta-hemolytic streptococci
ESBL = extended spectrum beta-lactamase
GISA = glycopeptide intermediate *Staphylococcus aureus*
MDRTB = multiresistant Mycobacterium tuberculosis
MRSA = meticillin resistant *Staphylococcus aureus*
PHLS = Public Health Laboratory Services
VLA = Veterinary Laboratory Agencies
VRE = vancomycin (glycopeptide) resistant enterococci

Country	**Systems for collecting data on antimicrobial resistance (AMR)**
Austria	MDRTB, MRSA, VRE, *Neissera meningitidis*, *Escherichia coli, Salmonella* spp., *Campylobacter* spp., *Shigella* spp., *Streptococcus pyogenes*, EARSS.
Belgium	MDRTB, MRSA, VRE, GISA, ESBL, *Streptococcus pneumoniae, Neisseria meningitidis, Streptococcus pyogenes.* Existing surveillance in hospitals: invasive *Streptococcus pneumoniae* and *Staphylococcus aureus* (EARSS);
Cyprus	No activity—lack of expertise and resources.
Czech Republic	Existing programmes (>5 years) for local and national surveillance in hospital and community. Working group for surveillance of antibiotic resistance (WGSAR).
Denmark	MDRTB, MRSA, VRE, GISA, *S pneumoniae, S pyogenes, E coli, Salmonella* spp, *Campylobater* spp. Existing programme "DANMAP" (5 years): local and national surveillance—coordination with veterinary surveillance. EARSS.
Finland	MDRTB, MRSA, VRE, *N meningitidis, E coli, Salmonella* spp., *Campylobacter* spp., *S pneumoniae, S pyogenes, H* influenzae, *M catarrhalis*, *N gonorrhoeae*, *Klebsiella spp*., *Pseudomonas* spp., Existing programme "FiRe/Finres" (10 years). Coordinated veterinary/human programme in existence. Yearly national report on many pathogens.

Country	Systems for collecting data on antimicrobial resistance (AMR)
France	MDRTB, MRSA, GISA, *S pneumoniae, H influenzae, Salmonella* spp., *N meningitidis, Helicobacter pylori*. EARSS (NCR for pneumococci 400 labs and three other networks 50 labs). Coordination between animal and human antimicrobial resistance. Mandatory notification of bacteria with new phenotype of resistance.
Germany	MRSA, GISA, VRE. MDRTB. No existing formal surveillance programme. Mandatory registration of ESBL and multidrug resistance in hospitals.
Greece	MDRTB, MRSA, VRE. Network (WHONET) 80% of hospitals, Gram-negatives. Methodological problems with *S pneumoniae* surveillance.
Hungary	National reporting system (not specified) covering 50% of clinical microbiology laboratories and all important pathogens (not specified).
Iceland	Participation in EARSS (100% coverage of invasive strains expected in 2001). Ongoing surveillance of resistance in *Salmonella* spp*., Campylobacter* spp., *S pneumoniae, S pyogenes* and *N meningitidis*.
Ireland	MDRTB, MRSA, GISA, *S pneumoniae*. No formal national surveillance programme. EARSS. *Salmonella* spp. *N meningitidis*. SARI—local, regional, and national infrastructure is called for and "surveillance scientists" shall be appointed to all hospital laboratories and health boards.
Italy	MDRTB, MRSA, GISA*, S pneumoniae, N meningitidis, Salmonella* spp., *Campylobacter* spp. No existing formal surveillance programme. EARSS. Pilot project in 70 hospitals monitoring resistance in blood isolates (*S aureus, S pneumoniae*, enterococci, *Klebsiella* spp.)
Lithuania	No information on resistance surveillance in bacteria in humans.
Malta	No formal national surveillance programme as yet but programme in development, WHONET, EARSS, annual newsletter.
Norway	MDRTB, MRSA, VRE, *S pneumoniae*. Formal national (<5 years) surveillance programme NORM (network of laboratories) with quantitative data (E-test), many bacteria. Coordinated veterinary programme (NORMVET) implemented 2001.
Portugal	MDRTB, MRSA, VRE, *S pneumoniae, H influenzae, N meningitidis, Moraxella catarrhalis, Pseudomonas* spp., *Acinetobacter* spp. No formal national surveillance. Local programmes in hospitals. Network of 16 laboratories coordinated by the NIH in Portugal. EARSS.
Romania	No formal national surveillance.
Spain	(Eurosurveillance data only). MDRTB.

Country	Systems for collecting data on antimicrobial resistance (AMR)
Sweden	MDRTB, MRSA, VRE, *S pneumoniae*. Formal national surveillance (8 years) (network of all laboratories), combined with external quality control system: *S pneumoniae, S pyogenes, H influenzae, E coli, Pseudomonas aeruginosa, Enterobacter* spp., enterococci, *Pseudomonas* spp. and all blood-culture isolates. EARSS (1999—present*): S pneumoniae, S aureus, E coli*, enterococci. Not coordinated with the veterinary programme. *Notifiable* : MRSA, VRE, high-level penicillin resistant *S pneumoniae.*
Switzerland	**No formal national surveillance apart from above. National surveillance programme planned for 2002.**
The Netherlands	MDRTB, MRSA, VRE, *S pyogenes* (ERGAS). Surveillance based on the consecutive results in 8 local clinical laboratories with IT-support for central analysis of all results. EARSS (administered by RIJVM).
United Kingdom	MDRTB, GISA, MRSA, VRE, *S pyogenes*. A national surveillance programme under development including both sentinel and routinely generated laboratory data. *N mengitidis, N gonorrhoeae, Salmonella* spp.. EARSS. External operative QC-programme with distributions to all European countries (NEQAS). Sentinel programmes in Scotland (15 organisms).
ESCMID	EUCAST, ESGAP, ESGARS, ARPAC

Annex 3. Antimicrobial Resistance Surveillance in Veterinary Medicine

Country	**Systems for collecting data on antimicrobial resistance (AR) in animal bacteria**	**Collaboration (human and veterinary medicine)**	**Comments**
Austria	No surveillance system established in veterinary medicine.	Not mentioned	
Belgium	Surveillance of AR through network of laboratories, standardization of antibiogram.	Not mentioned	
Cyprus	Nothing is mentioned about veterinary medicine.	Not mentioned	**Interested in participating in a European Surveillance system.** Including veterinary medicine?
Czech Republic	Nothing is mentioned about veterinary medicine.	Not mentioned	
Denmark	A continuous monitoring on the occurrence of antimicrobial resistance among food animals and food of animal origin was implemented in 1995 (DANMAP).	Results from the monitoring program are published annually and coordinated with monitoring of AR among bacteria causing infections in humans.	
Finland	1. Has been investigating resistance in bacteria since the 1960s. 2. In 2001, a continuous surveillance program on a number of key bacteria and antimicrobials has started.	A multidisciplinary report was published in 1999: ”Bacterial Resistance to Antimicrobial Agents in Finland FINRES 1999”	1. This monitoring has not been continuous or consistent for all relevant bacteria, but does provide perspective to the resistance situation 2. This program attempts to proceed in harmony with similar programs in Sweden, Norway and Denmark.

Country	Systems for collecting data on antimicrobial resistance (AR) in animal bacteria	Collaboration (human and veterinary medicine)	Comments
France	A network for surveillance of AR in pathogenic bacteria from cattle was established in 1985. In 2000 it was extended to pigs. A surveillance program of AR in intestinal bacteria was started for poultry in 1999 and for pigs in 2000. Surveillance of AR in *Salmonella* from animals, food and environment was improved concerning processing of data allowing discovery of new phenotypes and to perform surveillance parallel to human medicine.	Yes	Several committees are involved in the policy against AR. There is not, at present, a committee *ad hoc* against AR, but different aspects of the problem are discussed in multidisciplinary working groups.
Germany	AR in *Salmonella* is monitored since 1967. Currently 3 000 isolates/year are tested. It has been proposed to the Ministry that AR monitoring should be performed in zoonotic bacteria, sentinel bacteria and animal pathogens.	Cooperation with human medicine in an inter-ministry task group.	
Greece	Eleven laboratories are searching for AR bacteria, but there is no co-ordination in the processing of data.	Yes?	A Reference Centre for microbial resistance is proposed. Only veterinary medicine?
Hungary	Since January 2001, susceptibility testing of *E. coli*, *Salmonella*, *Campylobacter* and enterococci from food animals is performed. All 19 counties are participating.	Plans exist for an integrated program for monitoring trends in AR of bacteria from animals, food and humans.	Susceptibility testing of bacteria from carcasses, different samples from food animals and pets has been carried out in veterinary institutes for a long time but in different ways.
Ireland	4 000 samples of domestically produced and imported poultry meat has been analysed for AR bacteria since 1999.	Not mentioned	

Country	Systems for collecting data on antimicrobial resistance (AR) in animal bacteria	Collaboration (human and veterinary medicine)	Comments
Italy	A project for standardisation and harmonisation of susceptibility testing methods started in the end of 2000. The major goal is to obtain comparable data at national level on zoonotic/indicator bacteria and animal pathogens. In 2001, more than 500 salmonellas have been tested for AR.	A reference centre on AR is proposed to the Ministry. Collaboration has started in a discussion Forum (Forum on AR), gathered for the first time in 2000.	The aim of the project is to obtain a network of laboratories performing susceptibility testing. Results of inter/intralaboratory testing will be available at the end of September 2001.
Lithuania	Nothing mentioned about surveillance of resistance to antimicrobials.	Not mentioned	
Malta	Nothing is mentioned about veterinary medicine.	Not mentioned	
The Netherlands	Monitoring program started in 1998 – AR in zoonotic food-borne pathogens and commensal organisms.	Recommended by the Council and implemented for food-borne pathogens, but not for commensal organisms or for human nosocomial infections.	Since a great deal of information on resistance surveillance is currently collected at various locations, co-ordination needs to take place with respect to the checking, processing and interpretation of the data.
Norway	A continuous monitoring program for AR in the veterinary and food sector (NORM-VET) started in 2001.	Yes	In the veterinary and food sector, surveys regarding AR in relevant bacteria from various sources including pathogen and/or indicator bacteria, have been conducted annually in recent years.
Portugal	The authorities does not have a specific policy or co-ordination service for AR monitoring	No	Monitoring of AR is mainly a local goal at central laboratories, private laboratories and at veterinary hospital levels. Information concerning AR in animal bacteria is available since the end of the 70s.
Romania	Surveillance/registration systems has not been established		

Country	**Systems for collecting data on antimicrobial resistance (AR) in animal bacteria**	**Collaboration (human and veterinary medicine)**	**Comments**
Sweden	Monitoring of AR in *Salmonella* is conducted since 1978. A monitoring continuous monitoring program of AR in bacteria from animals was started in 2000 (SVARM)	No	Surveillance of AR in other animal bacteria than *Salmonella* has depended on point-prevalence studies of key pathogens carried out on an *ad hoc* basis.
Switzerland	A study on AR in *S.* Typhimurium isolates from humans, animals and other sources was launched in 2000.	Not mentioned	
United Kingdom	The action areas are for example: to establish and maintain systems in the UK, to improve data and info on antimicrobial use, AR organisms and the illnesses due to them; to improve correlation of data on patterns of antimicrobial use and AR in human and animal bacteria.	The PHLS and the VLA have signed a Memorandum of Understanding to provide a basis for closer collaboration. A close working relationship has been developed with the aim of co-ordinating the surveillance of AR in pathogens of human and animal origin.	Results were made public in June and December 2000. A public presentation of further results on prevalence of resistance is planned for this year.
Multi national			
FEDESA	The FEFANA study (see below) became EASSA and extended to include cattle, *Salmonella*, *E. coli*, *Campylobacter* and sentinel bacteria. Next step is veterinary pathogen surveys.	No	The overall intentions: To establish sensitivity baselines To track sensitivity changes Provide material for renewals
FEFANA	Surveillance of resistance among animal *E. faecium* to growth promoter antibiotics in the EU over 2 years.	No	

Annex 4 List of participants

Organizing Committee

Peet J Tüll,	chairman National Board of Health and Welfare, Sweden
Otto Cars	STRAMA – Swedish Strategic Programme for The Rational Use of Antimicrobial Agents and Surveillance of Resistance, Sweden
Anders Franklin	National Veterinary Institute SVA, Sweden
Christina Greko	National Veterinary Institute SVA, Sweden
Marja Larsson	National Board of Health and Welfare, Sweden
Håkan Wahren	National Board of Health and Welfare, Sweden

Family name	First name	Ministry/Authority	City	Country
Aarestrup	Frank	Ministry of Food, Agriculture and Fisheries	Copenhagen V	Denmark
Acar	Jacques	Université Pierre et Marie Curie	Paris Cedex 14	France
Aho	Matti	Ministry of Agriculture and Forestry		Finland
Alexandersson	Anders	National Board of Health and Welfare	Stockholm	Sweden
Allerberger	Franz	Bundesst. Bakt.-Serol. Untersuchungsanstalt	Innsbruk	Austria
Anderson	Ray	Veterinary Medicines Directorate	Surrey	United Kingdom
Andréasson	Peter	National Board of Health and Welfare	Stockholm	Sweden
Aronsson	Bo	EMEA	London E14 4HB	United Kingdom
Aspöck	Christoph	Vienna General Hospital	Vienna	Austria
Aubry-Damon	Hélène	Institut de Veille Sanitaire	St. Maurice	France
Baduel	Valerie	Ministry of Agriculture and Fisheries	PARIS CEDEX 15	France
Battisti	Antonio	Istituto Zooprofilattico Sperimentale Lazio e Toscana	Rome	Italy
Bauraind	Isabelle	Ministry of Social Affairs, Health and Environment	Brussels	Belgium
Bernardo	Fernardo	Ministry of Agriculture	Lisboa	Portugal
Bodur	Hürrem	Ministry of Health	Ankara	Turkey
Boisseau	Jacques	OIE	Fougeres	France
Borg	Michael A.	Ministry of Health - Malta	G'mangia	Malta
Borisov Velinov	Tzuetan	Ministry of Health	Sofia	Bulgaria
Brum	Laura	National Health Institute	Lisboa	Portugal
Bryskier	André	EFPIA	Romainville	France
Buchow	Hartmut	European Commission	Luxembourg	Luxembourg
Busani	Luca		Rome	Italy
Butaye	Patrick	Ministry of Social Affairs, Health and Environment	Brussels	Belgium
Bywater	Robin	FEFANA	Shropshire	United Kingdom
Caldeira	Luis	INFARMED-PORTUGAL	Lisboa	Portugal
Campagnoli	Carla	Ministry of Health	Roma	Italy
Canica	Manuela	Ministry of Health, National Insitute of Health	Lisboa	Portugal
Carlson	Johan	National Board of Health and Welfare	Stockholm	Sweden
Cars	Otto	Swedish Institute for Infections Disease Control	Solna	Sweden
Cassone	Antonio	Istituto Superiore di sanitá	Roma	Italy

Cluzeau	Alain	Europeean Commission	Luxembourg	Luxembourg
Coditá	Ìrina	Ministry of Health and Family Contaquizion	Bucharest	Romania
Cornaglia	Giuseppe	ESCMID	Verona	Italy
Courvalin	Patrice	Institut Pasteur		France
Cunney	Robert	National Disease Surveillance Centre	Dublin 2	Ireland
Cöplü	Nilay	Ministry of Health	Ankara	Turkey
da Gracas Freitas	Maria	General Directorate of Health	Lisboa	Portugal
Das	Pam	The Lancet	London	United Kingdom
de Neeling	A J	National Institute of Public Health and the Environment	Bilthoven	The Netherlands
De Roo	Charlotte	BEUC	Bruxelles	Belgium
Denecker	Nathalie	Ministry of Social Affaires, Health and Environment	Brussels	Belgium
Devlin	John	Department of Health and Children	Dublin 2	Ireland
Dumarcet	Nathalie	Agence Francaise de Sécurité Sanitaire des Products de Santé	SAINT-DENIS CEDEX	France
Dumpis	Uga	Department of Health	Riga	Latvia
Ekdahl	Karl	Swedish Institute for Infectious Disease Control	Solna	Sweden
Ekman	Åsa	National Board of Health and Welfare Sweden	Stockholm	Sweden
Finch	Roger G.	Nottingham City Hospital	Nottingham	United Kingdom
Follet	Ghislain	FEDESA	Brussels	Belgium
Franklin	Anders	National Veterinary Institute	Uppsala	Sweden
Friemondt-Möller	Niels	Statens Seruminstitut		Denmark
Füzi	Miklós	Johan Bela National Centre of Epidemiology	Budapest	Hungary
Garau	Javier	Hospital Mutua de Terassa		Spain
Giamarellou	Helen	FEMS	Maroussi-Attikis	Greece
Girma	Kinfe	Swedish Board of Agriculture	Jönköping	Sweden
Goossens	Herman	University of Antverpen	Belgium	Belgium
Gotrik	Jens Kristian	National Board of Health	Köpenhamn K	Denmark
Grave	Kari	Norwegian Zoonosis Center	Oslo	Norway
Greko	Christina	National Veterinary Institute	Uppsala	Sweden
Gunn	Michael	Dept. of Agriculture, Food & rural Development	Dublin 2	Ireland
Halbich-Zankl	Helga	Federal Ministry of Social Security and Generations	Wien	Austria
Hetland	Tharald	Ministry of Health and Social Affairs	Oslo	Norway
Honkanen-Büzaleski	Tuula	National Veterinary and Food Research Institute	Helsinki	Finland
Hoszowski	Andrzej	National Veterinary Research Institut	Pulawy	Poland
Howard	Anthony John	Public Health Laboratory Service (Wales)	Cardiff	United Kingdom
Huovinen	Pentti	Ministry of Social Affairs and Health	Turku	Finland
Högberg	Liselotte	Swedish Institute for Infectious Disease Control	Solna	Sweden
Jans	Didier	FEFANA	Brussels	Belgium
Juhaszne Kaszanyitzky	Eva	Central Veterinary Institute	Budapest	Hungary
Kahlmeter	Gunnar	Swedish Institute for Infectious Disease Control	Växjö	Sweden
Kangas	Susanna	Ministry of Agriculture and Forestry	Goverment	Finland
Karlsson	Stefan	Ministry of Health and Social Affairs	Stockholm	Sweden
Kaziliüniene	Kristina	Lithuanian State Inspection on Veterinary Preparations	Kaunas	Lithuania
Koppinen	Jouko	Ministry of Agriculture and Forestry	Goverment	Finland
Kreutz	Gottfried	Bundesinstitut für Arznelmittel und Medizinprodukte	Bonn	Germany
Kristinsson	Karl G.	Landspitali University Hospital	Reykjavik	Iceland

Kruse	Hilde	National Veterinary Institute	Oslo	Norway
Larsson	Marja	National Board of Health and Welfare	Stockholm	Sweden
Laurier	Lionel	Ministry of Social Affaires, Health and Environment	Brussels	Belgium
Le Quellec	Nat Han	Emploi Solidarité Sante'	Paris 07 SP	France
Leese	Jane	Department of Health	London	United Kingdom
Lindmark	Hans	National Food Administration	Uppsala	Sweden
Lithander	Eva	National Board of Health and Welfare	Stockholm	Sweden
Litske Petersen	Jens G.	Danish Plant Directorate	Lyngby	Denmark
Lømo	Ola Magnus	Ministry of Agriculture	Oslo	Norway
Lönnroth	Anna	European Commission	Brussels	Belgium
Maniatas	John	Ministry of Agriculture	Athens	Greece
Mckellar	Quintin	Moredlin Research Institute	Penicuik, Scotland	United Kingdom
Mevius	Dik	Institute for Animal Science and Health	Lelystad	The Netherlands
Mristov Kouzmanov	Andrey	Ministry of Health	Sofia	Bulgaria
Mudd	Antony	FEDESA	Brussels	Belgium
Myllymiemi	Anna-Liisa	National Veterinary and Food Research Insitute (EELA)	Helsinki	Finland
Mörner	Anne	FEDESA	Bro	Sweden
Nagler	Jan	Ministry of Social Affairs, Health and Environment	Brussels	Belgium
Nieuwenhuÿs	Jan	Inspectorate for Public Health	Den Haag	The Netherlands
Nilsson	Maj-Inger	EFPIA	Brussels	Belgium
Nilsson-Carlsson	Iréne	Ministry of Health and Social Affairs		Sweden
Nind	Fred	FVE	Brussels	Belgium
Norrby	Ragnar	Swedish Institute for Infectious Disease Control	Solna	Sweden
Odenholt	Inga	Universitetssjukhuset MAS	Malmö	Sweden
Ottevanger	Arie	Ministry of Health, Welfare and Sport	Den Haag	The Netherlands
Ottosson	Hans	Swedish Institute for Infectious Disease Control	Solna	Sweden
Pantosti	Annalisa	Istituto Superiore Di sanito	Rome	Italy
Patzer	Jan	Ministry of Health	Warsaw	Poland
Paulaskas	Vidmantas	National Veterinary Laboratory	Vilnius	Lithuania
Pieridou-Bagatzoum	Despo	Ministry of Health	Nicosia	Cyprus
Piffaretti	Jean-Claude	Swiss Society of Microbiology	Lugano	Switzerland
Poirier	Jacques	FEFANA	Antony Cedex	France
Pompa	Maria Grazia	Ministry of Health	Rome	Italy
Ponte	Helena	Miniatry of Agriculture	Lisboa	Portugal
Raeber	Pierre-Alain	Federal Office of Public Health	Bern	Switzerland
Rehnqvist	Nina	National Board of Health and Welfare	Stockholm	Sweden
Reiner	Helmuth	Federal Institute for Health Protection of Consumers and Veterinary Medecine	Berlin	Germany
Röstel	Barbara	OIE	Fougeres	France
Sanders	Pascal	Agence Francaise de Sécurité Sanitaire des Aliments	Fougeres	France
Sarris	Kriton	University of Thessalonica	Thessalonica	Greece
Schrijnemakers	Paul	Riksinstituut voor Volksgezondheid en Millieu	Bilthoven	The Netherlands
Shryock	Thomas R.	FEDESA	Greenfield	United States
Siemelink	Max Evert	Ministry of Agriculture, Nature Management & Fisheries	The Hague	The Netherlands
Skov Simonsen	Gunnar	Norwegian Organisation for Surveillance of Antibiotic Resistant Microorganisms-Norm	Tromsø	Norway
Stobberingh	E	Masstricht University Hospital	Maastricht	The Netherlands

Struelens	Marc	ESCMID	Brussels	Belgium
Tofftén	Anna	Ministry of Agriculture, Food and Fisheries	Stockholm	Sweden
Tokola	Olavi	National Agency for Medecines	Helsinki	Finland
Tronstad	Aase	Ministry of Agriculture, Food and Fisheries	Stockholm	Sweden
Tüll	Peet	National Board of Health and Welfare		Sweden
Ungemach	Fritz R.	University of Leipzig		Germany
Urbain	Bruno	Ministry of Social Affairs, Health and Environment	Brussels	Belgium
Wahren	Håkan	National Board of Heatth and Welfare	Norrköping	Sweden
Valinteliene	Rolanda	Institute of Hygiene	Vilnius	Lithuania
Wallén	Catarina	National Veterinary Institute	Uppsala	Sweden
Wallensteen	Karin	Ministry of Agriculture		Sweden
Wallgren	Per	National Veterinary Institute	Uppsala	Sweden
Walters	John	FEFANA	Surres	United Kingdom
van den Bogaard	Anthony	University of Maastricht	MD Maastricht	The Netherlands
van Dijk	Trudy	Ministry of Health	Postbus	The Netherlands
Van Wijngaarden	Jan	Inspectorate of Health Care	The Hague	The Netherlands
Van Vossel	Alain	European Commission	Brussels	Belgium
Vanhemelrijck	Johan	FEDESA	Brussels	Belgium
Wechsler-Fördös	Agnes	Austrian Ministry of Health	Vienna	Austria
Wegener	Henrik	MoA/Danish Veterinary Laboratory	Copenhagen V	Denmark
Verbast	Ludo	Ministry of Social Affairs, Health and Environment	Brussels	Belgium
Werling	Hans-Otto	EFPIA	WUPPERTAL	Germany
White	Anthony	EFPIA	Essex	United Kingdom
Willeberg	Preben	Danish Veterinary and Food Administration	Soborg	Denmark
Williams	Rosamund	World Health Organization	Geneva 27	Switzerland
VÍT	Michael	Ministry of Health of teh Czech Republic	Prague 2	Czech Republic
Witte	Wolfgang	Robert Koch Institute	Werngerode	Germany
Wretman	Svante	National Board of Health and Welfare	Stockholm	Sweden
Älfvåg	Carl	Ministry of Health and Social Affairs		Sweden