The Copenhagen Recommendations

Report
from the Invitational EU Conference on

The Microbial Threat

Copenhagen, Denmark
9 - 10 September 1998

Edited by:
Vibeke Thamdrup Rosdahl, Division Director, Statens Serum Institut and
Knud Børge Pedersen, Director, Danish Veterinary Laboratory

www.microbial.threat.dk

Foreword

 "The Copenhagen Recommendations" on antimicrobial resistance display the results of the European Union conference on "The Microbial Threat" hosted by the Danish Government in Copenhagen 9 - 10 September 1998. The conference was preceded by two days of intensive workshop activities.

The participants invited were representing the competent health, veterinary, agriculture and food authorities, the professional bodies, the pharmaceutical industry, the universities, the consumers and other interested parties in the European Union Member States. Moreover there were representatives from the EU-applicant States and from the EEA-countries. Thus, this report on the conference reflects the opinion of a broad section of those dealing with
"The Microbial Threat" due to antimicrobial resistance.

The conference was initiated by the European Union Chief Medical Officers, who at their meeting in Luxembourg October 1997 paid particular attention to the increasing resistance to antibiotics and other antimicrobial agents in human medicine. They agreed that inappropriate use of these agents is of causal importance to the accelerating resistance problem. It is of particular concern that effective mechanisms to limit the emerging problem of drug resistant microbes may not yet be in place and thus have to be carefully considered. There are considerable implications for the delivery and quality of health care.

The conference made it clear that action on the problem of antimicrobial resistance must be taken at the Community level and in accordance with "The Copenhagen Recommendations".

Einar Krag
Chief Medical Officer
Denmark

Table of contents

Introduction

The structure of this report is based on the activities performed before the conference, during the workshops and at the conference. The following sequence of events took place:

- The five main topics to be dealt with at the conference were defined by the vicepresidents and the programme committee. It was decided that the conference should be preceded by five workshops in order to produce the basic material for the conference.

- Appointment of chairman and vice-chairman for each workshop in collaboration with the Chief Medical Officers, from the EU Member States. Appointment of a Danish secretary for each workshop.

- For each workshop a preparatory meeting with the chairman, vice-chairman, secretary in question and the programme commmittee including the Danish vice-president took place. During these meetings a synopsis for the topic of the workshop including two or three specific questions were prepared. Selected participants of the workshops were asked to introduce these questions.

- During the workshops on 7-8 September 1998 the participants of each of the five workshops prepared a paper on the topic dealt with including answers to the specific questions and conclusions.

- During the conference on 9-10 September 1998 each workshop introduced their paper to the conference and after the discussion at the conference the conclusions were modified accordingly.

- Based on these revised conclusion papers the programme committee together with the rapporteur and the Danish   vice-president prepared the recommendations presented at the end of the conference.

This report therefore includes the following material:

- The Copenhagen Recommendations.

- For each workshop: Topic of the workshop, names of chairmanship, secretary and participants. Specific questions and synopsis to the workshop. Conclusion papers prepared by the workshops and subsequently discussed and revised at the conference.

- Total list of participants at the conference.

The Copenhagen Recommendations

"Conclusions of Responding the European Union Conference on The Microbial Threat"

The implications for human health of the increasing resistance of micro-organisms to antimicrobial agents

Resistance to antimicrobial agents is a major public health problem in Europe.

International spread of microorganisms means that resistance to antimicrobial agents can no longer be regarded as a national problem. It is a European and global problem and requires a common strategy.

Antimicrobial resistance among microorganisms that cause disease in the community and in hospital is leading to increased deaths, illness, and costs. The full extent of the problem is, however, not yet known.

All antimicrobial drugs can select microorganisms that are resistant.

There is an established but complex relation between the consumption of antimicrobial agents and the prevalence of drug resistance in microorganisms. Dissemination of resistant microorganisms occurs both in hospital and the community. The major route of transmission of resistant microorganisms from animals to man is through the food chain.

Pharmaceutical companies are making great efforts to develop new antimicrobial agents and ways of countering infectious disease, and they should be encouraged to continue this important work. But such innovations cannot be expected to solve the problems in the near future. It is thus essential to introduce policies on the rational use of antimicrobials to avoid further increases in resistance.

The need for surveillance of microorganisms resistant to antimicrobial agents

Good quality data on resistant microorganisms are essential to underpin effective interventions to counter the problem of resistance and for developing guidelines on the prescribing of antimicrobial drugs. Such data must be clinically and epide-miologically relevant.

The conference advocates setting up a European surveillance system of antimicrobial resistance based on national systems. These systems must collect data on trends in antimicrobial resistance in bacteria of animal and human origin. Medical and veterinary collaboration will be essential. These systems should be coordinated within the European Union.

Effective European surveillance must have the agreement and active involvement of all the participants.

The need to collect data on the supply and consumption of antimicrobial agents

Collection of information about national supply of antimicrobial agents shows changes over time and differences among countries. These data are important triggers for investigation and action.

Evaluation of the benefits and risks of antimicrobial agents depends on collecting detailed information about their consumption by animals and humans and their use in aquaculture and horticulture.

Every member state should be able to collect national data on the supply and consumption of antimicrobial agents. They should collect data on dispensing of antimicrobial agents by community and hospital pharmacies. Data should also be collected on antimicrobial agents used to treat animals (by species) and for growth promotion.

Collation of data to compare practices among countries will not occur unless there is clear European Union strategy for ensuring transparency and comparability between national databases. A central strategy is also required to develop a multinational database.

Research information should be collected on the consumption of antimicrobial agents by specific patients, including why they were prescribed the agents.
This information is essential for analysis of good clinical practice. Those setting up these research databases need political and financial support.

Encouraging good practice in the use of antimicrobial agents

Educational initiatives for both health professionals (human and animal) and the general public are of major importance for improving the use of antimicrobial agents.

Antimicrobials for therapeutic use should be prescription-only medicines and so should not be advertised to the public.

Antimicrobial teams (including clinical microbiologists, infectious disease specialists, and other appropriate specialists) should be introduced in every hospital. They should have the authority to modify antimicrobial prescriptions of individual clinicians in accordance with locally accepted guidelines, always taking account of the needs of the patient. Clinicians should be given an opportunity to approve the remit and recommendations of the teams. The teams should also cover the community, including nursing homes and other residential institutions, and the primary/ secondary care interface. Feedback should be provided to clinicians.

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

The conference noted that most guidelines on antimicrobial usage say what should not be done rather than what should be done. A preliminary attempt was thus made to define good practice. What follows must be developed, but it is worth sharing - Treatment should be limited to bacterial infections, using anti-biotics directed against the causative agent, given in optimal dosage, dosage intervals and length of treatment with steps taken to ensure maximum patient concordance with the treatment regimen, and only when the benefit of the treatment outweighs the individual and global risks.

Steps must be taken to increase access to diagnostic testing for patients with infections, and the range of tests needs to be improved.

Most of those at the conference considered the use of antimicrobials for growth promotion was not justified and that it was essential to have a systematic approach towards replacing growth promoting antimicrobials with safer non-antimicrobial alternatives including better farming practice. Others thought that it was essential to conduct a full risk assessment before taking any further decisions.

The need for research to counter the problem of antimicrobial resistance

There is an urgent need to implement research programmes aimed at a better understanding and control of antimicrobial resistance. These should examine the effect and cost effectiveness of interventions to control antimicrobial resistance in humans and animals.

Priority should be given to studies on:
  - The effects of antimicrobial resistance on human disease
  - The optimal use of antimicrobial agents in humans and animals to minimise the risk of microorganisms developing resistance
  - The precise effect of antimicrobial agents used for purposes other than treating or preventing infection in humans
  - Criteria to define better clinical diagnoses in patients with infections, algorithms for patient management, and assessment of clinical outcome
  - Prescribing behaviour of doctors and compliance of patients with treatment
  - Ecological modification driven by antimicrobial agents on normal microbial populations in humans and animals
  - Novel principles for treating or preventing infections in humans and animals.

The European Union, member states, and national research councils should make coordinated research on antimicrobial resistance a high priority. A multidisciplinary scientific committee should be created at European level to direct and evaluate the research efforts.

Recommendations

♦   The European Union and member states must recognise that antimicrobial resistance is a major 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 antimicrobial agents.

♦   The European Union, 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.

Workshop no. 1:
Human health implications of the increasing resistance to antimicrobial agents

List of participants

Chairman: Marta Di Gennaro, Ministry of Health, Italy
Co-Chairman: Wolfgang Witte, Robert Koch Institute, Germany
Secretary: Peter Skinhøj, The National Hospital (Rigshospitalet), Denmark

Antoine Andremont, Chu Bichat-Claude Bernard, France
Francisco Antunes, Hospital de Santa Maria, Lisboa Codex, Portugal
Christoph Aspöck, Vienna General Hospital, Austria
Richard Bax, SmithKline Beecham Pharmaceuticals, United Kingdom
Henri Belveze, European Commission DGXXIV-1, Belgium
H. Buchow, European Commission, DG V, Luxembourg
Antonio Cassone, Instituto Superiore di Santá, Italy
Gary K. Chikami, Division of Anti-Infective Drug Products, FDA, USA
J. E. Degener, Academic Hospital Groningen, The Netherlands
R. Finch, Nottingham City Hospital NHS Trust, United Kingdom
Darina O. Flanagan, Eastern Health Board, Dublin, Ireland
Javier Garau, Hospital Mutua de Terrassa, Spain
Robert Hemmer, Centre Hospitalier de Luxembourg, Luxembourg
Vincent Jarlier, Laboratoire Central de bactériologie, Paris, France
Mats Kalin, Karolinska Hospital, Stockholm, Sweden
JosÈ Campos Marqués, Instituto de Salud Carlos III, Spain
Ragnar Norrby, University Hospital, Lund, Sweden
Annalisa Pantosti, Instituto Superiore de Sanita, Italy
Jørgen Schlundt, Danish Veterinary & Food Administration, Denmark
Peter Schmid, FEFANA, Germany
Marc Struelens, U.L.B. Hospital Erasme, Belgium
Dirk Vogelaers, Universitair Zienenhuis, Gent, Belgium
Martti Vaara, National Public Health Institute, Finland
Henrik Westh, Hvidovre Hospital, Denmark
Rosamund Williams, World Health Organization, Switzerland

Topic:

In this workshop the disease consequences of resistance should be assessed with reference to available data on morbidity and mortality due to antibiotic resistant micro-organisms. It is reasonable to assume that resistant micro-organisms cause an increase in morbidity and mortality due to inappropriate therapy and that patients not receiving an appropriate treatment will have a longer course of disease or even a fatal outcome. These patients may remain infectious for a longer period with an increased risk of spread of the resistant micro-organisms. The aim of the workshop is to provide valid data on the increased morbidity in infected patients as well as in outbreaks of infectious diseases caused by resistant micro-organisms.

Synopsis on introductory papers for workshop no. 1 regarding the specific questions

What kind of clinical and epidemiological data do we have on the consequences of resistant micro-organisms in the European region

For the hospitals give an overview of the impact on increased mortality caused by resistant strains compared to susceptible, as well as data on longer hospitalisation and increased costs due to the longer stay as well as to use of more expensive antibiotics. In the community focus on increased mortality as well as increased costs. Focus on European data but include data from other countries where relevant.

Describe that the most important resistance problems we are dealing with in the European region are:

- In hospitals multiresistant staphylococci, enterococci, pseudomonas and a number of enterobacteriacea like klebsiella and enterobacter.

- In the community pneumococci, Haemophilus influenzae, Moraxella catharrhalis, some salmonellae (DT104),TB, gonococci and meningococci.

How do we manage the treatment of infections due to resistant micro-organisms minimising the risk of further resistance development

For the above mentioned micro-organisms describe the present alternative antibiotic treatment and a short evaluation of future alternatives. Discuss combination therapy and shifts between different treatment regimes. In the community also focus on the possibility of vaccination, for which micro-organisms is it possible (pneumococci). This question is mainly dealing with areas/countries with major resistance problems.

How do we handle hospitalised patients with resistant micro-organisms in order to prevent nosocomial spread of the resistant micro-organisms

Two scenarios one with few resistant strains and one with endemic occurrence.
In the case of few strains describe procedures for early detection and alert, relevant isolation procedures, the number of patients that can be handled with these procedures. Summarise the guidelines from, e.g. the Scandinavian countries describing how to prevent the spread when only a few cases occur (are imported). Describe procedures in endemic areas. Is it possible to isolate in special wards. Give examples (very few exist) where it has been possible to decrease the number of patients with resistant strains. Discuss the contact with the community including a number of different institutions (nursing homes for elderly etc.).

Workshop no. 1. Conclusion paper

What kind of clinical and epidemiological data do we have on the consequences of resistance to antimicrobial agents

Available data clearly indicate that antibiotic resistance is a major public health problem in Europe. There are an increasing number of reports of fatalities as a consequence of resistant infections notably MDRTB (multidrug resistant tuberculosis bacteria). Studies in hospitals affected by MRSA (methicillin resistant Staphylococcus aureus) outbreaks have reported excess mortality rates, prolongation of hospital stay and increases of antibiotic expenditures. There are only few data on morbidity. Data of additional costs of relevance include more expensive antibiotics and prolongation of hospital stay. However, the data is often highly selective (either hospital versus community; organism or disease specific data; there is international variation in defining in-vitro resistance; data are rarely denominator controlled). Distinguishing "pharmacokinetic resistance" from antibiotic resistance may be important; high profile uncommon isolates e.g. VISA (vancomycin intermediate resistant S. aureus) and ESBL (extended spectrum beta-lactamace producing bacteria) achieve greater attention than low profile common organisms, e.g. gut pathogens, Escherichia coli and MRSA.

Ideally, there should be an accurate assessment of the impact of infections caused by resistant organisms by diagnosis, pathogen, therapeutic agent, and geographic breakdown in comparison with matched infections caused by susceptible organisms. The data should be denominator controlled.

The data should distinguish between community and hospital acquired infection. Data should be able to distinguish attributable morbidity and mortality from total morbidity and mortality data caused by resistant and susceptible pathogens. Data should also be linked to antibiotic usage. Economic impact should be assessed in terms of prolonged length of stay, excess antibiotic use and other health care
indices. Also adverse effects should be monitored.

Currently there is a patchwork of information which varies by pathogen, disease and geography.

MRSA. The number of documented infections has increased rapidly in many parts of Europe. Sampling frequency and denominator controlled data is often lacking. Blood and CSF (cerebro spinal fluid) isolates stress the rising health care burden but need to be balanced against data for methicillin-sensitive S. aureus infections. Until now there are few reports on the importance of MRSA infections in the community. The incidence is largely unknown but appears to be increasing.
MRSE (methicillin resistant Staphylococcus epidermidis). Coagulase-negative staphylococci are primarily nosocomial pathogens complicating implant surgery and high-dependency care. Bacteraemia is a common complication and provides a useful measure of the clinical impact. Multiple antibiotic resistance is common amongst these organisms.
Group A streptococci. Although beta-lactam sensitivity remains, erythromycin and tetracycline resistance is of concern but appears to fluctuate in relation to the quantitative use of these agents. Their importance lies in relation to the management of URTI (urinary tract infections) and skin and soft tissue infections occurring in the community.
VRE (vancomycin resistant enterococci) isolation rates have increased rapidly, largely from specialist hospital units (intensive care units, renal and haematology). Speciation and genotype data are often lacking. VRE is currently a high profile pathogen with variable disease expression and limited therapeutic opportunities. Defining the true clinical impact is an urgent matter.

E. coli. A major community and hospital associated pathogen which is susceptible to many antibiotics. Multi-drug resistance is common and in particular quinolone resistance is increasing. The major impact of resistance is reflected in the poor outcome for patients treated empirically for serious sepsis.

ESBL positive pathogens and stable depressed mutants of chromosomal beta-lactamase. They occur among the Enterobacteriaceae and Pseudomonas spp. A high profile and geographically variable group of pathogens largely occurring within high dependency units. Their true incidence and impact remain largely unknown.

Mycobacterium tuberculosis. A re-emerging pathogen of increasing importance, also in Europe. Microbiological isolation usually represents disease expression and the condition is notifiable. In-vitro resistance to first line agents is predictive of poor clinical response. The clinical impact of drug resistant tuberculosis is likely to increase as latent infections become more widespread

PRSP (penicillin resistant Streptococcus pneumoniae). A major community pathogen. Severe infections such as meningitis are of major concern. Pneumonia due to S. pneumonia with low level resistance can still be treated with aminopenicillins, but resistant strains are frequently resistant to many drugs. New conjugated vaccines will be important for the control of this problem.

Zoonotic infections. Clinically important resistance has emerged in enteric salmonella and campylobacter which is linked to antibiotic use in veterinary medicine.

Superinfections with candida spp. and other pathogens can follow broad spectrum antibiotic therapy given as a consequence of antibiotic resistance.

Conclusions

- Review and agree on a selection of pathogens for disease surveillance based on their current and likely future public heath importance. Data should include clinical outcome and costs.
- International agreement on surveillance standards including the laboratory definitions of sensitive, intermediate and resistant organisms.
- Data should be denominator controlled and include information on sensitive and resistant infections.
- Community based surveillance of the impact of resistance through sentinel centers should be established in view of the fact that 80% of prescribing occurs in the community.
- Data should be linked to information on antibiotic use.
- The economic impact of antibiotic resistant infections should be defined.

How do we manage the treatment of infections due to resistant micro-organisms minimising the risk of further resistance development

Selective antibiotic pressure and transferable resistance (clonal spread or horizontal resistance gene transfer) are major determinants of resistance development. Selective antibiotic pressure has created large reservoirs of transferable antibiotic resistance in hospitals in the community, as well as in animal husbandry which can communicate by different routes of transmission (e.g. patient to patient, food chain, waste water).

The following examples illustrate the role of selective pressure.

In Finland a marked increase of the use of erythromycin had resulted in very high frequencies of macrolide resistant group A beta-haemolytic streptococci. When the consumption of macrolides was reduced by about 50%, resistance decreased significantly.

Another example where a clear correlation between human use of antibiotics and emergence of resistance has been proven is for carriers of penicillin-resistant pneumococci. In Iceland a high frequency of day-care children were found to carry such organisms. The carriers had received antibiotic treatment during the preceding 6 months and they had recived co-trimoxazole significantly more often than other antibiotics (including penicillin). A third example where evidence exits for a correlation between amounts of antibiotics used and risk of emergence of resistance is for frequencies of Class I cephalosporinase in hospital isolates of aerobic Gram-negative enteric bacilli, e.g. Enterobacter spp. In hospitals with very high frequencies of that type of resistance an effective counter-measurement has been to drastically reduce the use of 3rd generation cephalosporins in the hospital environment.

The influence of selective pressure is however specific for bacterial species and groups of antibiotics.

There are well-documented examples for decline of resistant frequencies after reduction of selective pressure. Prudent use of antibiotics should be a way to reduce further resistance development. This includes reduction in length of treatment and use of narrow spectrum drugs when ever possible.

Presently there are still treatment options for most Difficult-To-Treat microorganisms although rare cases of Pseudomonas aeruginosa and other bacteria are reported for which treatment were unavailable.

However, in case of MRSA, VISA, VRE and other organisms second line treatment is often suboptimal and complex requiring 3 or 4 drugs. The regime are often toxic and costs greatly increased. Furthermore, resistance is already known for some of these drugs.

Some new compounds, which are expected on the market during the next few years, will be effective against some of the Difficult-To-Treat organisms. A number of modified or new antibiotics are in clinical trials such as ketolides, streptogramins, oxazolidinones and new carbapenems. However, none of these are active against important gram-negative rods.

There have been almost no totally new class of antibiotics put on the market for the past 20 years.

New technologies in research such as genome mapping of bacteria is likely to produce totally new classes of antimicrobial agents but not for some years. There is likely to exist, a window of vulnerability for some years where common pathogens become increasingly resistant and no totally new antimicrobials with novel modes of action are available.

Priority should therefore be given not only to the development of drugs but likewise to hygienic and other preventive efforts in containment of resistant infections.

Attemtps to use prebiotics and probiotics to protect the intestinal flora from replacement by resistant bacteria need further validation.

Isolation procedures is relevant in low prevalence areas.

No vaccine is available for any of the nosocomial bacteria but research in this field should be encouraged – as well as other areas of immune therapy.

How to prevent and control the nosocomial transmission of antimicrobial-resistant micro-organisms?

A major cause of increasing antibiotic resistance is transmission of resistant bacteria within hospitals by cross-colonisation of patients and subsequent spread between hospitals and from hospitals to other institutions by transfer of colonised patients. Current problem pathogens include multiple-drug resistant strains of the Gram-positive cocci Staphylococcus aureus, Enterococcus faecalis and E. faecium; and of the Gram-negative bacilli Klebsiella pneumoniae, Enterobacter spp., *Pseudomonas aeruginosa* and *Acinetobacter baumannii.*

Most commonly, nosocomial transmission occurs by contact between patients via the contaminated hands of health care personnel. Factors predisposing to this transmission include the severity of underlying illness, length of stay in hospital, intensity and duration of exposure to broad-spectrum antibiotics. Compliance of health care staff with basic infection control practices like hand washing or hand disinfection is incomplete and shortage of health care personnel often makes isolation precautions difficult to implement.

Less commonly, outbreaks of multiple-resistant bacteria, often caused by organisms like Pseudomonas spp. and Acinetobacter spp., are related to exposure of patients to contaminated food, equipmentís, medication or fluids, for instance during invasive procedures like mechanical ventilation or endoscopy, due to breaches of disinfection or sterilisation processes.

More than one-half of the patients in acute care hospitals receive antibiotics for therapy or prophylaxis. Hospital physicians often prescribe antibiotics excessively and inappropriately. Antibiotic therapy enhances transmission of MRB (multiple- drug resistant bacteria) by replacement of susceptible organisms of the endogenous microflora with resistant strains from the hospital microflora.

Strategies for prevention and control of nosocomial spread of multiple drug-resistant bacteria (MRB)

Strategies include: (1) general infection control practice, particularly hand hygiene (2) rational use of antibiotics, (3) specific measures of control of transmission of epidemic resistant bacteria, (4) laboratory detection, surveillance and reporting of the antibiotic resistant strains as support for and indicator of outcome of strategies (1) to (3). The growing recognition that infection control is essential for hospital accreditation is welcomed and supported.

Strategy no. 1: Improving hand hygiene practice in hospitals

There is an obvious rationale for improving the compliance of hospital staff with systematic use of hand hygiene precautions including the use of gloves for contact with body fluids, secretions and skin lesions, hand washing, and hand disinfection with alcohol based preparations. Guidelines for standard precautions such as the

HICPAC guidelines (1996) are proposed. There is circumstantial evidence that pro-motion of hand hygiene precautions can be associated with a reduction in antibiotic resistant bacteria transmission in acute care hospitals. New initiatives are needed.

Leadership and example by senior clinical staff appear important in this regard, as well as assigning responsibility to the health care team by feedback of surveillance on trends in MRB transmission in their own wards. The feasibility of this strategy depends also largely on providing sufficient staffing level, particularly in critical care departments. Also sufficient staffing levels of infection control nurses and infection control doctors are required to implement an effective prevention programme.

Strategy no. 2: Rational and prudent antibiotic policy

A number of scientific societies have recently published guidelines for optimising antibiotic use and curtailing antibiotic resistance in hospitals. We regard them as important tools. Key components of these guidelines include: multi-disciplinary coordination between hospital administrators, clinicians, infectious diseases specialists, infection control team, microbiologists and hospital pharmacists; formulary-based local guidelines on anti-infective therapy; education and regulation of prescriptors by consultant specialists; monitoring and auditing of drug use.

Strategy no. 3: Specific measures for the control of transmissible MRB

Specific guidelines were published and regularly updated on methods to control the spread of micro-organisms such as methicillin-resistant strains of Staphylococcus aureus (MRSA), vancomycin intermediate S. aureus (VISA), glycopeptide-resistant enterococci and ESBL-producing K. pneumoniae.

The basic components of these measures include geographical and technical isolation of patients infected or colonized by MRB, use of barrier precautions for patient care (including gloves, gowns and occasionally mask), carrier screening among hospitalized patients or hospital staff, antibiotic treatment of carriers and precautions during the transfer of colonized patients between hospitals and to other health care facilities.

We believe there is a need for local implementation of such specific control measures but they need to be tailored to a number of factors, including the risk of developing serious infection among the patients exposed to MRB, evidence of spread, the general level of endemicity of this MRB (in the country and the hospital concerned), and resources, including the organization of clinical activities, ward design, and staffing level.

Strictly intensive policies of MRSA control by screening, carrier decolonization, and isolation (the so-called "search-and-destroy" strategy) is only feasible in endemic areas.

In general, early intervention when less than 30 cases of MRSA colonized patients are affected in a non-endemic setting can lead to successful eradication of the epidemic. When the spread is affecting more patients in many wards, eradication is generally not achieved but sustained control can be obtained. The gradation of the intensity of the control measure based on clinical impact and available resources need to be continuously reappraised in endemic environments because new micro-outbreaks regularly occur.

Strategy no. 4: Laboratory detection of MRB and epidemiological surveillance and typing

The laboratory has a key role to play in the timely detection of resistant organisms, surveillance of trends in local resistance rates, notification to the infection control team of patients with "alert-organism". Interlaboratory networking is required for regional, national and international surveillance to provide early warning of newly emerging and spreading MRB and estimates of global success of local control strategies.

Conclusions

1) **Present situation**

   Antimicrobial resistant strains of community pathogens has lead to increased mortality, morbidity and cost of treatment. Examples of such pathogens are *Streptococcus pneumoniae, Mycobacterium tuberculosis* and *Salmonella typhi.*

   Hospitalised patients are increasingly infected with antimicrobial resistant micro-organisms such as staphylococci, enterococci, Pseudomonas, Klebsiella and Enterobacter spp. There are reports of increased mortality and prolonged hospitalisation for some of these pathogens when compared with susceptible strains.

   Resistant infections lead to increased costs both due to switch to more expensive or toxic antibiotics and isolation procedures as well as prolonged hospital stay. However, at present there are not sufficiently robust data available to quantify accurately the impact of resistance. However, available data clearly point to increasing impact.

2) **Suggested efforts**

   Due to the international spread of micro-organism the resistance can no longer be regarded as a national but rather a European or even a global problem and requires a common strategy.

   International agreement on definitions of antibimicrobial resistance is an urgent prerequisite.

   Although we acknowledge the great effort of pharmaceutical companies to develop and introduce new antibiotics, immune modulators and vaccines, such innovations can not be expected to solve the problems, if resistance continues to develop. Rational antibiotic policies and adoption of established infection control measures are needed in order to contain the spread of resistant organisms.

   Clinically relevant surveillance systems supported by laboratory and antibiotic consumption data should be used to develop therapeutic guidelines appropriate to local need.

   Existing clinical data from hospitals and the community should be aligned nationally and regionally to enable better analysis of impact and trends in antimicrobial resistance.

Workshop no. 2:
Surveillance of data on micro-organisms resistant to antimicrobial agents

List of participants

Chairman: Hans Jørn Kolmos, Hvidovre Hospital, Denmark
Co-Chairman: Cliodhna Foley-Nolan, Department of Public Health, Ireland
Secretary: Henrik Wegener, Statens Veterinære Serumlaboratorium, Denmark

Franz Allerberger, Bundesstaatliche bakt. serol. Untersuchung, Austria
Flemming Bager, Danish Veterinary Laboratory, Denmark
Ana Ruiz Bremon, Instituto de Salud Carlos III, Spain
Elisabeth Chaslus-Dancla, Institut National de Recherche Agronomique, Tours, France
Barry Cookson, PHLS Central Public Health Lab., United Kingdom
Melo Cristino, Hospital de Santa Maria, Lisboa Codex, Portugal
A. J. de Neeling, National Institute of Public Health & Environment, The Netherlands
Jeffry Edwards, Zeneca Pharmaceuticals, United Kingdom
Anders Franklin, National Veterinary Institute, Sweden
I. M. Gould, Aberdeen Royal Infirmary, United Kingdom
Pierette Huberty-Krau, Direction de la Sante, Luxembourg
Hein Imberechts, Veterinary and Agrochemical Research Centre, Belgium
A. Johnston, Royal Veterinary College, United Kingdom
Gunnar Kahlmeter, Central Hospital, Växsjö, Sweden
D. J. Mevius, ID - DLO, The Netherlands
Maria Luisa Moro, Instituto Superiore de Sanita, Italy
Juan Antonio Sáez Nieto, Instituto de Salud Carlos III, Spain
Antti Nissinen, Central Hospital of Central Finland, Jyväskylä, Finland
José Aguiar Nogueira, Hospital de S. João, Porto, Portugal
Ian Phillips, ESMID, United Kingdom
Franz Pirro, Fedesa, Belgium
Dorothée Andre Schoboboda, European Commision DGVI BII.1, Belgium
Henrik Schønheyder, Aalborg Hospital South, Denmark
Tom Shryock, Fedesa, Belgium
João Carlos Sousa, Faculdade de Farmácia do Porto, Portugal
Claude-James Soussy, Hopital Henri Mondor, France
M. J. W. Sprenger, National Institute of Public Health & the Environment, The Netherlands
John Stelling, World Health Organization, Switzerland
Frank Van Loock, Institute of Public Health, Belgium
Robert Vanmoorde, European Commission DGXXIV-B3, Belgium
J. Weinberg, Public Health Laboratory Service, United Kingdom
Frank Møller Aarestrup, Danish Veterinary Laboratory, Denmark

Topic:

Some data are available on the occurrence of resistant micro-organisms among human isolates. Different programmes are at work or being discussed, but no covering picture of the total situation in the EU Member States exists. Very few data exist comparing resistance in micro-organisms of animal, food and human origin. An applicable method for comparing resistance data from different sources using different methods is also discussed. A correlation between antibiotic consumption and resistance development has been shown for a number of micro-organisms and antimicrobial agents, and some epidemioligical data on dissemination of resistance in the microbial population have been collected.

Synopsis on introductory papers for workshop no. 2 regarding the specific questions

What are the minimum requirements for a future antibiotic resistance surveillance programme in the EU Member States incorporating both humans and animals

Summarise the present situation on surveillance programmes in each of the EU member states. National surveillance programmes exist in some countries/areas especially within the human area, but very few also within the animal and food area. Describe which data are recorded. Give a short evaluation on which resistance data on which micro-organisms are sufficiently valuable and pinpoint any area where resistance data from routine functions might not be valuable. Describe inter-national programmes on antibiotic resistance registration (especially the ENARE project and WHO projects, a few remarks on CDC initiatives).

What evidence exists on the correlation between consumption of antibiotics in humans and animals and development and dissemination of resistance. Are some antibiotics more prone than others to lead to development of resistance

Summarise data where the consumption in a ward/hospital is compared with resistance frequencies (exists at least for aminoglycosides, macrolides quinolones and tetracyclines). Review the available literature on national consumption for humans compared to resistance. Describe data on correlation between therapeutic consumption in animals and resistance in animal isolates. Describe the data on usage of antibiotics as growth promoters and the development and possible spread of resistant strains. Discuss the connection between resistance in animal isolates and spread to humans. Deal with the problem of coselection.

Which mechanisms play a role in the dissemination of resistant micro-organisms and resistance genes

Describe the epidemiology of the dissemination of resistant micro-organisms as well as resistance genes. Give examples of clinical situations where both mechanisms have played a role. Evaluate the relative importance of the different mechanisms.

Workshop no. 2. Conclusion paper

The format of this report deals with (part A) the current state of knowledge of the emergence and dissemination of antimicrobial resistance and (part B) recommen-dation for a future antibiotic resistance surveillance program.

Part A

Antibiotics are used for humans and animals for therapy and prophylaxis of infec-tious disease and for animals also for growth promotion and to a lesser extent for other uses like plant protection and industrial uses.

Some pathogenic bacteria resistant to all available therapeutic agents exist in Europe today.

In general an association between the use of antibiotics and the selection of resistance exists. Antibiotics affect both pathogens and normal flora. Normal flora of skin and

mucous membranes has important protective properties, but it may also serve as a reservoir for resistance.

All antibiotics can select for resistance. However, in general broad-spectrum antibiotics are more likely to lead to superinfection with resistant bacteria than narrow-spectrum antibiotics because they have an increased potential for inter-ference with the normal flora. Other factors, such as pharmacokinetic properties, route of administration, dose etc. may also play a role.

One antibiotic may select for resistance to one or more other antibiotics, because resistances may be genetically linked (co-selection). This plays a part in the spread and persistence of resistant bacteria.

Transmission of resistant bacteria and resistance genes from animals to man especially via the food chain takes place, and is well documented for some bacteria. There are also examples of transmission from man to animals.

Pre licensing studies of antibiotic resistance and post licensing surveillance is recommended, including the definition of baseline levels of resistance and the setting of alert levels of resistance, at which to take action.

The availability of antimicrobial consumption data to the public authorities and scientists is very limited. This constitutes an important gap in the surveillance information required.

Good quality surveillance data form the platform on which educational and other interventions can be built. Interventions, including the prudent use of antimicrobials, should be targetted at professionals (doctors, veterinarians, farmers) and the general public. And they should include the provision of information and other relevant incentives.

Antimicrobial use is a major driving force of dissemination for antimicrobial resistance in humans and animals. However, other factors such as infection control in institutions and community, and in animal husbandry also play an important role.

Dissemination of resistance could occur, both by spread of resistant bacteria as well as by resistance genes transferred between bacteria.

Successful control of antibiotic-resistant organisms depends on a good understanding of the factors involved in their dissemination. The factors and interventions are likely to vary with a number of parameters.
European antimicrobial resistance monitoring system should be designed to provide information to determine the relative importance of the different factors involved in the emergence and spread of antibiotic resistance. This information could then be used in appropriate mathematical models.

The information generated about antibiotic usage and key infection control practices (for example hand washing and equipment decontamination practices) provide the basis for development of codes of good practice.

Part B

A European antimicrobial resistance surveillance system is proposed. The system should have as its aim to examine trends in antimicrobial resistance in bacteria of animal and human origin. It would be appropriate that this system be coordinated within the EU.

The system should deliver timely information to those responsible for undertaking action. It would be required to be sufficiently sensitive to detect threats to health resulting from antimicrobial resistance. It should assist in the monitoring of the effect of changes in the consumption of antibiotics, infection control practices, etc. Accessability for use in such areas as antibiotic prescribing and education is a requirement.

The program must be one of medical and veterinary collaboration.

There are both regional and member state differences in bacterial antimicrobial resistance in Europe. A resistance surveillance system should, in conjunction with surveillance of antimicrobial usage, etc., provide data to identify risk factors for antimicrobial resistance, e.g. pattern of use of antimicrobial or health care.

Effective EU surveillance must have the agreement and active involvement of all the participants. It can only be built on effective national surveillance systems.

The starting point of an EU antimicrobial resistance surveillance system should be based on routinely available data. As many laboratories as possible should be encouraged to participate. The existing European multicentre surveillance system will undoubtedly contribute to the system (a network of networks).

Data to be included must fulfil the following criteria:

- 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).

The following issues were highlighted in relation to the criteria outlined above:

1) Resistance testing should be based on quantitative methods (MIC or agar diffusion) ensured through ongoing quality assurance. It is anticipated that the comparability of data will be achieved gradually.

2) Sampling frames should be designed to minimise bias. Isolates from humans should represent vulnerable and community population and potential risk settings (e.g. day care centers, nursing homes, hospitals, etc.). While animal samples should put emphasis on food producing animals including both healthy and diseased animals. Sampling methodologies need to be agreed.

3) Clinically important bacteria, zoonotic organisms and bacteria representing the normal flora of animals and humans should be included. Bacterial isolates should be reliably identified to an appropriate level.

4) The antibiotics included should start with what is already tested, targetting what is used in human therapeutics.

5) Data analysis and interpretation should make use of available computer programs and epidemiological expertise.

6) Data exchange should be easy to encourage laboratories and countries to participate. Feed back mechanisms should convince those who provide data of the added value of their contribution.

Workshop no. 3:
Recording of:
- the clinical use of antimicrobial agents in human and veterinary medicine
- other use of antimicrobial agents including animal feeding practices in the EU Member States

List of participants

Chairman: Jussi Huttunen, National Public Health Institute, Finland
Co-Chairman: P. Davey, University of Dundee, United Kingdom
Secretary: Lasse Larsen, Danish Medicines Agency, Denmark

Jacques F. Acar, Fondation Hôpital Saint- Joseph, Paris, France
Carlo Beretta, Instituto di Farmacologia e Tossicologia Veterinaria, Milano, Italy
N. Boisseau, Centre National d'Etudes Vétérinaires et Alimentaires (CNEVA), Fougere, France
P. Clappison, Department of Health, United Kingdom
Mário Simões Costa, Direccão General de Veterinária, Portugal
Albert Costelloe, Department of Agriculture and Food, Ireland
Miguel Forte, INFARMED - National Drug Agency, Portugal
Herman Goossens, UZ Antwerpen, Belgium
R. Helmuth, Bundesinstitut für Gesundheitlichen Verbraucherschutz & Veterinärmedizin, Germany
Rikke Hoff-Jørgensen, Danish Veterinary Laboratory, Denmark
Albert Huberty, Administration des Services Veterinaires, Luxembourg
Hans Kemmler, Bundesinstitut für Arzneimittel und Medizinal Produkte, Germany
Timo Klaukko, Social Insurance Institution, Finland
Stany Lens, Fedesa, Belgium
Herbert Lundstrom,Federation des Veterinaires d'Europe, Sweden
E. Bisgaard Madsen, Danske Slagterier, Denmark
Carmen Torres Manrique, Universidad de La Rioja, Spain
Noel McCarthy, Food Safety Authority of Ireland, Ireland
Jacques Poirier, FEFANA, France
A. Pÿpers, University of Utrecht, The Netherlands
Benoit Schlemmer, Hopital Saint Louis, Paris, France
E. Stobberingh, Academic Hospital Maastricht, The Netherlands
Klaus Stöhr, World Health Organization, Switzerland
Thomas Lund Sørensen, State Serum Institute, Denmark
Olavi Tokola, National Agency for Medicines, Finland
Maria Ruiz Tovar, Instituto de Salud Carlos III, Spain
Roy Vancauwenberghe, Pharmaceutical Inspectorate, Belgium
Anders Wessling, Pharmaceutical Affairs, Sweden
Tiina Ööpik, Estonian Agricultural University, Estonia

Topic:

In order to investigate how antibiotic consumption may influence the resistance development it is essential to have access to data regarding antibiotic consumption. These data are also essential if a change in consumption is recommended in the antibiotic policy. The present situation regarding registration of antibiotic consumption for treatment of humans and animals and for growth promotion does not give comparable data within the EU Member States, and the information that can be obtained differs widely.

Synopsis on introductory papers for workshop no. 3 regarding the specific questions

How do we provide a simple, uniform and comprehensive registration of data on the consumption of antimicrobial agents in the EU Member States

Based on the public health problems caused by antibiotic resistant micro-organisms and the correlation between antibiotic consumption and resistance development this workshop should cover the problems around antibiotic consumption. The workshop should summarise the data at present collected and available in each of the EU Member States regarding antibiotic consumption divided in usage for human as well as animal treatment and as growth promoters. Describe how detailed these data are (divided on hospitals, wards, herds, counties etc.) and discuss if they are valid and comparable from country to country. Based on these information outline what the minimum requirements should be for a registration system covering anti-microbial agents used for treatment of humans, animals and for growth promotion. Discuss the possibility for using the international code-numbers for antibiotics and the "Defined Daily Dosages" system. Evaluate the problems in bringing such a system into function and describe the relevant different steps in the establishment of such a system.

How do we extend such a monitoring system to the clinical use (e.g. hospitals, general practice) in human and veterinary medicine and other use including animal feeding practices

Discuss the possibilities for ascribing the usage:
- in humans: to patients, wards, hospitals, general practice, certain infectious diseases etc.
- in animals: to therapeutic treatment of herds, different production units/ methods, areas, different animal species etc.
- for growth promotion divided in animal species and period of production.
  Evaluate which data would be valuable in an ongoing recording, and which should be collected only during project periods. State the reason for the usefulness of the different data and if relevant place them in priority.

How do we make these data available for the authorities and other relevant bodies in order to support and follow the implementation of "Good Antibiotic Practice"

Describe and argue the number and content of reports of relevance at the local level, at national levels as well as at EU level. Discuss how to co-ordinate the reports regarding human treatment with the reports regarding animal treatment as well as the usage for growth promotions. Consider if an annual EU paper with these informations and with comparison within countries be of relevance?

Workshop no. 3. Conclusion paper

Monitoring the use of antimicrobial agents

Justification for the collection of information about antimicrobial supply and consumption, and for the involvement of the European Union in data collation:

- Antimicrobials have had major beneficial effects on human and animal health but the value of antimicrobials is threatened by the emergence of antimicrobial resistance.
- There is an established, but complex relationship between the consumption of antimicrobials and the prevalence of drug resistance in bacteria.
- Collection of information about national supply of antimicrobials reveals changes over time and differences between countries. These are important triggers for action and investigation.
- Evaluation of the benefits and risks of antimicrobials is dependent on the collection of detailed information about their consumption by animals or humans and about their use in aquaculture or horticulture.
- Benchmarking by comparison between clearly defined, comparable peer groups is an important stimulus to quality improvement.
- Development and implementation of guidelines requires information about current practice, including variations within and between countries.
- Collation of data to compare practices between countries will not occur unless there is a clear strategy for ensuring transparency and compatibility between national data.
- A comprehensive quality control program must be able to measure current practice against evidence from published research in order to identify targets for continuing education.
- The problem of antimicrobial resistance crosses bounderies and requires common action in all EU Member States.

1. *How do we provide a simple, uniform and comprehensive collection of data on the supply of antimicrobial agents in the EU Member States ?*

1.1. Background

1.1.1. All countries require licensing for manufacturers, importers and suppliers of antimicrobials. It should herefore be possible to identify these companies and then to collect data from them.
1.1.2. Nonetheless, information is currently difficult to obtain, particularly about the supply of antibiotics for veterinary practice.
1.1.3. Assembling data about the total supply of antimicrobials at the national level within each member state is not a substitute for collection of more detailed, local information about human and veterinary utilisation.
1.1.4. Collection of "top down" information about total national sales is an important quality check for the completeness of the "bottom up" data collection processes described under 2 below.

1.2.Recommendations

1.2.1. Collection of national supply data should be achievable by every member state and will reveal important variations between countries, as well as within countries over time.
1.2.2. The information must clearly separate:
- To hospital pharmacies.
- To community pharmacies or doctors licensed for dispensing to humans.
- To community pharmacies, veterinary practitioners, animal feed manufacturers and others licensed to dispense or supply antibiotics for animal consumption.
- To suppliers of antimicrobial agents for aquaculture or horiculture.
1.2.3. Governments should collect, use and publish data about the supply of antimicrobial agents.

2. How do we extend such a monitoring system to the clinical use (e.g. hospitals, general practice) in human and veterinary medicine and other use including animal feeding practices ?

2.1. *Background*

2.1.1. Monitoring of clinical use requires more detailed information than can be obtained from the supply data outlined in 1 above.

2.1.2. Collection of more detailed information about consumption will inform local or national prescribing policies. There is also an opportunity to collate national information to compare practice between countries. Ideally data collection systems should be able to meet both objectives.

2.2. *Recommendations*

2.2.1. All EU member states will require a national database that contains information about all packages or vials of antimicrobials that are licensed and could be on the market. This provides a basis for uniform collection of information about antimicrobial agents dispensed.

2.2.2. This national database should be applicable to dispensing of antimicrobial agents under the following headings:
   - For human consumption in the community or in hospitals.
   - For animal consumption in the treatment of infections, either by individual animals or by groups of animals.
   - For animal consumption for the purpose of growth promotion.
   - For use in aquaculture or horticulture.

2.2.3. Commercial systems for collection of information about human consumption of antimicrobial agents are based on samples which are not necessarily representative of the total population. While these data collection systems may be important for research, they should not form an important part of routine data collection.

2.2.4. Meaningful assessment of clinical use of antimicrobials requires information about the treatment of individual patients, including the indication for treatment.

2.2.5. There was complete consensus about the need for governments and the EU to support research databases which can provide detailed information about the indications for prescribing to individual patients. The support must be political, emphasising the important public health role of such databases, as well as financial.

2.2.6. Consensus could not be achieved on a strategy for national collection of patient specific data by all member states. The issues which could not be resolved concerned feasibility, confidentiality and the value of the additonal data relative to the cost of its collection.

3. How do we make these data available for the authorities and other relevant bodies in order to support and follow the implementation of "Good Antibiotic Practice" ?

3.1. *Background*

3.1.1. National databases are likely to use different systems for drug classification and for measurement of antibiotic consumption.

3.1.2. Implementation of Good Antibiotic Practice within the EU requires information about practice within member states which can be integrated into an overall strategy for training, quality improvement and clinical effectiveness.

3.2. *Recommendations*

3.2.1. Collation of data to compare practices between countries will not occur unless there is clear EU strategy for ensuring transparency and comparability between national databases. Collection of national consumption data should remain the responsibility of the individual member states, but a central strategy is required to develop a multinational database.

3.2.2. National data must be made available equally to all those involved in its collection, while maintaining confidentiality.

3.2.3. Quality standards should be developed to define the key information that is required to monitor the use of antimicrobials to ensure the implementation of evidence based guidelines about best clinical practice.

3.2.4. These standards should be a part of a comprehensive policy that includes continuing education, implementation of the results of published clinical research and monitoring of antimicrobial resistance.

3.2.5. It is important that quality standards for information allow flexibility to take account of existing data collection systems and differences in drug classification between countries.

3.2.6. Patient specific databases are maintained for research purposes in several member states. These should be supported and maintained to provide the basis for research, e.g.:
- Linking information about prescribing and resistance and validating the use of measures of prescription which can be used in routine data collection (e.g. DDD/1000 population).
- Quantifying the value of data about patient specific prescribing or indication for prescription which may be used to review the potential for routine collection of these data.

Workshop no. 4:
Elements of good practice in the use of antimicrobial agents

List of participants

Chairman: Jeremy Metters, Department of Health, United Kingdom
Co-Chairman: Otto Cars, University Hospital, Uppsala, Sweden
Secretary: Niels Frimodt-Møller, State Serum Institute, Denmark

Isabelle Bauraind, Ministry of Social Affairs Public Health and Environment, Belgium
André Bryskier, Hoechst Marion Roussel, France
Robin Bywater, Fedesa, Belgium
Antonio Saenz Calvo, Instituto de Salud Carlos III, Spain
Roberto Cauda,Universitá Cattolica del Sacro Cuore, Roma, Italy
Pierre Choraine, Federation des Veterinaires d'Europe, Belgium
Teresa Coucello, Direccão-Geral da Saúde, Portugal
Helen Giamarellou, Athens University School of Medicine, Greece
J. Gilley, British Medical Association, United Kingdom
Bart Gordts, A.Z. Sint Jan, Belgium
Beatriz Pérez Gorricho, Hospital del Niño Jesús, Madrid, Spain
Danielle Hansen-Koenig, Direction de la Sante, Luxembourg
Mary Horgan, Cork University Hospital, Ireland
Sven Erik Jorsal, Danish Veterinary Laboratory, Denmark
G. Kreutz, Bundesinstitut für Arzneimittel und Medizinprodukt, Germany
Karl G. Kristinsson, National University Hospital, Iceland
B. J .Kullberg, Academic Hospital Nejmegen, The Netherlands
Jens K. Møller, Aarhus University Hospital, Denmark
Sigvard Mölstad, University Hospital MAS, Malmö, Sweden
Jan Nagler, Cabinet of the Minister of Public Health, Belgium
Leena Nünistö, Health & Social Welfare Department, Vontee, Finland
M. Powell, Medicines Control Agency, United Kingdom
Peter Rudman, Agriculture House, United Kingdom
Pascal Sanders, Centre National d'Etudes Vétérinaires et Alimentaires, Fougeres, France
Melico Silvestre, Hospitais da Universidade de Coimbra, Portugal
David J. Taylor, University of Glasgow Veterinary School, United Kingdom
A. van den Bogaard, University of Limburg, The Netherlands
Agnes Wechsler-Fördös, Rudolfstiftung, Austria

Topic:

The antibiotic policies in the different EU Member States as well as within each member state differ considerably. A number of different elements could be used in order to change the usage of antimicrobial agents and the occurrence of resistant micro-organisms. This might include: pre- and postgraduate training, availability of data on consumption and resistance, local and nation-wide recommendations, reim-bursement policy of selected antibiotics, committees, guidelines etc. The workshop should not prepare guidelines for the good practice.

Synopsis on introductory papers for workshop no. 4 regarding the specific questions

Which elements should be considered to support an antibiotic policy towards more prudent use of antimicrobial agents in humans and animals

Describe briefly the main elements of a prudent antibiotic policy for human and animal usage (relevantly prescribed antibiotics, preferable narrow spectrum usage of the old before the new etc.) and their legislative background. Present and evaluate pros & cons for each of the elements described below, consider which are applicable in the human and the animal field or both, respectively.
  - The role of restricted registration, mandatory prescription and reimbursement.
  - The usefulness of national recommendations/guidelines for human and animal usage.
  - Recommendations by local committees at hospitals, in general practice and for specific animal usage.
  - The importance of microbiological diagnostic investigations and the availability of specific as well as general information on antibiotic resistance.
  - Presentations of local consumption and resistance data (wards, hospitals general practice, herds) comparison with data from other areas/countries.
  - Does marketing including advertising and promotion play a role? Should ethical rules be considered?
  - General information in journals, news letters and at meetings to the professionals.
  - Information and campaigns towards the public (news papers, TV etc.).
  - Pre- and post-graduate training of medical doctors and veterinarians, revision of curriculum.
  - Consider who should be responsible for the three above-mentioned information and teaching activities.
  - More focus on prudent usage at scientific congress and conferences.
  - Audit in wards/hospitals, in general practice and among veterinarians.

How could the Commission and the EU Member States collaborate in establishing guidelines to support this

Discuss measures and recommendations that could support a prudent antibiotic usage in the EU Member States. Discuss the possibility of EU recommendations as well as national recommendations. Try to spot cases/examples where local or national guidelines have worked. Consider whether the formation of an EU expert group might

Workshop no. 4. Conclusion paper

Introduction

The present pattern of antimicrobial usage in human and animal health care not only encourages the development of resistance with the long term disadvantage that will follow, but also adds unnecessary extra costs to the treatment of human and animal diseases.

We realize that any change from the present practice will require additional financial and human ressources, but these will be more than recovered through more cost effective use of antimicrobials with reduction in expenditure, and will also reduce the rate of development of antimicrobial resistance. The workshop recognizes, however, that the development of resistance could not be entirely prevented.

This workshop was asked to consider the following two questions:
1. Which elements should be considered to support an antibiotic policy towards more prudent use of antimicrobial agents in humans and animals, and

2. How could the Commission and the EU Member States collaborate in establishing guidelines to support this?

1) Elements to be considered to support an antibiotic policy towards more prudent use of antimicrobial agents in humans and animals

Education and training

A major element in improving practice in the use of antimicrobial agents must follow from educational initiatives for both health professionals (human and animal) and of the general public, who have in many countries come to expect antibiotics as a routine automatic treatment for any infectious disease.

The opinion of the workshop is that the level of knowledge among the general public and many health professions needs to be improved, particularly regarding the benefits and disbenefits of antibiotics. They are not the routine treatment for any infectious illness that many people believe. It follows that action should be taken to inform, educate and improve the public knowledge of the reasons for antimicrobial use and the circumstances, where antimicrobials are of no value.
In this way the public will gain a more realistic understanding of the rational use of antimicrobial treatment.

Improving public knowledge of the use and place of antibiotics

Insufficient is known of how to modify public perception of antimicrobials and their use. We need more and better information concerning this issue bringing in expertice from sociology and other areas. However, in the meantime it is important to work with the media to influence expectations, that for example, any child with a cough and common cold should automatically be given an antibiotic.

Improving health professionals´ knowledge and attitudes

It is important to begin the education of health professionals, doctors, veterinarians, nurses, pharmacists and all others involved in the administration of antimicrobials at an early stage of their training. The member states should ensure that the authorities responsible for the education and training curricula of all these health pro-fessionals are kept up-to-date with regard to the benefits and risks of antimicrobials. The universities have an important role in the education of undergraduates and postgraduates.

Similarly all health professionals have a personal responsibility, and bodies responsible for their registration have a corporate responsibility to ensure that practitioners' up-to-date knowledge of antimicrobials is maintained.

Availability of antimicrobials

The workshop was concerned that for therapeutic use all antibiotics should remain prescription-only medicines. We were aware that in some member states other antimicrobials were available over the counter (OTC) and of the potential that this has for development of resistance to fungi and viruses. At the next review of the license for such products the potential for development of resistance should be taken into consideration before continued availability OTC is authorized.

Better data to improve prescribing

In many hospitals and some localities commendable steps have been taken to allocate resources so that surveillance of antibiotic usage and the prevalence of resistance can be monitored at the local level, and the results fed back this data to prescribers whose practice is thereby improved. Regrettably, these opportunities to enhance prescribing patterns by such measures are not widespread.

In the opinion of the workshop improved surveillance preferably on the community rather than solely hospital basis with subsequent collation analysis and feedback to the prescriber should become routine throughout the EU.

In some hospitals infection-control teams have proved to be effective in reducing the spread of hospital acquired infection and limiting the development of antimicrobial resistance. However, they do not often have the necessary power to control antimicrobial prescribing practice. In the opinion of the workshop "antibiotic teams" (e.g. including clinical microbiologists and infectious disease specialists) should be introduced in every hospital and given the authority to modify antimicrobial prescription of individual clinicians in accordance with predetermined, locally approved guidelines, but always taking account of the needs of the patient. Clinicians should be given an opportunity to approve the remit and recommendation of the team. Ideally, the antibiotic team should cover the hospital and the community it serves, including nursing homes and other residential institutions (e.g. old peoples homes). Feedback should be provided to clinicians.

The antibiotic team should supervise arrangements for antimicrobial policies to cover the primary/secondary care interface in the locality they serve. Where antibiotic teams and infection control groups exist in the same insitution they will need to work very closely together.

Guidelines

Historically each prescriber has had the right to decide on the antimicrobial of his own choice. Until resistance occurred such a policy was accepted but this degree of clinical freedom is no longer tenable.

Formularies and guidelines are now widespread but mainly confined to hospitals and rare in veterinary practice.

In view of the workshop guidelines for appropriate antimicrobial usage should be introduced everywhere and become the norm. The workshop agreed upon the following description of appropriate antimicrobial use: Treatment should be limited to bacterial infections,using antibiotics directed against the causative agent, given in optimal dosage, dosage intervals and lentgh of treatment with steps taken to ensure maximum patient concordance with the treatment regimen, and only when the benefit of the treatment outweighs the individual and global risks. In any locality they should cover both hospital and community. Guidelines should be readily accessible, drawn up with multidiciplinary prescriber involvement, subject to peer review and compatible with national guidelines, where these have been adopted.

The "antibiotic team" should be responsible for ensuring compliance with the guide-lines locally agreed. Adoption of guidelines, while placing some limits to the clinical freedom of the individual clinicians will in the workshops' view be in the best interest of patients by reducing the development of resistance. The guidelines must not be so restrictive that a patient is denied an antimicrobial needed for his care.

Diagnostic tests

While access to diagnostic tests in hospitals are regularly available in the community there is insufficient access. This can be a serious disadvantage to logical antimicrobial treatment. While many infections treated in the community do not need diag-nostic workup before treatment is commenced, an expansion of diagnostic testing for community care is needed in many settings. The workshop recognized the impor-tance of providing adequate facilities for diagnostic testing. Separately there is an important need for the development of rapid diagnostic tests that can be applied in community care.

Reimbursement

Policies for reimbursement vary widely among different member states of the EU. An objective of some reimbursement policies have been to reduce the drug budget.
The workshop recognized that prescribing patterns can be modified through reim-bursement. It follows that reimbursement policies may be used to reduce the development of antimicrobial resistance. This should only be utilized where a structured risk assessment or clear evidence shows that reimbursement has a role to play in encouraging appropriate antimicrobial usage.

Registration

It has been suggested that change in registration procedure could be used to restrict the licensing of medicines where there is a wide therapeutic choice. Current legislation criteria are founded on the quality, safety and efficacy of any medicinal product submitted for registration.
The workshop agreed that there was no reason to change these criteria which are set out in EU registration. However, if restrictions were to be placed on the availability of an antimicrobial this should be achieved through national arrangements and in accordance with nationally agreed prescribing guidelines. In the context of development of resistance to antimicrobials all relevant information should be included in the dossier submitted to the medicines regulatory authority prior to registration and before the five yearly renewal of a product license. All information available on the development of resistance should in the opinion of many members of the workshop be made available to those with a scientific interest. Also, the workshop participants have identified antibiotic dosage and length of treatment as an area where basic knowledge is still lacking. An increased interaction between academia, pharmaceutical industry and regulatory authorities is necessary to gain more information on how these drugs should be dosed to minimise the risk for emergence of resistance.

Advertising and promotion

Different practices apply in member states of the EU regarding advertising and pro-motion of antimicrobial agents. Some members of the workshop were concerned about direct promotion of antimicrobials to lay audiences particularly in the veterinary field.

In the workshops' view the advertising and promotion of licensed antimicrobial agents should be strictly in accordance with the Summary of Product Characteristics (SPC). Any advertisement for antimicrobials should be only in terms allowed by EU legislation and in compliance with WHO criteria for ethical drug promotion. Each member state should have in place arrangements to ensure observance.

Use of antimicrobials as growth promoters

For many years antibiotics have been used in animal husbandry as growth promotors. The potential for resistance development is our particular concern where similar or closely related antibiotics are or will be developed for use both as growth promoters and for the treatment of human infectious disease. The workshop recog-nized that this was a controversial subject. The large majority of the workshop considered the use of antibiotics for growth promotion was not justified and agreed with the opinion of the WHO expert meeting that "increased concerns regarding risks to human health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth promoting antimicrobials with safer non-antimicrobial alternatives"; and recommendations from the Economic and Social Committee of the EU (ECOSOC), that "the emphasis should be first and foremost on limiting the use of antibiotics that can provoke cross resistance to drugs that are or will become relevant to human health care". Several members felt that before an antibiotic is permitted as a growth promoter its lack of any risk for human health should be demonstrated. The workshop was, however, unanimous that the use of an antibiotic as a growth promoter should be stopped whenever there was a clear evidence of a significant risk to human health from such usage.

2) How could the Commission and the EU Member States collaborate in establishing guidelines to support this?

In the opinion of the workshop the Commission and the member states individually have a vital role in improving the pattern of use of antimicrobials throughout the EU and in the adoption of strategies for the avoidance of antimicrobial resistance. In the workshops' view the treaty of Maastricht had empowered the Commission to coordinate initiatives to improve and protect public health. The Commission also has responsibilities with regard to promotion of animal welfare. The Commissions opportunities to strengthen public health will be strengthened when the treaty of Amsterdam is ratified.

The workshop noted that a number of directorates general (DG's) have responsibilities that effect the use and regulation of antimicrobials for human and animal health. In the workshops' view in respect of antimicrobials these responsibilities and initiatives need to be coordinated, and the lead should fall to the DG responsible for human health.

The workshop believes the Commission working closely with the member states should coordinate action to collect, analyse and disseminate information on:

- antimicrobial usage,
- strategies to identify resistance,
- incidense of resistance,
- strategies to reduce resistance,
- development of guidelines,
- the effectiveness of different intervention methods,
- adoption of common definitions,
- promotion on education and research strategies.

As a start the commission might sponsor a conference of member states to consider optimal strategies to reduce inappropriate use of antimicrobials in the human and animal fields.

The commission also has an important lead in cooperating with other international agencies and in developing policies with other European countries outside the Union, as infectious disease does not respect geographical boundaries. Member states can encourage and support the strategies the workshop has proposed in Section 1 of this document.

The workshop realize that this is a large and challenging agenda with significant human and financial ressource implications, but leave it to be fully justified if the microbial threat is not to become the microbial disaster.

Workshop no. 5:
Framework for development of guidelines for research programmes to prevent the emergence and spread of antimicrobial resistant micro-organisms

List of participants

Chairman: Jacques A. Drucker, Direction Génerale de la Santé, France
Co-Chairman: Steven van Hoogstraten, Director of Public Health, The Netherlands
Secretary: Nils Strandberg Pedersen, State Serum Institute, Denmark

Preben Aavitsland, Statens Institut for Folkehelse, Norway
Mary Couper, World Health Organization, Switzerland
Kees de Joncheere, WHO/ Euro, Denmark
C. Dougan, University of London, United Kingdom
Youri Glupgzynski, Cliniques Universitaire UCL de Mont-Godinne, Belgium
Christina Greko, National Veterinary Institute, Sweden
F. Haesebrouck, University of Gent, Belgium
Peter Hohl, Hoffmann-La Roche, Switzerland
R. Hone, Mater Misericordiae Hospital, Dublin, Ireland
Pentti Huovinen, National Public Health Institute, Finland
Guiseppe Ippolito, Centro di Riferimento AIDS, Roma, Italy
Jean Paul Klein, BMAGS, Austria
J. P. Lafont, Station de Pathologie Aviaire, Monnaie, France
Jorge Ricardo, Instituto Nacional de Saúde, Portugal
Manfred Lützow, FEFANA, Switzerland
Alasdair P. MacGowan, Southmead Hospital, Bristol, United Kingdom
Emilia Cercenado Mansilla, Hospital General Universitario, Madrid, Spain
J. v. d. Meer, Academic Hospital Nejmegen, The Netherlands
Fernando Baquero Mochales, Hospital Ramón y Cajal, Madrid, Spain
Dominique Monnet, State Serum Institute, Denmark
Eric Mulvihill, St. James's Hospital, Dublin, Ireland
Staffan Normark, Swedish Institute for Infectious Disease Control, Sweden
John Elmerdahl Olsen, The Royal Veterinary and Agriculture University, Denmark
Ørjan Olsvik, University of Tromsø, Norway
Hervé Richet, Institut de Biologie des Hopitaux de Nantes, France

Topic:

In order to support the development towards a better antibiotic policy with less development of resistance, investigations and research projects addressing this area are essential. They should deal both with the human aspect as well as with the food and animal aspect. Special attention should be given to applied projects and international collaborations as these problems cross borders.

Synopsis on introductory papers for workshop no. 5 regarding the specific questions

Describe the present situation for such research projects and major obstacles

Collect information and summarise EU and WHO supported projects in this field already in progress and projects and plans supposed to start within the next year or two. By contact with local experts in the EU Member States describe other major international projects in this field; these projects should include a high percentage of EU Member States. From the same source collect information on major national projects. Based on these projects summarise the major obstacles for future research in this area. Describe whether all these projects comprise the following items:
- Data on antibiotic resistance over time or prevalence.
- Consumption data over time or prevalens.
- Correlation between consumption and resistance.
- Intervention studies.
- Hospital hygiene elements.
- Epidemiological typing in order to investigate mechanism of spread.
- Information on resistance from animal and food isolates.
- Information of veterinary consumption for therapy and growth promotion.

Which areas future research projects should especially focus on

Based on the above mentioned picture given by the answer of the first question, describe which areas need further support in order to obtain new knowledge supporting future initiatives aiming at less antibiotic resistance. Contact before and during the workshop the other 4 workshops (chairpersons and secretary) in order to gain information about areas which the other workshops have disclosed as important research areas. If possible try to put priority to the proposed future projects.

How such projects could be established and financed

Describe which bodies (international, EU or national) should be responsible for the initiative to plan and obtain sufficient funding for the research projects described above. Detect in which of the EU areas (DG....) future research projects are best placed and describe the added values obtained by EU collaboration. Recommend a future frame for the EU and national support for research programmes to prevent the emergence and spread of antimicrobial resistant micro-organisms.

Workshop no. 5. Conclusion paper

The continuous worldwide emergence and dissemination of antimicrobial-resistant microorganisms during the last decades clearly demonstrates that knowledge and information, when available, have not been used in adequate control programmes. This emphasises the urgent need to implement research programmes that can create a basis for interventions to control antimicrobial resistance in humans and animals.

Present status of research

In preparation for the workshop, characteristics of multicenter surveillance and research projects on antimicrobial resistance have been identified and reviewed (1-3).
This review shows that the majority of projects is within the field of surveillance, and a smaller number of projects is dealing with research. These research projects generally aim at a better understanding of the genetic basis, the emergence, and the spread of resistance. Projects aiming at the implementation and evaluation of interventions to control antimicrobial resistance are rare. Research projects in veterinary medicine are also rare, but generally include both the human and animal aspects of the problem. There is a difference between the United States and Europe since European research projects are less often integrated in surveillance systems.

Financial support for research is provided:
- at the national level, by governmental bodies, public health institutes, veterinary research institutes, universities, professional societies, charity funds, pharmaceutical/animal health industry,
- at the multi-national level, under the 4th Community RTD framework programmes by major specific programmes such as BIOMED, BIOTECH, and FAIR, professional societies, pharmaceutical/animal health industry, and by international organizations such as WHO.

Obstacles

Historically, Europe has put too much confidence in the power of antimicrobial agents. Antimicrobials have been considered as other drugs, without taking into account that antimicrobial resistance is a multifactorial problem and that microorganisms are able to adapt to their environment. Several points have been identified as obstacles for rational research in the past. Genetical, biochemical and epidemiological studies describing antimicrobial resistance form the basis for our current understanding of this problem. However, research has not focused on finding the reasons for the emergence of resistance, its evolution and its geographical distribution.

The available surveillance data have only found limited use for a rational control of antimicrobial resistance. The lack of a European reference method and interpretative criteria for quantifying resistance is still an obstacle for cooperation between laboratories and between countries in Europe. Furthermore, different levels in recognition of the problem among medical specialties, between human and veterinary medicine, decision makers, scientists, pharmaceutical industry, and among countries, have been an obstacle. Finally, there has been a lack of coordination of research, including funding. As a consequence, more coherent and well-funded research initiatives are needed.

Areas of future research

To document the impact of antimicrobial resistance on society, priority should be given to studies on human morbidity and mortality, including risk assessment and the estimation of the cost of infections due to resistant microorganisms (TOP PRIORITY)

Additional research is needed on the quantification of the ecological and epidemiological aspects of antimicrobial resistance in humans and animals such as studies on:
- the genetic background and mechanisms of emerging resistance, the possible reversibility of such resistance, the development and spread of resistant genes including marker genes, the selection of specific clones, and the relationship between resistance and virulence;
- the antimicrobial-driven ecological modifications of normal microbial populations in humans and animals, as well as alterations in the normal microbial gene pool;
- the effect of the release of antimicrobials and resistant microorganisms in the environment on resistance.

More research is needed to investigate human and veterinary use of antimicrobials such as studies on:
- optimal antimicrobial use practices, in humans and animals, that minimize the risk of development of resistance, including the influence of the type of drug, the dose, the mode and timing of administration, the duration of treatment, and total amount of drug used (TOP PRIORITY);
- the correlation between genetic background or minimal inhibitory concentration (MIC) of antimicrobials, and clinical outcome of antimicrobial treatment;
- the influence of other factors such as individual risk factors or infection control practices;
- the effect of antimicrobials used for other purposes than the treatment or prevention of infections in humans, i.e. antimicrobials used as growth promoters in animals, in fish farming, and in agriculture, on the development of antimicrobial resistance and on the emergence of antimicrobial-resistant microorganisms in humans (TOP PRIORITY);

- the evaluation of the necessity for antimicrobials in the treatment of common infections such as otitis media, sinusitis or bronchitis, thus encouraging evidencebased decisions in clinical practice (TOP PRIORITY);
- changing prescribing behaviours of physicians and other health care professionals, and improving compliance of patients to treatment (TOP PRIORITY);

New methods, strategies and products must be developed such as:
- methods for the rapid identification of microorganisms, their antimicrobial susceptibility patterns, and their resistance mechanisms, to be used in the inpatient and outpatient settings, and in animal husbandry;
- a European (global) reference method for susceptibility testing and interpretative criteria for quantifying resistance, that can be used to harmonize existing methods and criteria;
- novel treatment principles for humans and animals, e.g. targeted antimicrobials, targeted vaccines, virulence inhibitors, probiotics, resistance inhibitors, immunomodulators, immunotherapy, gene therapy of antimicrobial-resistant microorganisms (anti-sense therapy) (TOP PRIORITY);
- better criteria to define clinical diagnoses, algorithms for patient management, and assessment of clinical outcome (TOP PRIORITY);
- mathematical models for a better prediction of future trends, i.e. the emergence of novel resistance determinants and the possible disparition of existing ones;
- communication tools and techniques, e.g. ways to promote guidelines, education material, software, for physicians, veterinarians, and the general public.

Finally, we strongly need to implement and evaluate the effect and the costeffectiveness of interventions to control antimicrobial resistance in humans and animals (TOP PRIORITY).

These interventions should include:
- implementation of measures to control cross-transmission,
- implementation of antimicrobial control programmes,
- implementation of optimal antimicrobial use practices,
- factors influencing antimicrobial prescribing decisions,
- review of antimicrobials used as growth promoters.

Recommendations for establishment and funding of future projects

Antimicrobial resistance is a global problem. No country is spared and antimicrobial-resistant organisms are likely to spread from a country to another. Therefore, international cooperation is needed within Europe, with the United States, with developing countries, with WHO and other relevant international organizations. Administrative procedures for research funding are complex because the field of antimicrobial resistance encompasses many areas of research study, and therefore involves different administrative bodies.

A multidisciplinary approach integrating epidemiology, laboratory aspects, and interventions should be promoted. Projects should involve disciplines such as clinical microbiology, clinical medicine, epidemiology and public health, social sciences, medical informatics, veterinary medicine, pharmacy, etc. Data from existing surveillance projects should lead to relevant research projects.

It is strongly recommended that coordinated research on antimicrobial resistance, as defined in this workshop, should be made a high priority and that adequate resources should be allocated for this type of research, both at the European level through EU programmes, and in individual countries through national research councils.
The European Commission through its different DG should propose and implement a coordinated research programme, avoid funding of redundant projects, and simplify administrative procedures.

We learned that a multidisciplinary scientific advisory group has recently been created at the EU level. This consultative body should identify areas of research in which information is lacking, design call for research proposals, and evaluate the results of the research programmes financed by EU. It should evaluate both surveillance and research projects in this field.

References

1. The current status of antimicrobial resistance surveillance in Europe: report of a WHO workshop held in collaboration with the Italian Associazione Culturale Microbiologia Medica, Verona, Italy, 12 December 1997î. WHO/EMC/BAC/98.1

2. The medical impact of the use of antimicrobials in food animals. Report of a WHO meeting, Berlin, Germany, 13-17 October 1997. WHO/EMC/ZOO/97.4

3. Characteristics of multicenter surveillance and research projects on antimicrobial resistance in Europe and the United States. Preparatory document for "The Microbial Threat" Workshops and Conference.

List of participants in the conference

Host organization

Presidency
Minister for Health, MP, Carsten Koch, Denmark
Minister for Food, Agriculture and Fisheries, MP, Henrik Dam Kristensen, Denmark

Vicepresidents
W. J Hunter, European Commission, Public Health and Safety at Work, Luxembourg
Einar Krag, National Board of Health, Denmark

General Rapporteur
Richard Smith, British Medical Journal, United Kingdom

Programme Committee
Jussi Huttunen, National Public Health Institute, Finland
Jens Ole Nielsen, Hvidovre Hospital, Denmark
Knud Børge Pedersen, Danish Veterinary Laboratory, Denmark
Jørgen Bartels Petersen, Ministry of Health, Denmark (Chairperson)
Vibeke Thamdrup Rosdahl, State Serum Institute, Denmark (Vice-chairperson)
Peet Tüll, Socialstyrelsen, Sweden

Local Organizing Committee
Maiken Bork Clausen, Ministry of Health, Denmark
Lisa Kronvang, National Board of Health, Denmark
Michael Nakskov, Ministry of Food, Agriculture and Fisheries, Denmark
Jette Nedergaard, Ministry of Health, Denmark
Gunnar Schiøler, National Board of Health, Denmark (Chairperson)
Henrik Vestergaard, Ministry of Health, Denmark

Press Secretary
Susanne Louw, Denmark

Advisory Board
Herman Goosens, Laboratory for Microbiology, Belgium
Isabelle Bauraind, Ministry of Social Affairs, Public Health and Environment, Belgium
F. Haezebrouck, University of Gent, Belgium
Martti Vaara, Department of Bacteriology, Finland
Pentti Huovinen, National Public Health Institute, Finland
Timo Klaukka, Social Insurance Institution, Finland
Antoine Andremont, Service de bactériologie, France
J. P. Lafont, Station de Pathologie Aviaire, France
D. Bitter-Suermann, Institut für Medizinische Mikrobiologie, Germany
K. Naber, Urologische Klinik St. Elisabeth Krankenhaus, Germany
Ungemach, Institut für Pharmakologie und Toxikologie der Veterinär Medizinische
Fakultät der Universität, Germany
Mary Horgan, Cork University Hospital, Ireland
C. T. Keane, Dept. of Microbiology, Central Pathology, St. James's Hospital, Ireland
Carlo Beretta, Instituto di Farmacologia e Tossicologia Veterinaria, Italy
Donato Greco, Instituto Superiore di Santá, Italy
Giuseppe Ippolito, Centro de Riferimento AIDS, Italy
Robert Hemmer, Centre Hospitalier de Luxembourg, Luxembourg
A van den Bogaard, University of Limburg, The Netherlands
J. E. Degener, Academic Hospital Groningen, The Netherlands
Francisco Antunes, Hospital de Santa Maria, Portugal
Melo Christino, Hospital de Santa Maria, Portugal
Miguel Forte, INFARMED, National Drug Agency, Portugal

Fernando Baquero, Hospital Ramón y Cajal, Spain
José Campos Marquès, Instituto de Salud Carlos III, Spain
Staffan Normark, Swedish Institute for Infectious Disease Control, Sweden
Mats Kalin, Karolinska Hospital, Sweden
Ragnar Norrby, University Hospital, Sweden

Country delegations

Austria
Franz Allerberger, Bundesstatliche bakteriologisch-serologische Untersuchungsanstalt
Christoph Aspöck, Vienna General Hospital
Werner Brueller, Republik Österreich Bundeskanzleramt
Helga Halbich-Zankl, Bundesministerium für Arbeit, Gesundheit und Soziales
Oskar Janata, Donauspital
Jean Paul Klein, BMAGS
Johann Krutzler, Bundesministerium für Land- und Forstwirtschaft
Uwe Kønig, Hanusch Krankenhaus
Barbara Streicher, Institute for Microbioloy and Genetics, Vienna Biocenter
Werner Thiel, National Salmonella and Meningocco Center
Agnes Wechsler-Førdøs, Rudolfstiftung

Belgium
Isabelle Bauraind, Ministry of Social Affairs
Romain Bogaerts, Ministry of Public Health
Baudouin Byl, Erasme Hospital
Patrick De Mol, University of Liege
Marc Dejongh, Kliniek M. Middelares
Benedicte Delmere, U.C.L.
Youri Glupgzynski, Cliniques Universitaire UCL de Mont-Godinne
Herman Goossens, UZ Antwerpen
DBart Gordts, A.Z. Sint Jan
F. Haesebrouck, University of Gent
Hein Imberechts, Zoonoses Section, Veterinary and Agrochemical Research Centre
Sabine Lauwers, Academisch Ziekenhuis Vrije
Jan Nagler, Cabinet of the Minister of Public Health
Hugo Robays, University Hospital Gent
Marc Struelens, U.L.B. Hospital Erasme
Frank Van Loock, Institute of Public Health
Roy Vancauwenberghe, Pharmaceutical Inspetorate
Gerda Verschraegen, University Hospital Gent
Dirk Vogelaers, Universitair Zienenhuis
Marc Wyndaele, Ministry of Agriculture

Czech Republic
Pavla Urbaskova, National Institute of Public Health

Denmark
Søren Abildgaard, Ministry of Food, Agriculture and Fisheries
Kaj Andreasen, Veterinær- og Fødevaredirektoratet
Anders Asmind, Ministry of Food, Agriculture and Fisheries
Flemming Bager, Danish Veterinary Laboratory
Morten Blom, Ministry of Food, Agriculture and Fisheries
Niels Frimodt-Møller, State Serum Institute
Rikke Hoff-Jørgensen, Danish Veterinary Laboratory
Bente Krag Ingvardsen, Danish Medicines Agency
Henrik G. Jensen, Veterinær- og Fødevaredirektoratet
Helle Landberger Johansen, Danish Medicines Agency
Sven Erik Jorsal, Danish Veterinary Laboratory
Hans Jørn Kolmos, Hvidovre Hospital

Michael Krause, Plantedirektoratet
Lasse Larsen, Danish Medicines Agency
Alice Moltke Lisberg, Ministry of Health
Bo Lumholtz, Danish Medicines Agency
Dominique Monnet, State Serum Institute
Anette Haurum Munk, Grønlands Hjemmestyre, Greenland
Jens K. Møller, Aarhus University Hospital
Lise Søe Naldal, Ministry of Food, Agriculture and Fisheries
Vagn Nielsen, Ministry of Health
John Elmerdahl Olsen, The Royal Veterinary and Agriculture University
Poul Ottesen, Ministry of Food, Agriculture and Fisheries
Jens Hauge Pedersen, Ministry of Food, Agriculture and Fisheries
Morten Frank Pedersen, Ministry of Health
Nils Strandberg Pedersen, State Serum Institute
Carsten Phillipsen, Königliche Dänisches Botschaft, Austria
Anne-Marie Plesner, National Board of Health
Jan Renneberg, Danish Medicines Agency
Jørgen Schlundt, Danish Veterinary & Food Administration
Henrik Schønheyder, Aalborg Hospital South
Peter Skinhøj, The National Hospital (Rigshospitalet)
Thomas Lund Sørensen, State Serum Institute
Ib Valsborg, Ministry of Health
Eva Vinding, National Board of Health
Bent Toft Viuf, Plantedirektoratet
Henrik Wegener, Statens Veterinære Serumlaboratorium
Henrik Westh, Hvidovre Hospital
Frank Møller Aarestrup, Danish Veterinary Laboratory

Estonia
Kuulo Kutsar, Health Protection Inspectorate
Irina Milerman, Health Protection Inspectorate
Katrin Sutt, Ministry of Agriculture
Tiina Ööpik, Estonian Agricultural University

Finland
Pentti Huovinen, National Public Health Institute, Turku
Jussi Huttunen, National Public Health Institute
Timo Klaukko, Social Insurance Institution
Sirpa Kärenlampi, University of Kuopi
Päivi Mannerkorpi, Ministry of Agriculture and Forestry
Pia Mäkelä, Ministry of Agriculture and Forestry
Antti Nissinen, Central Hospital of Central Finland
Leena Nünistø, Health & Social Welfare Department, City of Vontee
Ulla-Maija Rautakorpi, The National Public Health Institute
Olavi Tokola, National Agency for Medicines
Martti Vaara, National Public Health Institute

France
Jacques F. Acar, Fondation Hôpital Saint-Joseph
Antoine Andremont, Chu Bichat-Claude Bernard
N. Boisseau, Centre National d'Etudes Vétérinaires et Alimentaires (CNEVA)
Anne Brisabois, Centre National d'Etudes Vétérinaires et Alimentaines
Jean Carlet, Hôpital Saint-Joseph
Elisabeth Chaslus-Dancla, Institut National de Recherche Agronomique
Patrick Choutet, Hôpital Bretonneau
Patrice Courvalin, Institut Pasteur
Jean-Claude Desenclos, Reseau National de Santè Publique
Jacques A. Drucker, Direction Génerale de la Santé
Alain Durocher, Hôpital Albert Calmette
Jean Fabry, UHEIM - Paviccon 1 M, Centre Hospitalier Lyon Sud
Didier Guillemot, INSERM / Unite 21

Bénédicte Herbinet, Ministére de l'Agriculture et de la PÍche
Vincent Jarlier, Laboratoire Central de bactériologie
J. P. Lafont, Station de Pathologie Aviaire
Roland Leclercq, CHRU de CAEN, Laboratoire de Microbiologie
Agnés Lepoutre, Direction Génerale de la Santé
Véronique Loncle-Provot, Sanofi Pasteur
Frederic Lucht, Hôpital Bellevue
Jean-Louis Martel, Centre National d'Etudes Veterinaires et Alimentaires
Marie- Hélèle Nicolas, Hôpital Amboise-Paré
M. Colin Pierre, Centre National d'Etudes Veterinaires et Alimentaires
Thomas Remi, Chu de Rennes Reanimations Médicales
Hervé Richet, Institut de Biologie des Hopitaux de Nantes
Pascal Sanders, CNEVA-Laboratoire des Mèdicaments Vètèrinaires
Benoit Schlemmer, Hôpital Saint Louis
Claude-James Soussy, Hôpital Henri Mondor

Germany
Holger Andreas Elsner, Institut für Medizinische Mikrobiologie, Hamburg
Roswitha Füssie, Institut für Medizinische Mikrobiologie, Giessen
Heinz Grimm
R. Helmuth, Bundesinst. für Gesundheitlichen Verbraucherschutz & Veterinärmedizin
Hans Kemmler, Bundesinstitut für Arzneimittel und Medizinal Produkte
Gerhard Kothmann, Bundesministerium für Gesundheit
G. Kreutz, Bundesinstitut für Arzneimittel und Medizinprodukt
H. Lode, Städtlische Klinikum Zehlendorf
G. Peters, Institut für Medizinische Mikrobiologie, Münster
Ralf Rene Reinert, Institut für Medizinische Mikrobiologie, Aachen
Arne C. Rodloff, Institut für Medizinische Mikrobiologie, Leipzig
Erika Rosenthal, Frankfurt am Main
Andrea Sanwidi, Bundesministerium für Ernärung, Landwirtschaft und Forsten
R. Staalmann, Universitätsklinikum "Benjamin Franklin"
Christof von Eiff, Institut für Medizinische Mikrobiologie, Münster
Jutta Wagner, Institut für Medizinische Mikrobiologie, Berlin
Wolfgang Witte, Robert Koch Institute

Greece
Helen Giamarellou, Athens University School of Medicine
Nicolas Iliadis,Veterinary Faculty, Aristotelian University
Christos Hadjichristodoulou,University of Athens
M. Legakis,University of Athens

Hungary
Ferenc Fábián, Chief Medical Officers Office

Iceland
Haraldur Briem, Directorate of Health
Karl G. Kristinsson, National University Hospital

Ireland
Lune Clancy, St. James Hospital
Martin Cormican, University College Hospital, Galway
Albert Costelloe, Department of Agriculture and Food
Darina O. Flanagan, Eastern Health Board
Cliodhna Foley-Nolan, Department of Public Health, Cork
R. Hone, Mater Misericordiae Hospital
Mary Horgan, Cork University Hospital
Zachady Johnson, Eastern Health Board, Dr. Stevens Hospital
Noel McCarthy, Food Safety Authority of Ireland
Eric Mulvihill, St. James' Hospital, Dublin
Patrick Salmon, Irish Medicine Board

Italy
Carlo Beretta, Instituto di Farmacologia e Tossicologia Veterinaria, Milano
Antonio Cassone, Laboratorio de Batteriologia e Micrologia Medica, Roma
Roberto Cauda, Instituto di Clinica delle Malatine Infettive, Roma
Marta Di Gennaro, Ministry of Health
Donato Greco, Instituto Superiore di Santá, Roma
Guiseppe Ippolito, Centro di Riferimento AIDS, Roma
Guiseppe Nanni, Univ. Cattolica S. Cuore
Annalisa Pantosti, Laboratory of Medical Bacteriology and Micrology

Latvia
Rasa Andersone, Latvian Food Center

Lithuania
Rolanda Volintéliené, Institute of Hygiene

Luxembourg
Danielle Hansen-Koenig, Direction de la Sante
Robert Hemmer, Service National des Maladies Infectieuses
Albert Huberty, Administration des Services Veterinaires
Pierette Huberty-Krau, Direction de la Sante

Norway
Anne Alvik, Norwegian Board of Health
Bodolf Hareide, National Institute of Public Health
Stig Harthug, Haukeland Sykehus
Idar Magne Holme, Social and Health Department
Steinar Høie, Det Kongelige Landbruksdepartement
Ørjan Olsvik, University of Tromsø
Andreas Skulberg, Norwegian Board of Health
Preben Aavitsland, Statens Institut for Folkehelse

Portugal
Francisco Antunes, Hospital de Santa Maria
Mário Simıes Costa, Veterinarian Services Animal Feeding
Teresa Coucello, Direccão-Geral da Saúde
Melo Cristino, Hospital de Santa Maria
Miguel Forte, INFARMED - National Drug Agency
Maria Paula Lavado, Instituto Nacional de Saúde Dr. Ricardo Jorge
José Aguiar Nogueira, Hospital de S. João, Porto
Constantino Sakellarides, Direccão-Geral da Saúde
Antonio Sarmento, Hospital Pedro Hispano
Melico Silvestre, Hospitais da Universidade de Coimbra
João Carlos Sousa, Faculdade de Farmácia do Porto

Slovak Republic
Deputy Minister for Agriculture Norbert M. Benuska
Ingrid Jenezova, Ministry for Agriculture
Leon Langsadl, National Public Health Institute
Jozef Sokol, Ministry for Agriculture

Slovenia
Zoran M. Arnez, Ministry of Health
Joze Bemec, Ministry for Agriculture, Forestry and Food
Franc But, Ministry for Agriculture, Forestry and Food
Vesna Ciusek, Ministry for Agriculture, Forestry and Food
Evelyn Dreo, Ministry for Agriculture, Forestry and Food
Boris Jez, Ministry for Agriculture, Forestry and Food
Zoran Kovac, Ministry for Agriculture, Forestry and Food
Minister for Agriculture, Forestry and Food Ciril Smrkolj
Marko Verbic, Ministry for Agriculture, Forestry and Food

Spain
Ana Ruiz Bremon, Instituto de Salud Carlos III
Antonio Saenz Calvo, Instituto de Salud Carlos III
Carlos Cuenca, Ministry of Agriculture
Javier Garau, Hospital Mutua de Terrassa
Beatriz Pérez Gorricho, Hospital del Niño Jesús, Madrid
Carlos Lymbreras, Hospital "Doce de Octubre", Madrid
Carmen Torres Manrique, Universidad de La Rioja, Logroño
Emilia Cercenado Mansilla, Hospital General Universitario Gregorio Marañon
José Campos Marqués, Instituto de Salud Carlos III
Fernando Baquero Mochales, Hospital Ramón y Cajal, Madrid
Juan Antonio Sáez Nieto, Instituto de Salud Carlos III
Jesus Martinez Ruiz, Subdireccion General de Sanidad Exterior y Veterinaria
Maria Ruiz Tovar, Instituto de Salud Carlos III

Sweden
Otto Cars, University Hospital, Uppsala
Lars-Erik Edquist, Statens Veterinärmedicinska Anstalt
Anders Franklin, National Veterinary Institute
Christina Greko, National Veterinary Institute
Gunnar Kahlmeter, Central Hospital, Växsö
Mats Kalin, Karolinska Hospital, Stockholm
Sigvard Mölstad, University Hospital MAS, Malmö
Marie Nordén, Swedish Ministry of Agriculture, Food and Fisheries
Erik Nordenfelt, Swedish Institute for Infection Disease Control
Staffan Normark, Swedish Institute for Infectious Disease Control
Ragnar Norrby, University Hospital, Lund
Aase Tronstad, Swedish Ministry of Agriculture, Food and Fisheries
Peet Tüll, Socialstyrelsen
Ingrid Uhnoo, Medical Products Agency (MPA)
Anders Wessling,Pharmaceutical Affairs
Ulrika Winroth,Ministry of Health

Switzerland
Andre P. Burnens, University of Berne
Daniel Guidon, Swiss Federal Research Station for Animal Production
Jean-Claude Piffaretti, Istituto Cantonale Batteriosierologico, Lugano
Anne Florence Piquet, Swiss Federal Veterinarian Office
Pierre-Alain Raeber, Swiss Federal Office of Public Health
The Netherlands
L. Abelsma, Ministry of Agriculture
M. Bilkert-Mooiman, Inspectorate of Health Care
Th. Daha-Vuurpijl, Academic Hospital Leiden
A. J. de Neeling, National Insitute of Public Health & Environment
J. E. Degener, Academic Hospital Groningen
M. I. Esveld, Ministry of Public Health, Welfare and Sports
R. G. W. Huibers, Ministry of Agriculture, Nature Management and Fisheries
B. J. Kullberg, Academic Hospital Nejmegen
J. A. Lisman, Ministry of Health, Welfare and Sport
J. v. d. Meer, Academic Hospital Nejmegen
D. J. Mevius, ID - DLO
J. H. M. Nieuwenhuis, Inspectorate of Veterinary Health
J. F. M. Nouws, Rikilt- DLO
Arie Ottevanger, Dept. Public Health, Welfare and Sports
A. Pÿpers, University of Utrecht
M. J. W. Sprenger, National Institute of Public Health & the Environment
E. Stobberingh, Academic Hospital Maastricht
A. van den Bogaard, University of Limburg
P. J. van den Broek, Academi C. Hospital Leiden
A. J. van Hof, Ministry of Health, Welfare and Sport

Steven van Hoogstraten, Ministry of Health, Welfare and Sport
J. K. van Wijngaarden, Inspectorate of Health Care
H. A. Verbrugh, Erasmus University, Rotterdam
Desiree Beaujean, University Hospital Utrecht
C. J. G. Wever, National Reference Centre for Agriculture

United Kingdom
P. Clappison, Department of Health
J. Cooke, Withington Hospital, Manchester
M. Cooke, Department of Health
Barry Cookson, PHLS Central Public Health Lab.
P. Davey, University of Dundee
C. Dougan, University of London
B. Duerden, Public Health Laboratory Service, London
Alison B. Ewing, Countess of Chester Hospital
Robert Fenner, Department of Health
R. Finch, Nottingham City Hospital NHS Trust
I. M. Gould, Aberdeen Royal Infirmary
Judith Hilton, Department of Health
Aileen Keel, The Scottish Office, Department of Health
Karl Linklater, Veterinary Services, Scottish Agricultural College
Alasdair P. MacGowan, Bristol Centre for Antimicrobial
S. Macqueen, Great Ormond Street Childrens Hospital
Quentin McKellar, Moredun Research Institute, Edinburgh
Jeremy Metters, Department of Health
M. Powell, Medicines Control Agency
Peter Rudman, Agriculture House
J. M. Rutter, Veterinary Medicines Directorate
Norman Simmons, Guys and St. Thomas Hospital Trust
David J. Taylor, University of Glasgow Veterinary School
M. Wale, Public Health Laboratory, Nottingham
J. Weinberg, Public Health Laboratory Service
P. Wilkie, Standing Medical Advisory Committee
R. Wise, City Hospital, Birmingham,United Kingdom

USA
David M. Bell, Centers for Disease Control
Gary K. Chikami, Division of Anti-Infective Drug Products, FDA

Organizations

Karin Andresen, Forbrugerrådet, Denmark
Richard Bax, SmithKline Beecham Pharmaceuticals, United Kingdom
Gunnar Berge, FEFANA, c/o Alpharma, Norway
P. Biggs, British Veterinary Association, United Kingdom
André Bryskier, Hoechst Marion Roussel, France
Robin Bywater, Fedesa, Belgium
Mireille Chaton-Schaffner, Fedesa, Belgium
Pierre Choraine, Federation des Veterinaires d'Europe, Belgium
Alexander Døring, FEFAC, Belgium
Jeffry Edwards, Zeneca Pharmaceuticals, Cheshire,United Kingdom
Anette Espersen, Forbrugerrådet, Denmark
Ghislain Follet, Fedesa, Belgium
J. Gilley, British Medical Association, United Kingdom
Eggert Gunnarsson, The Icelandic Veterinary Association, Iceland
Toon Hoek, Fedesa, Belgium
Mikael Hoffmann, Swedish Medical Association, Sweden
Peter Hohl, Hoffmann- La Roche, Switzerland
Marjut Hämäläinen, The Finnish Veterinary Association, Finland

Jens Ingwersen, Leo Animal Health A/SB, Denmark
Erik Jacobsen, Danmarks Apotekerforening, Denmark
A. Johnston, Royal Veterinary College, United Kingdom
Børge Jørgensen, Den Danske Dyrlægeforening, Denmark
H. P. Kluza, Fachverband der chemische Industrie, Austria
Erik Kirkegaard, Løvens Kemiske Fabrik A/S, Denmark
Christina Krasemann, Bayer AG, Germany
Michael Kresken, Rhone Poulenc Rorer GmbH, Germany
H. Lablschinski, Forschungszentrum Bayer AG, Germany
Stany Lens, Fedesa, Belgium
Herbert Lundstrom, Federation des Veterinaires d'Europe, Belgium
Manfred Lützow, FEFANA, Switzerland
E. Bisgaard Madsen, Danske Slagterier, Denmark
Anthony Mudd, FEFANA, United Kingdom
Ulf Nonboe, FFFF, Denmark
Ian Phillips, ESMID, United Kingdom
Franz Pirro, Fedesa, Belgium
Jacques Poirier, FEFANA, France
Jürgen Reden, EFPIA, Belgium
Anguera Sanso, Consejo General de Colegios Veterinarios de Espana, Spain
Peter Schmid, FEFANA, Germany
Tom Shryock, Fedesa, Belgium
Knud Siboni, Odense Universitetssygehus, Denmark
Olli Soininen, The Finnish Veterinary Association, Finland
Runa Sturlason, Danish Medical Association, Denmark
Gunnela Ståhle, Federation of Swedish Farmers, Sweden
Valerie Thomas, Fedesa, Belgium
Herman Valgaeren, FEFANA, Belgium
Johan Vanhemelrijck, Fedesa, Belgium
Jorunn Vormeland, The Norwegian Veterinary Association, Norway
John Walthers, FEFANA, United Kingdom
Jochen Wieda, FEFANA, Germany
Kevin Woodward, Fedesa, Belgium

European Commission

Henri Belveze, European Commission DGXXIV-1, Belgium
H. Buchow, European Commission, DG V, Luxembourg
Gudrun Gallhoff, European Commission DGIII E3, Belgium
Lene Mølsted Jensen, The Permanent Representation of Denmark to the EU, Belgium
Anna Lønnroth, European Commission DG XII, Belgium
Dorothée Andre Schoboboda, European Commision DGVI, Belgium
Turid Strøm, Economic and Social Committee of the EU, Belgium
Annika Søderberg, Swedish Permanent Representation to the EU, Belgium
Robert Vanmoorde, European Commission DGXXIV-B3, Belgium
Kerstin Ödman, Swedish Permanent Representation to the EU, Belgium

World Health Organization

Jo Asvall, WHO Regional Office for Europe, Denmark
Sieghart Dittmann, WHO Regional Office for Europe, Denmark
Massimo Ciotti, WHO Regional Office for Europe, Denmark
Kees De Joncheere, WHO Regional Office for Europe, Denmark
Serguei K. Litvinov, WHO Regional Office for Europe, Denmark
Colette Roure, WHO Regional Office for Europe, Denmark
John Stelling, World Health Organization, Switzerland
Klaus Stohr, World Health Organization, Switzerland

Rosamund Williams, World Health Organization, Switzerland

Professional Journals

Martin Alder, The Veterinary Record, United Kingdom
Liselotte Højgaard, Ugeskrift for Læger, Denmark
Richard Smith, British Medical Journal, United Kingdom