Antimicrobial Resistance - European Commission support to research

Dr. Alain Vanvossel
Head of Unit
Dr. Anna Lönnroth
Scientific Officer

Unit of Infectious Diseases
Research Directorate General
European Commission

Antimicrobial Resistance RECENT COMMUNITY AND INTERNATIONAL INITIATIVES

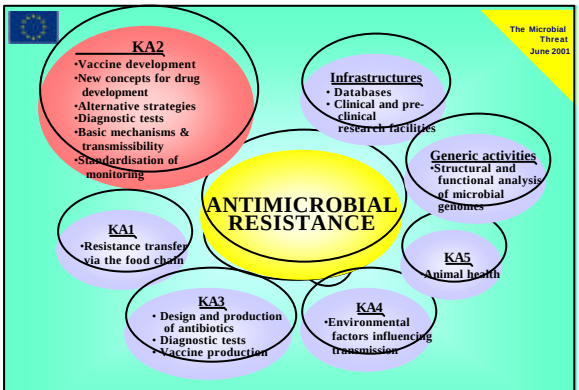
- EU Conference on the Microbial Threat in Copenhagen - *September 1998*
- Opinion of the Economic and Social Committee - *9 September 1998*
- E. P. and Council co-decision 2119/98/EC - setting up a network for the epidemiological surveillance and control of communicable diseases in the Community - *24 September 1998*
- Opinion of the Scientific Steering Committee - *28 May 1999*

RECENT COMMUNITY AND INTERNATIONAL INITIATIVES

- Council Resolution "A strategy against the microbial threat" - *8 June 1999*
- Council Conclusion on future actions - *8 December 1999*
- WHO Draft Global strategy for containment of antimicrobial resistance - *September 2000*
- CDC/NIH/FDA Public health action plan to combat antimicrobial resistance - *18 January 2001*

The key actions of the Quality of Life Programme 1998-2002 (€ 1860 million)

	€ million
Food, nutrition and health	290
Control of infectious diseases	300
The "cell factory"	400
Environment and health	160
Sustainable agriculture, fisheries and forestry	520
The ageing population and their disabilities	190



Projects on antimicrobial resistance

- Basic mechanisms of resistance
- Mechanisms of action of antibiotics
- New concepts for antibiotics aiming at novel molecular targets
- Novel approaches
- New strategies to control antimicrobial resistance
- Improved technologies for bacterial molecular characterisation
- Multi-drug resistant tuberculosis
- Monitoring antibiotic residues in foodstuff

Approx. 62 Mill. €

A new Research Framework Programme (FP) designed to help realise the European Research Area (ERA)

The ERA project

- A ***joint*** effort by EU and MS to address structural deficits in European research
  - fragmentation
  - under-resourcing
  - unfavourable environment for research and innovation
- Raison d'être of new FP must be to help ***realise ERA***
  - previous FPs have had little impact on the structure and integration of European research
  - therefore the concept of an FP needs to be thoroughly rethought

Main principles underlying new FP

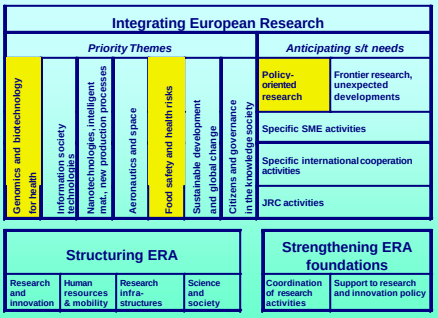
- Greater concentration
  - on a limited number of priorities
  - of strategic importance to the EU
  - where EU action can add greatest value
- More effective instruments
  - to exert structuring and integrating effects on
  - European research
- Simplified implementation
  - including larger longer-term projects with
  - more flexibility and autonomy for contractors

Proposed budget of new FP

- **€ 17.5 billion** *(compared to € 14.96 billion in FP5)*
  - an increase of 9% in real terms

	€ billion	
Priority themes (7)	10.425	*60%*
Anticipating S/T needs	2.345	*13%*
- Policy supporting research		
Structuring ERA	3.050	*17%*
Strengthening ERA foundations	0.450	*3%*
Euratom	1.230	*7%*
	17.500	*100%*

Structure of new FP*



*excluding Euratom

The major instruments

Capable of exerting a significant impact through their integrating effect and scale of effort mobilised

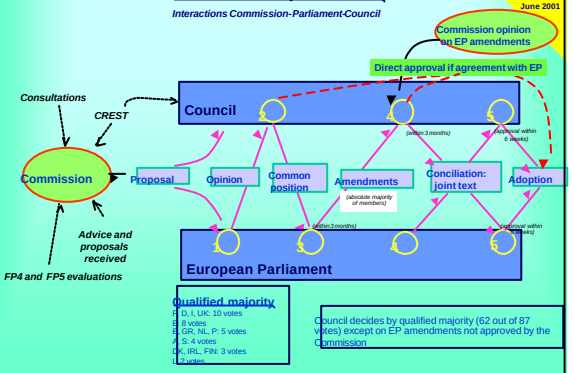
- Networks of excellence
  - to boost European excellence by integrating research capacities across Europe around a common programme of activities
  - up to several € millions a year over 5+ years
- Integrated projects
  - to deliver a pre-established product of research by creating critical mass
  - up to several € tens of millions

Timetable of new FP

February 2001	Commission's proposals for new FP
May 2001	Commission's proposals for SPs
Autumn 2001	EP first reading FP
Autumn 2001	Council's common position FP
Summer 2002	Decisions FP, SPs...
Autumn 2003	First contracts

Co-decision procedure

Interactions Commission-Parliament-Council



Genomics and biotechnology for health

1. Fundamental knowledge and basic tools for functional genomics
2. Application of genomics and biotechnology for health
3. *Application of medicine and public health*
4. Confronting the major communicable diseases linked to poverty

Genomics and biotechnology for health

APPLICATION OF MEDICINE AND PUBLIC HEALTH

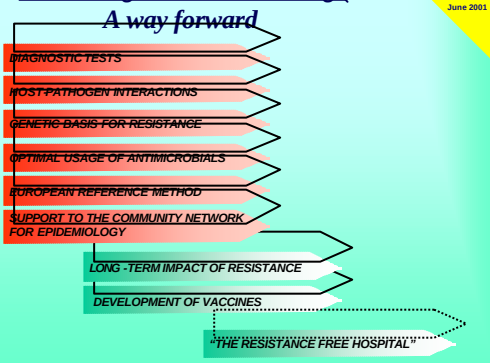
1. Combating cancer, cardiovascular disease and rare diseases
2. *Combating resistance to drugs*
3. Studying the brain and combating diseases of the nervous system
4. Studying human development and the ageing process

COMBATING RESISTANCE TO DRUGS

1. Microbial genomes
2. Host-pathogen interaction
   - vaccines
   - therapeutic strategies
3. Strategies for optimal use of anti-microbials
4. Support to the Community network for surveillance

Combating resistance to drugs

A way forward



CONTACT POINTS

Anna LÖNNROTH
- *anna.lonnroth@cec.eu.int*

Alain VANVOSSEL
- *alain.van-vossel@cec.eu.int*

EXPERT DATABASE

http://www.cordis.lu/expert-candidature/home.html

INFO PACK

http://www.cordis.lu/life/calls/200002.html

A Community Strategy against Antimicrobial Resistance

European Commission
DG Health & Consumer Protection
Directorate Public Health
Unit for Communicable, Rare & Emerging Diseases
Hartmut.Buchow@cec.eu.int

Goals of the Community Strategy

- Minimise morbidity and mortality due to antimicrobial resistant infections
- Preserve effectivenenss of antimicrobial agents for prevention & treatment of infectious diseases
- Contain antimicrobial resistance by prudent use of antimicrobial agents

Key Areas of Action

- Surveillance of antimicrobial resistance (AMR)
- Surveillance of consumption of antimicrobial agents
- Containment of AMR by reducing the needs for antimicrobials
- Preparing for the future by research & product development
- International co-operation

Surveillance on Antimicrobial Resistance (AMR) in Humans:

A priority of the Community network for the epidemiological surveillance and control of communicable diseases (Dec. 2119/98/EC)

Surveillance on AMR within that Community network

- **EARSS** - European Antimicrobial Resistance Surveillance System
- **Enter-Net** - International Surveillance network for the enteric infections salmonella and VTEC 0157
- **EURO-TB –** Surveillance of tuberculosis in Europe
- **EU network on nosocomial infections**

Surveillance on AMR in Veterinary medicine

- Council Directive 92/117/EC on monitoring and control of zoonoses : revision planned for 2001
- Concerted action and research projects on monitoring resistance in bacteria of animal origin

Surveillance of consumption of antimicrobial agents

- In Humans:
  Pilot project within the Community network starting this year
- In Animals:
  Monitoring on antimicrobials as feed additives since January 2000

Containment of AMR by reducing the needs for antimicrobials:

- Towards improving prevention of infections and control of communicable diseases
- Towards prudent use of antimicrobial agents in all areas
- Towards improving market authorisation and user information

Improving prevention of infections and control of communicable diseases

- Progressive development of the Community network over the next 5 years
- Support of immunisation programmes
- New legislation on zoonoses to be submitted this year
- The White Paper on Food Safety – a proactive new policy for safer food from healthier animals

Prudent use of antimicrobial agents

- Proposal for a Council Recommendation on the prudent use of antimicrobial agents in humans
- Phase out and replace antimicrobial agents as growth promoters
- Review their use as food additives
- Consider phasing out AMR markers in genetically modified organisms whenever feasible

Proposal for a Council Recommendation on the prudent use of antimicrobial agents in humans

Towards reducing the misuse and overuse of antimicrobial agents in order to

- contain or even reverse the spread of AMR
- preserve their effectiveness in treatment and prevention of communicable diseases

Recommended actions for Member States (I)

- Establish a multi-disciplinary, cross-sectoral national organisation to set up and implement specific strategies
- Co-ordinate activities via the Community network on communicable diseases (Dec. 2119/98/EC)

Recommended actions for Member States (II)

Key areas:

- **Surveillance** on resistant pathogens and consumption of antimicrobial agents;
- Antibacterial agents by **prescription only**;
- **Principles** on good management of communicable diseases:
  - **Prevention** of infections by immunisation programmes
  - **Infection control standards** in hospitals, institutions and in the community

Recommended actions for Member States III

Key areas (cont.):

- **Research** on rapid diagnostics and susceptibility testing;
- **Information** to the general public;
- **Education and training** of health professionals;
- **Monitoring of prescribing practices** of antimicrobial agents;
- **Control** systems on good practice of **marketing** of antimicrobials

Actions for the Commission I

- **Facilitate** co-operation and co-ordination through the **Community network**
- Establish an **advisery group** of representatives of the national organisations to the **Community network**
- Establish **principles and guidelines** of best practice on the prudent use of antimicrobials under the auspices of that **Community network**

Actions for the Commission II

- Develop within that **Community network** an **information system** linking interested parties and the public to the surveillance systems on AMR and the consumption of antimicrobial agents
- Strengthen participation of **EEA/EFTA countries** and **candidate countries** within the framework of that Community network
- **Encourage co-ordination with** international organisations, such as **WHO**

Time frame for action

Time after adoption of the Recommendation

	6 Months	1 Year	2 Years	3 Years	4 Years
Member States	Set up multidisciplinary organisation				
	Develop Strategy plan for action				
	Implement plan for action				
	Indicators for of monitoring prescribing practices				
	Evaluation of monitoring prescribing practices				
Commission	Establish scientific advisory group				
	Principles/guidelines of best practice on the prudent use of antimicrobials				
	Develop information system on surveillance on antimicrobial resistance and consumption of antimicrobials for prescribers, pharmacists, other interested parties and the general public				

Improving market authorisation and user information

EMEA activities, particularly on the quality of the Summary of Product Characteristics (SPC) with regard to

- Regular updating of acquired resistance
- Better rationale for dose recommendations
- conflicting pharmacodynamic information in the EU for same or similar products

Preparing for the future by research & product development

Key areas:

- Development of new **antimicrobial agents**
- Development of **alternative treatments and vaccines**
- Development of rapid and reliable **diagnostic and susceptibility tests**

International Co-operation

- Continue & extend co-operation with candidate and developing countries
- Strengthen co-operation, co-ordination and partnership at international level via international organisations and action plans

Next EU follow-up conference addressing AMR:

Brussels
15 - 17 November 2001 hosted by the Belgian Presidency

European Federation of Pharmaceutical Industries and Associations

Efforts by the Pharmaceutical Industry to curb Antimicrobial Resistance

Tony White
(GlaxoSmithKline)

Co-chair EFPIA Antimicrobial Resistance Working Group

EFPIA: Antimicrobial Resistance Working Group

Members / Affiliations

Inge Boe:	Leo	Andre Bryskier:*	Aventis
Bob Clay:	Pfizer	Peter Hohl:	Roche
Konstanze Machka :	BPI/VFA (D)	Angela Milne:	AstraZeneca
Maj-Inger Nilsson:	Pharmacia	Jergen Reden:	EFPIA R&D
David Roberts:	Lilly	Rainer Schmid:	Gruenenthal
Richard Tiner:	ABPI (UK)	Louis Speizer:	MSD
Hans-Otto Werling :	Bayer	Frank Verbeeck	BMS
Tony White:*	GSK	Luigi Xerri:	Farmindustria (It)

Includes top 5 AI Companies (GSK, Pfizer, Bayer, BMS, Aventis)
*** Co-chair**

EFPIA members

- Companies with significant track records in antimicrobials discovery & development
  - more lives saved through use of antimicrobials than any other medicinal class
  - antimicrobials play a central role in human health
- Antimicrobials remain a key weapon : there is an urgent need to preserve the value of antimicrobials due to increasing resistance development

EFPIA member activities to overcome the problem of resistance

1. Continuing Research and Development to find efficacious innovative antimicrobials
   - the most effective way
2. Research into the mechanisms, driving factors and epidemiology of resistance
   - surveillance and other studies
3. Guidance on how to maintain the clinical value of antimicrobials
   - communications and education on appropriate use of antibiotics
   - collective EFPIA position and response on resistance

EFPIA member activities to overcome the problem of resistance

1. Continuing Research and Development to find efficacious innovative antimicrobials
   - the most effective way
2. Research into the mechanisms, driving factors and epidemiology of resistance
3. Guidance on how to maintain the clinical value of antimicrobials

Research and development

- Discovery and research
  - new targets and strategies to combat resistance
  - new molecules and vaccines
- Development
  - new molecules and vaccines to regulatory approval and clinical use
  - new formulations/dosage regimens to overcome resistance

The situation

Antibiotics to which there is no resistance

Research and development: *Cost, time and risk*

- Of >500,000 compounds
  - ~ 150 into feasibility/development
  - ~ 10 product candidates (clin dev)
  - ~ 1 final marketed product

At a cost of ……$600m / £400m / 700m Euros
Over…...10 years

- **Need to increase chances**
- **Less than 20% known targets are utilised**

Research and development: *Wide-ranging approaches*

- Novel genomic technologies for identification of molecular targets
- Novel antibacterial structures directed against essential bacterial targets
- Structure/activity-based screening of natural products and potential lead products
- High-throughput screening

Research and development: *Identification and screening of new targets*

- Bacterial genome: entire characterisation for *S. aureus*, *H. influenzae*, *M. tuberculosis* *S. pneumoniae*, *E.coli*, *H.pylori*
  - **opens up huge opportunities**: microarrays and global transcripteome profile techniques
- *e.g. S. aureus*
  - ~2100 genes
  - 90% arrayed and studied for effects of agents on gene products

Research and development: *High-throughput screening*

- c**1990**: A bench chemist used to make 30–40 new molecules a year
  - a few hundred were screened for biological activity
- **1999**: 100,000s per year made and screened by automated combinatorial chemistry libraries/ high-throughput screening (HTS)
- **2000s**: 60,000 ***per day***: ULTRA HTS

Research and development:
Increased quality and quantity of output

Strategy/Technology	Impact
Genomics	More basic knowledge
Functional genomics	More/improved targets
Bioinformatics	More processing of data
High throughput screens	More validated hits
Combinatorial Chemistry	More/diverse substances
Toxicogenomics	More quality candidates
Pharmacogenomics	Tailored treatments

Research and development:
New classes/sub-classes

- Gram-positive activity (MRSA/PRSP etc)
  - Linezolid (Zyvox, Pharmacia) : new class : oxazolidinone
  - Daptomycin (Cidecin, Cubist)
  - Oritavancin (LY 333328, Lilly)
  - Quinupristin/dalopristin (Synercid, Aventis)
- Ketolides : RTIs
  - telithromicin (Ketek, Aventis)
  - ABT 773 (Abbott)
- β-lactam/penem
  - faropenem (Bayer): community/hospital RTI
  - ertapenem (Ivanz, Merck): broad use

Research and development:
New classes/sub-classes

- Improved molecules in current classes
  - New "respiratory" fluoroquinolones
    - improved potency/PK vs *S. pneumoniae*

      moxifloxacin (Avelox, Bayer), gemifloxacin (Factive, GSK), gatifloxacin (BMS; Bonoq, Grunenthal)
  - Des-fluoro quinolones
    - BMS 284756 (BMS)

emphasis on improved eradication, patient outcomes and economic benefits

Research and development:
New doses and developments

- Pharmacokinetic enhancement
  - amoxicillin/clavulanate (Augmentin, GSK)
    - based on PK/PD principles, maximised for eradication
    - increased time above higher MICs (PRSP)
    - paediatric and adult formulations for RTI

Research and development:
Vaccines/immunomodulators

- Conjugated vaccines
  - for *S. pneumoniae* and other respiratory pathogens
  - potential to reduce morbidity/mortality and pressure on antibacterial use
- Pegylated interferons
  - e.g. Hepatitis C (Roche/ Schering Plough)

EFPIA member activities to overcome the problem of resistance

1. Continuing Research and Development to find efficacious innovative antimicrobials
2. Research into the mechanisms, driving factors and epidemiology of resistance
   - surveillance and other studies
3. Guidance on how to maintain the clinical value of antimicrobials

Research into resistance
Examples:

- Support for PK/PD principles
  - studies into, and application of population PK/PD to guide appropriate prescribing (drug, dose, duration)
  - dialogue with regulators/others through EMEA discussion paper (EMEA 9880/99)
- Studies into
  - dosage duration/short-course
  - consumption vs resistance
    - not always a simple correlation
    - co-selection, compensatory genes
  - resistance mechanisms / evolution

Research into resistance

EFPIA partnership in EU-sponsored research progamme

EU FP5 , Framework Programme on Research and Technological Development

`Dynamics of the Evolution of Antimicrobial Drug Resistance`

Under the leadership of the Swedish Institute for Infectious Disease Control

Research into resistance
Surveillance

- Many established good quality industry sponsored surveillance studies
- For regulatory (label/updates), marketing (differentiation), and discovery (leads)
  - % susceptibility
  - emerging resistant mechanisms
  - epidemiology
- Some pre-date “national” programmes

Research into resistance
Surveillance

- Registration
  - EU-wide, broad range of organisms, when needed + updates, % resistance
- Post-registration / marketing
  - global / key countries, focussed target organisms (eg S.pneumo / RTI), longitudinal, resistance trends, differentiation, discovery
- Collaborative / national
  - key centres/regions , focussed target organisms/indications, longitudinal, local susceptibility trends and patterns

All are valid

Surveillance:
Global studies

Study	Duration	Sponsor
Alexander Project	1992–2001	GSK
CESAR	1993–2001	Bayer
SPAR	1995–1999	RPR
SENTRY	1995– 2001	BMS
ARTEMIS	1996	Pfizer
MYSTIC	1997–2001	AstraZeneca
LIBRA Surveillance	1997–2001	Bayer
SMART	1998	RPR
PROTEKT	1999–2001	Aventis
ZAPS	1999	Pharmacia

Surveillance:
Collaborations / National Studies

- PEG,Observatoire/ONENBA,Sentinella, SEPRA, Viriato,Bactro, SAUCE,SCOPE
- BSAC (British Society for Antimicrobial Chemotherapy)
  - respiratory and bacteraemia protocols
  - joint pharmafunding
  - BSAC, PHLS, pharma committee
  - core drugs plus investigational agents
  - non-proprietary data will be available on web

A good example of shared aims and value

Surveillance: *Collaborations*

- GAARD
  - collaboration with Alliance for Prudent Use of Antibiotics (APUA) and CDC
  - GSK (Alexander Project) , BMS (Sentry) and MRL collaborating to provide global surveillance data for public use
  - single data-base for comparisons across projects/data sources
- ESCMID : support for Working Parties
- WHOnet: support and collaborations

Surveillance: *Considerations*

- Surveillance itself is not an intervention
- Surveillance data need to be related to the definition of "resistance" and impact on patient outcomes
- The success of interventions should be measured against "resistance" and patient outcomes
- Many studies: differing objectives, methodologies and measurements (breakpoints)
- Objectives and standards need to be set for cross-EU surveillance

Surveillance: *Summary*

- EFPIA companies instrumental in initiating and continuing to support high-quality longitudinal surveillance studies: at global an national level
- Regulatory, commercial and research aims
- Increasing industry collaborations for cost and quality and access considerations
- Prioritisation, collaboration and standardisation needed across Europe to provide a quality network of surveillance
- Industry as partners

Until new investment and technologies deliver…

we need to preserve the utility of our current antimicrobials
we need to foster appropriate use of existing agents
we need to ensure best and appropriate use of new agents

to maintain beneficial patient outcomes
to maintain incentives to develop new agents

EFPIA member activities to overcome the problem of resistance

1. Continuing Research and Development to find efficacious innovative antimicrobials

2. Research into the mechanisms, driving factors and epidemiology of resistance

3. Guidance on how to maintain the clinical value of antimicrobials
   - communications and education on appropriate use of antibiotics
   - collective EFPIA position and response on resistance

Communication / education

- Many educational activities supported by industry
  - CME accredited symposia/workshops
  - increasing emphasis on appropriate prescribing
- Emphasis on defining appropriate use based on **"right drug, right dose, right duration"**
- Distinction between
  - unnecessary: not needed/non-bacterial
  - inappropriate: sub-optimal drug/dose/duration
  - appropriate: optimal drug/dose/duration

Communication/education

- EFPIA companies initiatives/support:
  - "Consensus" group on principles for appropriate prescribing (GSK)
    - principles to guide appropriate use developed by leading experts
  - Libra (Bayer)
    - international initiative to foster appropriate use
    - educational activities / collaboration with leading health organisations and experts
    - www.librainitiative.com

Communication/education: *National initiatives*

- Pharmindustria, Spain
  - `a new culture for the proper use of antibiotics`
- Pharmindustria, Italy
  - Antimicrobial Resistance Forum
  - industry, academia, health authorities
  - analysis, priorities, interventions, impact
- ABPI, UK
  - CARER group
    - correlation between community prescribing and impacts
    - educational booklet on use of antibiotics

Collaboration: *EFPIA position on containment of antimicrobial resistance*

- EFPIA supports appropriate use of antibacterials/ antimicrobials through collaborative actions based on science-based principles and evidence
- EFPIA supports the use of antimicrobials
  - when necessary (reduction of unecessary use)
  - at the right dose and duration
  - to maintain / maximise patient outcomes and minimise potential for resistance
  - to reduce economic burden : sequelae / hospitalisation

May mean increased usage of optimal agents

Collaboration: *EFPIA position on containment of antimicrobial resistance*

- Resistance
  - natural phenomenon consequent on antibacterial use
- Antimicrobials
  - indispensable to save/maintain quality of life
  - discovered/developed by EFPIA companies
- Appropriate use
  - support for collaborative science- based actions
- Collaborations
  - industry, regulators, health care professionals, patients, public

Summary

1. Continuing commitment to find efficacious innovative antimicrobials
   - despite high risks and cost
2. Continuing investment and collaboration in surveillance and resistance research
   - to monitor and target resistance and mechanisms
3. Engagement and pro-active efforts in fostering the appropriate use of antibiotics
   - to preserve the effectiveness of current and future antibiotics

www.efpia.org

EFPIA position paper on Containment of Antimicrobial Resistance

Antimicrobial Resistance - EMEA Initiatives

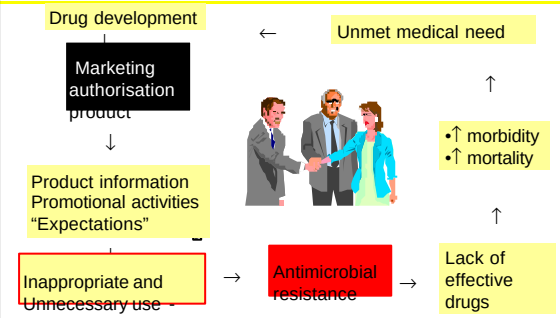
Visby 13 June 2001

Bo Aronsson
EMEA

EMEA initiatives

- **Criteria for marketing authorisation**
- **Product information**

The problem



EMEA mission

To contribute to protection and promotion of public and animal health by:

- mobilising scientific resources in the EU
- to allow timely access to innovative medicines through a single European marketing authorisation
- controlling the safety of medicines for humans and animals

EMEA activities/current communications

Data requirements for licensing - laid down in EU Regulation

- **CPMP Nfg on evaluation of new anti-bacterial medicinal products (ESCMID GI -93)**
- **CPMP Nfg on the pharmacodynamic section of the SPC for anti-bacterial medicinal products**
- **CPMP Ptc on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products**
- **EMEA discussion paper**

- **CVMP report on Qualitative Risk Assessment making recommendations on minimising resistance development in the veterinary sector**

Product information

Product information - efforts already made:

- Indications
  - Umbrella terms avoided
- "Consideration should be given to official guidance regarding the appropriate use of antibacterial agents".
- Pharmacodynamic section: tabulated information on variation in prevalence of resistance across the EU - with caveats.

EMEA activities -what next?

•efforts have been made to encourage industry and prescribers to take note of guidelines and local prevalence rates of resistance

•lack of evidence regarding the factors most important for the selection of drug-resistant bacteria

•difficulty of defining prudent use

•the importance of patient-specific decisions on prescribing at all times

EMEA activities

Section 4.1 of the SPC/Indications

•***A more critical policy might be adopted prospectively for the approval of indications in which a high proportion of patients may have a self-limiting condition and/or a non-bacterial infection?***

•Major draw backs - industry and prescribers

•Solutions:
- •Education of HCW and Public
- •Improved clinical trial designs

EMEA activities

•***The Licensing Authorities might use section 4.1 to encourage limiting the use of new agents to more severe infections, with the intent of reducing the chance that the efficacy of these newer agents be prematurely exhausted***.

•"Second-line" positioning of a novel agent on any grounds other than concerns over safety and efficacy is not acceptable Unequivocal evidence that it would lead to a reduced rate of detectable drug resistance?

•Solutions:
- •Education of HCW and Public
- •Improved clinical trial designs

EMEA activities

Section 4.2 of the SPC/Dose

•Provision of guidance to industry for improved dose justification Points to consider document on pharmacokinetic and pharmacodynamic principles which might better identify the dose regimens (dose, route and dose interval) to be taken into phase III trials and, thus, form the basis of the dose recommendations.

•Duration of treatment

EMEA activities

Section 5.1 of the SPC/ Pharmacodynamics
Information to prescribers on prevalence of antibiotic resistance

•Acceptable sources of data?

•Agreement on breakpoints (PK/PD; Epidemiological?)

•Where cross-resistance between agents in a class is known; possible to derive some standard information on prevalence which could be routinely applied to new agents in the same class. This alignment would prevent competitive claims based on difference in percentages in the tables for very similar agents

EMEA activities

For nationally approved antibiotics: lack of harmonisation of the SPC for products in the same class between the different Member States

•Few agents approved before the 1990s would meet the more stringent standards required in the EU for trials to support individual indications.
•ESCMID: information on duration of dosing should be put in the SPC for new and older agents.
•Guideline re the format of section 5.1, it is a national responsibility to consider how this information should be included in the SPCs for old products.

EMEA activities (Veterinary)

Risk Management Strategic Plan adopted by CVMP taking account of recommendations in earlier report

- ◆Pharmacokinetic/Pharmacodynamic modelling to optimise use of MICs in setting dose limits
- ◆Pre-authorisation Sensitivity Testing Guidelines
- ◆Consolidation of standard phrases & format in SPCs for Antimicrobials linked to Prudent Use Principles
- ◆Guidelines on prophylactic use in veterinary medicines, plus combination therapies, in-feed and water medications

EMEA activities (Veterinary)

Ongoing:

- Requirement for all antimicrobials authorised centrally to be the subject of resistance monitoring post-authorisation.
- Active support for development of guidelines for minimising resistance development in the veterinary sector under the VICH initiative (EU, USA & Japan).

EMEA planned activities (human)

Revisiting guidelines

- Inclusion and exclusion criteria in clinical trials
- Active control vs Placebo controlled trials
- Information on optimal duration of treatment
- Explore "potential" of PK/PD relationships
- Prevalence of antibiotic resistance
- Clinical implications of resistance - PM studies (ESCMID)
- Ecological impact study - part of early clinical development?

Workshop with Academia under the Belgian Presidency to address product information of old antibiotics

Progress Report on Antimicrobial Resistance

Initiatives of the European Federation for Animal Health

FEDESA

Visby, 13 June 2001

J Vanhemelrijck

The Copenhagen Recommendations Antibiotic Use and Resistance in Humans

1. **Stimulate prudent use / appropriate use**
2. **Monitor resistance**
3. **Monitor volume use**
4. **Evaluation of the benefits and risks of antimicrobials**
5. **Novel principles for treating infections**
6. **Replace antimicrobial growth promoters by safer non-antimicrobial alternatives including better farming practice, or conduct a risk assessment**

Industry has Acted on Recommendations From:

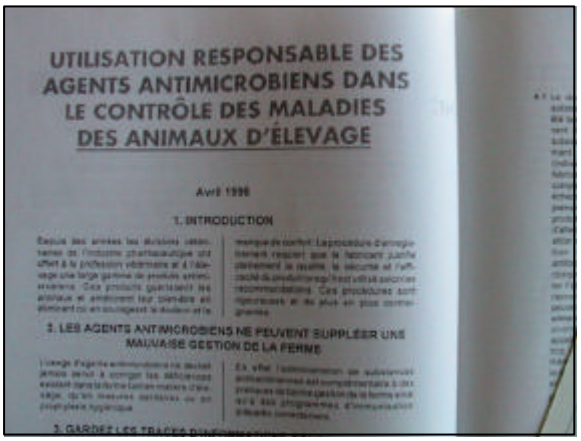
- CVMP in the "Risk Management Guidelines"
- WHO - Berlin and Geneva meetings
- OIE Symposium, Paris, 2000
- Scientific Steering Committee (European Commission)

Approaches Adopted:

- At the farm / vet level: emphasized rational application of antibiotics
- At the national and international levels: prudent/responsible use guidelines
- Quantified volumes used
- Embarked on surveillance studies of veterinary and zoonotic pathogens
- Sponsored risk assessments

Copenhagen Recommendation

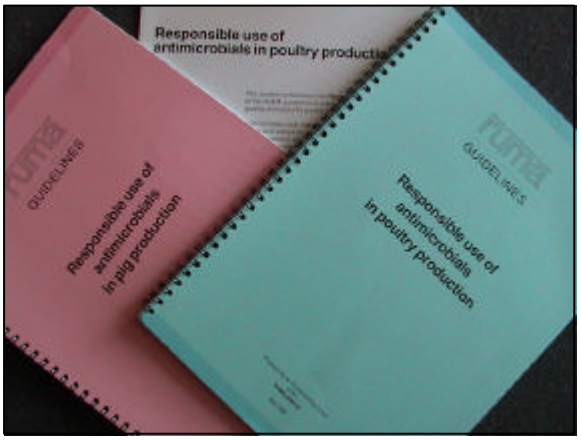
Stimulate Prudent Use & Appropriate Use

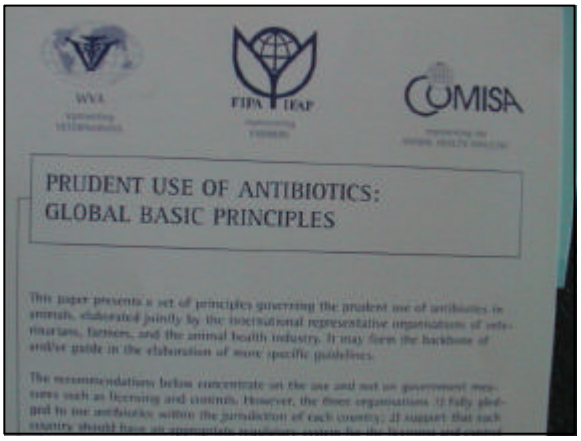

UTILISATION RESPONSABLE DES AGENTS ANTIMICROBIENS DANS LE CONTRÔLE DES MALADIES DES ANIMAUX D'ÉLEVAGE

Avril 1998

1. INTRODUCTION

3. LES AGENTS ANTIMICROBIENS NE PEUVENT SUPPLÉER UNE MAUVAISE GESTION DE LA FERME





Overview Principles

(directed to veterinarian)

- Prevention strategies emphasized
  - Minimize environmental contamination
- Minimize therapeutic use
  - Treat only at-risk or ill animals
- Utilize culture and sensitivity
- Use narrow spectrum antibiotics when possible
- Vet-client-patient relationship encouraged
- Record keeping
- Periodically review usage practices

The Animal Health and Nutrition Industry Initiatives

1. Stimulate prudent use
2. IFAH – FEDESA – National Associations
3. RUMA – Responsible Use of Medicines in Agriculture
4. Models for the vets: FVE, National vet associations…

Stimulate Prudent Use

Question:

- What we consider to be prudent use factors
- Have they been tested scientifically?
- Is resistance influenced at all?
- Is resistance reduced or increased?
- However, a full prudent use campaign resulted in a full awareness of the veterinary profession

Copenhagen Recommendation

Monitor Resistance

Objective(s) of Surveillance

What question do you want to address?

- Public and Animal Health Aspects
  - To produce data for gauging effectiveness of judicious use practices and other activities
  - To produce data for scientific risk assessments
  - To serve as an "early warning" system
- Regulatory Agency Activities
  - To produce data for licensing and/or restriction of use up to withdraw decisions (include risk assessments)
- Research Directions
  - To produce data for determining effectiveness of intervention activities and in-depth studies

Surveillance Studies

- Industry gained tremendous experience in running the FEFANA / Commission / Members State survey on *E. faecium*
  - Healthy pigs and poultry sampled in 6 countries in two consecutive years
  - Isolation made at country level and samples send to 1 central lab
  - Central lab co-ordinated entire process - standardization
  - Over 4 000 isolates available for testing!

'FEFANA' study then adapted...

- Became EASSA* study - extended to include cattle, Salmonella, *E. coli* and Campylobacter and 2 more countries
- Unique collaboration: companies (8) and EU Member States (8)
- So far approximately 3 000 isolates at the central laboratory
- MIC testing started against a range of generic human use antibiotics
- Target completion in 4Q 2001

*European Antimicrobial Sensitivity Surveillance in Animals

EASSA Study ... next steps

- Conclude the MIC testing and review the findings with CVMP
- Publish
- Contribution to the risk assessment
- Seek EU funding for extension into future years

Veterinary Pathogen Surveys

- Step 1: Industry to develop an extensive bank of *pre-treatment* isolates
  - Companies looking to pool existing collections at central lab
- Step 2: Instigate a pro-active survey of *pre-treatment* isolates:
  - 1000 strains per year
- Overall intentions:
  - To establish sensitivity baselines
  - To track sensitivity changes
  - To provide material for renewals

Industry Surveys

- Value is that these are pan European surveys run on standardized lines
- In this regard they are unique
- Isolates will be *pre-treatment* from healthy animals (not treatment failures)

Copenhagen Recommendation

Monitor Volume Use

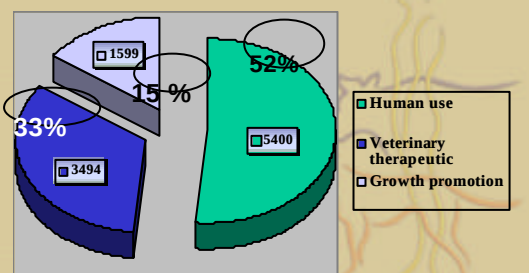
FEDESA Usage Survey

- In 1998, FEDESA published a European survey on the 1997 volumes of antibiotics used in animals / humans
- In 2000, the survey has been repeated amongst member companies for 1999

1997-1999 Evolution of Antibiotic Volume Tonnage and Percentage

	Total	Human Use	Vet. Ther.	GP
1997	10 500	5 400	3 494	1 599
1999				
99 / 97				

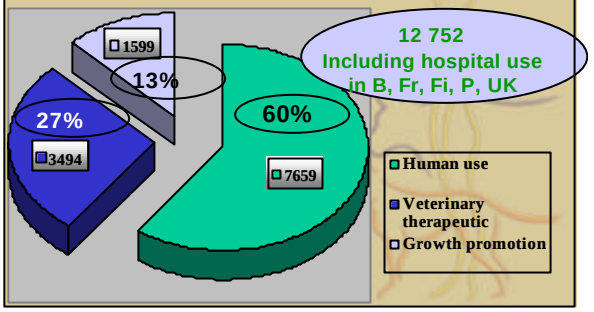
Usage of Antibiotics in Humans and Animals in the EU (1997(1), 10,500 tons)



1997-1999
Evolution of Antibiotic Volume
Tonnage and Percentage

	Total	Human Use	Vet. Ther.	GP
1997	10 500 100%	5 400 52%	3 494 33%	1 599 15%
1997	12 752 100%	7 659 60%	3 494 27.5%	1 599 12.5%
1999				
99 / 97				

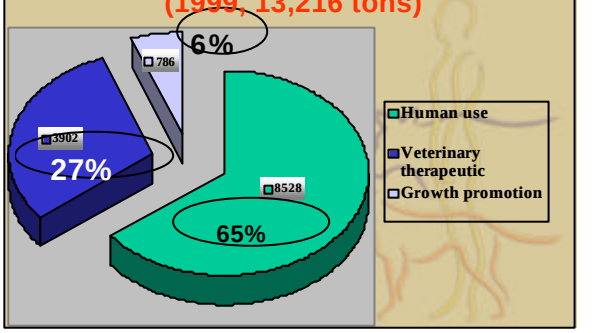
Usage of Antibiotics in Humans and Animals in the EU (1997(2), 12,752 tons)



1997-1999
Evolution of Antibiotic Volume
Tonnage and Percentage

	Total	Human Use	Vet. Ther.	GP
1997	12 752 100%	7 659 60%	3 494 27.5%	1 599 12.5%
1999	13 216 100%	8 528 65%	3 902 29%	786 6%
99 / 97	**+ 10%**	**+ 11.3%**	**+ 9.5%**	**- 50%**

Usage of Antibiotics in Humans and Animals in the EU (1999, 13,216 tons)



Copenhagen Recommendation

Evaluate
Benefits and Risks of Antimicrobials

Evaluation of Benefits and Risks of Antimicrobials

- On individual products ⇒ the registration process ⇒ CVMP /CPMP and SCAN become more stringent and have new requirements!
- What is the risk without antibiotics?
- Licensing is the systematic use of the precautionary principle, let us hope it is a proportional use.

Evaluation of Benefits and Risks of Antimicrobials

- State/society evaluation ⇒ laws and rules
  - Licensing
  - Prudent use
- Individual evaluation of risk and benefits
  - Dr. & Veterinarian: efficacy /side effects
  - + Education ⇒ Resistance in animals
  - + More data ⇒ Resistance present in human bacterial isolates
  - = Public: "Save my animals" / "Make them fit"

Conduct a Risk Assessment

- Data from studies are becoming available
- No firm proof of large-scale systematic transfer of resistance from animal bacteria to human bacteria
- Interaction in zoonosis is obvious because bacteria are the same
- Has resistance been induced by treating the animal and/or the human?

Copenhagen Recommendation

Novel Principles for Treating Infections

Novel Principles for Treating Infections

- Hygiene and management
- Vaccination
- Antimicrobials
- Eradication
- Treatment: new agents influencing the Host / Bacteria relationship

= Maybe Antibiotics, Maybe Not

Copenhagen Recommendation

Find Non-Antimicrobial Alternatives

Replace Antimicrobial Growth Promoters with Ones that are Safer

- What does safer mean?
- In order to decide, you need a licensing process for individual products according to well-established and validated criteria
- A regulatory approval and refusal system
- Already exists

Summary

- Industry has taken the recommendations of the Copenhagen meeting seriously and acted upon them
- Will continue to do so in cooperation with other stakeholders
- Food safety procedures vs. antibiotic use
- All bacteria not just resistant fraction

Summary

- Authorisation of products according to scientifically established data provided for in the regulatory approval process is a first, very important principle.
- Predicts resistance evolution for candidate products and monitors this for approved products

And…

- If a new risk occurs - refine the system of evaluation
- CVMP - Committee for Veterinary Medicinal Products RISK MANAGEMENT!!!
- Decisions taken hastily on partial information contrary to the registration are creating new risk.

- The animal health industry is proud to provide safe products to its patients according to well-established procedures.
- The animal health industry supports the licensing system based on good scientific evaluation and adaptable to progress.
- The decision making process should not be in opposition to the scientific recommendation.

OFFICE INTERNATIONAL DES EPIZOOTIES

Organisation mondiale de la santé animale World organisation for animal health Organizacion mundial de sanidad animal

ANTIMICROBIAL RESISTANCE

ACTIVITIES OF THE O.I.E.

12, rue de Prony - 75017 Paris - France Tel: 33 (0) 1 44 15 18 88 Fax: 33 (0) 1 42 67 09 87
Email: oie@oie.int Website: http://www.oie.int

OFFICE INTERNATIONAL DES EPIZOOTIES

"ANTIMICROBIAL RESISTANCE" ACTIVITY

1997 : report requested by the Regional Commission for Europe

1998 : presentation of the report by the OIE Collaborating Centre for Veterinary Medicinal Products

1999 :
Recommendations of the OIE International Committee
➔ Creation of an ad hoc expert group
➔ Definition of its reference terms

Creation of the expert group

2000 : Work of the expert group

OFFICE INTERNATIONAL DES EPIZOOTIES

COMMITTEE OF INTERNATIONAL EXPERTS

- 12 experts : Europe - USA - Japan - Australia - South Africa - India
- Chairmanship : France : Prof Acar
- Meetings : March 2000
  May 2000
  November 2000
- Consultation : 4 months, mid-June, mid-October 2000

OFFICE INTERNATIONAL DES EPIZOOTIES

COMMITTEE OF INTERNATIONAL EXPERTS

- Objective
  - ☞ Elaboration of 5 guidelines
    - Risk analysis and antimicrobial resistance
    - Code of prudent use of antimicrobials
    - Study of the consumption of antimicrobials in animal husbandry
    - Harmonisation of surveillance plans
    - Harmonisation of laboratory methods

OFFICE INTERNATIONAL DES EPIZOOTIES

Organisation mondiale de la santé animale World organisation for animal health Organizacion mundial de sanidad animal

METHODOLOGIES FOR THE EVALUATION AND CONTAINMENT OF ANTIMICROBIAL RESISTANCE IN BACTERIA OF ANIMAL ORIGIN

12, rue de Prony - 75017 Paris - France Tel: 33 (0) 1 44 15 18 88 Fax: 33 (0) 1 42 67 09 87
Email: oie@oie.int Website: http://www.oie.int

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE RISK ANALYSIS AND ANTIMICROBIAL RESISTANCE

- Objective : method to conduct a risk analysis
  - Transparent and objective
  - Valid basis for any decision of risk management
- Content
  - Definition of the components of risk analysis
  - Definition of different approaches in risk assessment
    - Qualitative
    - Semi-quantitative
    - Quantitative

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE

RISK ANALYSIS

- Recommendations
  - Separation of risk assessment from risk management
  - Establishment of a risk assessment policy
  - Conduct of risk analysis based on scientific facts
  - Conduct of risk analysis according to an iterative process
  - Systematical conduct of a qualitative risk analysis before considering, if necessary, a quantitative approach
  - Development of technical assistance for developing countries lacking the necessary resources

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
PRUDENT USE

- Objectives
  - to maintain the efficacy of antimicrobials used in animal husbandry
  - to avoid the contamination of humans by resistant bacteria or resistance determinants through food
- Adressed to
  - Competent authorities
  - Veterinary pharmaceutical industry
  - Veterinarian practitioners
  - Dispensing pharmacists
  - Farmers

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
PRUDENT USE

RESPONSIBILITIES OF AUTHORITIES

- Requirements before granting a MA
  - Control of the product quality
  - Control of the therapeutic efficacy
    - Pre-clinical tests
    - Clinical tests
  - Assessment of the selection pressure
  - Establishment of MRL - ADI
  - Protection of the environment
  - Establishment of an SPC
- Requirements after granting of a MA
  - Specific surveillance
  - Non specific surveillance

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
PRUDENT USE

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

- Quality of the MA dossiers
- Marketing
- Advertising

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
PRUDENT USE

RESPONSIBILITIES OF VETERINARIANS

- Use of antimicrobials if necessary
  - diagnosis
- Choice of the right antimicrobial substance
  - Efficacy
  - Absence of selection of resistant bacteria
- Appropriate use

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
PRUDENT USE

RESPONSIBILITIES OF FARMERS

- Use in accordance with prescription
  - Treatment specifications
  - Compliance with withdrawal periods
- Shelf-life
- Disposal

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
CONSUMPTION OF ANTIMICROBIALS

- Objective : to develop a methodology to
  - Assess the amounts of antimicrobials used
  - To supply data to be used for risk analysis
  - To improve guidance for use (DDD)
- Sources of information
  - Authorities
  - Industry
  - Users
- Useful information
  - Amounts of antimicrobials used per year, per family, per antimicrobial substance
  - Oral or parenteral route
  - Oral route : therapeutics or additives

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
HARMONISATION OF
SURVEILLANCE PLANS

- Definition of monitoring and surveillance
- Objectives
  - To generate data to
    - To detect the emergence of resistant bacteria
    - To determine the prevalence of resistant bacteria
    - To conduct specific studies
    - To assess risks for public health
    - To establish a risk management policy
    - To improve the specifications of prudent use of antimicrobials in animal husbandry
    - To compare the situations between regions, countries
    - To consolidate results at the national, international level

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
HARMONISATION OF
SURVEILLANCE PLANS

- Harmonisation of specific factors
  - Animal species
  - Sampling
    - Faeces
    - Foods
    - Statistics
  - Bacteria(zoonotic, indicator)
  - Antimicrobials
  - Laboratory methods
  - Data (qualitative, quantitative)
  - Structure of data bases
  - Structure of reports

OFFICE INTERNATIONAL DES EPIZOOTIES

GUIDELINE
HARMONISATION OF
LABORATORY METHODS

- Definition of thresholds for bacteria
  - Sensitive
  - Resistant
  - Intermediate
- Analysis of existing methods
  - Dilution in liquid medium
  - Dilution in agar medium
  - Disk diffusion
- Recommendations
  - Validation of methods
    - Reference laboratory
    - Work under quality assurance
  - Standardisation is necessary
  - Equivalence of methods

OFFICE INTERNATIONAL DES EPIZOOTIES

International Committee
69th General Session
Paris, 27 may - 1er june 2001

RESOLUTION
ANTIMICROBIAL RESISTANCE

OIE Specialists Commissions
to develop standards
for antimicrobial resistance

OFFICE INTERNATIONAL DES EPIZOOTIES

International Committee
69th General Session
Paris, 27 may - 1er june 2001

RESOLUTION
ANTIMICROBIAL RESISTANCE

OIE Specialists Commissions:
Code Commission
Standards Commission

OFFICE INTERNATIONAL DES EPIZOOTIES

International Committee

69th General Session
Paris, 27 may - 1er june 2001

RESOLUTION
ANTIMICROBIAL RESISTANCE

Ad hoc scientific expert committee
targeted risk assessments
for human and animal health risks
due to resistant bacteria in animals
as a consequence of the use of
specific antimicrobials in food-producing animal

OFFICE INTERNATIONAL DES EPIZOOTIES

International Committee

69th General Session
Paris, 27 may - 1er june 2001

RESOLUTION
ANTIMICROBIAL RESISTANCE

Technical assistance
for OIE Member Countries
with the help of its
Collaborating Centre for
Veterinary Medicinal Products

OFFICE INTERNATIONAL DES EPIZOOTIES

1ST INTERNATIONAL CONFERENCE ON ANTIMICROBIAL RESISTANCE

- Paris
- March 1999
- 400 participants

- Objectives :
  - No assessment of the risks to public health associated with the use of a particular antimicrobial
  - Proposals to
    - Structure a risk analysis model applicable to a problem of public health associated with resistant bacteria
    - To present the existing codes of prudent use of antimicrobials in animal husbandry
    - To harmonise the surveillance plans of resistant bacteria

OFFICE INTERNATIONAL DES EPIZOOTIES

2ND INTERNATIONAL CONFERENCE ON ANTIMICROBIAL RESISTANCE

- Paris
- 2-4 October 2001

- Objectives :
  - Review of actions undertaken since March 1999
    - Progress in knowledge
    - Actions undertaken in the area of risk assessment and management
    - Presentation of the work of the OIE expert group
    - Identification of actions to be pursued

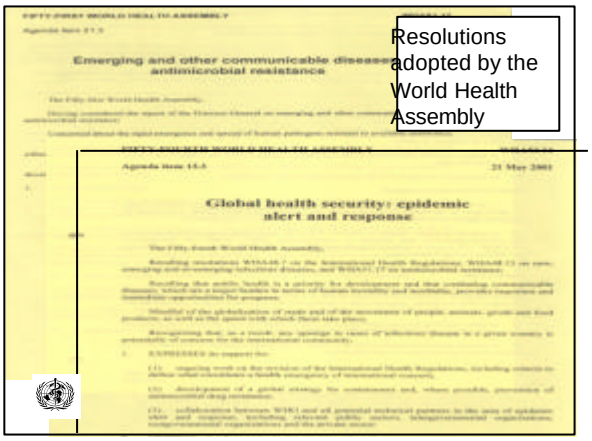
OFFICE INTERNATIONAL DES EPIZOOTIES

2ND INTERNATIONAL CONFERENCE ON ANTIMICROBIAL RESISTANCE

- Programme
  - New scientific knowledge
  - Perception of the problem by society
  - International activities
  - Antimicrobial resistance and risk analysis
  - Prudent use of antimicrobials in animal husbandry
  - Surveillance programme
  - Laboratory methods
  - Consumption of antimicrobials in animal husbandry

WHO Initiatives

- Raising awareness
- Promoting partnership and information-sharing
- Assisting countries to establish surveillance
- Providing strategic & technical guidance on interventions;
- Stimulating research to fill knowledge gaps

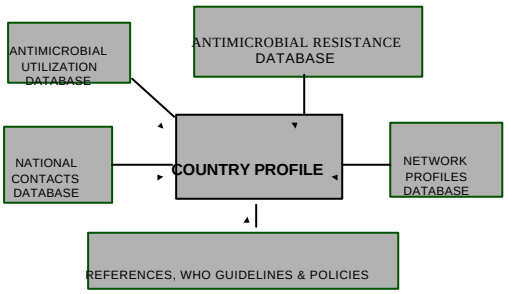


Resolutions adopted by the World Health Assembly

WHO Initiatives

- Raising awareness
- Promoting partnership and information-sharing
- Assisting countries to establish surveillance
- Providing strategic & technical guidance on interventions;
- Stimulating research to fill knowledge gaps

WHO Antimicrobial Resistance Information Bank



WHO AR InfoBank

Resistance Surveillance Networks

WHO Region	National networks	Countries with national networks	Countries participating in multinational networks
Europe	44	23	33
All	62	34	90

Obstacles reported by national networks

- Lack of funding
- Low level of awareness amongst physicians of antimicrobial resistance issues
- Lack of standardisation of methods
- Poor information exchange with government; lack of government support

WHO Initiatives

- Raising awareness
- Promoting partnership and information-sharing
- Assisting countries to establish surveillance
- Providing strategic & technical guidance on interventions;
- Stimulating research to fill knowledge gaps

LaboratoryTraining

Partners: AIHA, CDC, PHLS, Nat PH Labs in Sweden, Denmark, Beijing, Institut Pasteur Algeria; Universities & University Hospitals of Athens, Bangkok, Beijing, California, Galway, Hanoi, Kuala Lumpur, Leeds, Liverpool, Lugano, Lyon, Manila, Oslo, Singapore, Seoul, Vellore,

Software Tools

WHONET 5 is a Windows-based database software for management of microbiology laboratory data and analysis of antimicrobial susceptibility test results

Objectives:

- to enhance local use of laboratory data for guiding therapy, assisting infection control, characterizing resistance epidemiology and identifying laboratory testing errors;
- to promote collaboration in surveillance activities through the exchange of data in a common format

Downloadable from: www.who.int/emc/amr

External Quality Assurance Schemes

- 42 countries and >130 labs in WHO EQAS
  (WHO Collaborating Centre at CDC*, Atlanta)
- 100 countries participating in EQAS for MDR-TB via international lab network (Antwerp)
- >33 countries in 2 WHO Regions in *Neisseria gonorrhoeae* EQAS
  (WHO Collaborating Centre, Sydney)

*Tenover et al J Clin Microbiol 2001 241-250

Surveillance Standards

- Provide a framework for surveillance of resistance integrated with disease surveillance
- Link epidemiological and microbiological inputs to better monitor the impact of resistant disease
- Generate information for public health action

Draft for comment on www.who.int/emc/amr

WHO Initiatives

- Raising awareness
- Promoting partnership and information-sharing
- Assisting countries to establish surveillance
- Providing strategic & technical guidance on interventions
- Stimulating research to fill knowledge gaps

WHO Global Strategy for Containment of Antimicrobial Resistance

Provides a framework of interventions with the aim to:

slow the emergence

and reduce the spread

of antimicrobial resistance

Global Strategy - Six Key Points

- Disease prevention & infection control
- Access to antimicrobials
- Appropriate antimicrobial use
- Legislation & regulation
- Surveillance
- Focused research

1. Disease prevention & infection control

- Priority to prevention
- Accelerate global improvements in water, sanitation and housing
- Improve immunization coverage
- Implement effective infection control in all health facilities

2. Access to antimicrobials

- Identify & remove barriers to access
- Update essential drugs lists & formularies
- Strengthen drug distribution systems
- Detect & remove counterfeit & substandard antimicrobials
- Phase out as growth promoters antimicrobials used in human medicine

3. Appropriate antimicrobial use

- Improve knowledge & understanding of antimicrobial use & resistance among all prescribers & consumers
- Monitor practices & feedback results
- Remove financial incentives favouring inappropriate use

4. Legislation and Regulation

Introduce and/or enforce mechanisms to:

- support improved access to antimicrobials
- encourage continuing professional education
- control inappropriate pharma promotion activities
- provide incentives for new drug development

5. Surveillance

- Strengthen laboratory capacity for disease diagnosis and resistance detection
- Build 'joined-up' surveillance systems (disease, resistance & antimicrobial use)
- Ensure that surveillance information is used for action

6. Focused Research

- Develop public-private partnerships for R&D for new drugs for unmet needs
- Encourage development of regimens for max. safety & efficacy and min. resistance selection
- Initiate new research to fill knowledge gaps; not 'more of the same'

Global Strategy Implementation

- Much of the responsibility will fall on individual countries
- Implementation of interventions should be phased and customized to national realities

Global Strategy Implementation

- Provision of 'public goods' is critical (e.g. information, surveillance, research)
- Inter-disciplinary co-operation, international action and bilateral support essential

WHO Initiatives

- Raising awareness
- Promoting partnership and information-sharing
- Assisting countries to establish surveillance
- Providing strategic & technical guidance on interventions;
- Stimulating research to fill knowledge gaps

WHO gratefully acknowledges the valuable support of:-

The United States Agency for International Development

The UK Department for International Development

The Ministry of Health, Labour and Welfare, Japan

EU Member States and the many partner organizations and individual experts who have contributed to our work on surveillance and containment of antimicrobial resistance

For further information - amr@who.int