International Symposium

Towards a Risk Analysis of Antibiotic Resistance

Berlin 9 - 11 November 2003

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In co-operation with

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Towards a Risk Analysis of Antibiotic Resistance

9-11 November 2003, Berlin

General information for participants

Hotel	Best Western Hotel Steglitz International Albrechtstraße 2 12165 Berlin Tel: +49-30-790-05-0 Fax:+49-30-790-055-50
Conference Location	Bundesinstitut für Risikobewertung Martin-Lerche-Hörsaal Diedersdorfer Weg 1 12277 Berlin Tel.: +49-30-8412-2145 Fax.:+49-30-8412-2962
Conference Language	English with simultaneous translation to German.
Transport	*All transport indicated in the programme will be organized by BfR. Please assemble in the lobby in time.*

Programme

Sunday 9th November 2003

Arrival of participants at Hotel Steglitz International

From 15.00 Registration at:

BfR Dahlem
Thielallee 88-92
D-14195 Berlin
Tel.: +49-1888-412-0

Speakers and invited experts are kindly requested to bring their travel documents for reimbursement.

18.00-21.00 Welcome reception with buffet in the BfR Casino (see above)

Monday 10th November 2003

08.00-09.00 Late registration at BfR Marienfelde, Diedersdorfer Weg 1

08.15 Departure from Hotel Steglitz International to BfR Marienfelde

09.00-09.10 Welcome of the Federal Ministry of Consumer Protection, Food and Agriculture
Secretary of State Alexander Müller

09.10-09.20 Welcome and opening by the President of the BfR
Andreas Hensel

09.20-09.30 Introduction and scope of the meeting. Technical remarks
Reiner Helmuth

09.30-09.50 Towards a rational risk analysis of antimicrobial resistance
David Vose

Session I: Hazard Identification
Chair: JohnThrelfall, Stefan Schwarz

09.50-10.10 Use of antimicrobials in veterinary medicine and food animal production
Fritz Ungemach

10.10-10.30 Spread of resistance determinants
Patrice Courvalin

10.30-10.50 Spread of resistant clones - molecular epidemiological approaches
Trudy Wassenaar

10.50-11.00 Discussion

11.00-11.30 Coffee break

Session II: Hazard Characterization
Chair: Linda Tollefson, Helmuth Tschäpe

11.30-11.50 Veterinary use of antimicrobials and emergence of resistance in zoonotic and sentinel organisms in EU countries
Robin Bywater

11.50-12.10 Spread of resistant bacteria and resistance genes from animals to humans
Kåre Mølbak

12.10-12.30 Antibiotics triggering local bacterial evolution
Fernando Baquero

12.30-12.40 Discussion

12.40-14.00 Lunch break

14.00-14.15 Hazard characterization in practice, examples from human medicine
Uwe Frank

14.15-15.00 Examples of contemporary problems:
14.15-14.30 Glycopeptide resistant Staphylococcus, *Wolfgang Witte*
14.30-14.45 ESBLs, *Patrice Nordmann*
14.45-15.00 Fluoroquinolones, *Fred Angulo*

15.00-15.15 Discussion

Session III: Exposure Assessment
Chair: Fred Angulo, Fernando Baquero

15.15-15.30 Consumption of antimicrobial agents in EU, data from IFAH-Europe
Tom Shryock

15.30-16.00 Coffee break

16.00-16.20 Monitoring antimicrobial resistance - Principles and limitations
Frank Aarestrup

16.20-16.35 Presentations from monitoring programmes and their consequences, USA
Paula Fedorka-Cray

16.35-16.50 Presentations from monitoring programmes and their consequences, EU
Dik Mevius

16.50-17.00 Short presentations on the situation in Germany: Humans
Klaus Huppertz

17.00-17.40 Short presentations on the situation in Germany: Animals
17.00-17.10 Salmonella, *Andreas Schroeter*
17.10-17.20 Campylobacter, *Edda Bartelt*
17.20-17.30 Commensals, *Lüppo Ellerbroek*
17.30-17.40 Animal pathogens, *Jürgen Wallmann*

17.40-18.00 Discussion

Session IV: Risk Characterization - Food and Public Health Aspects
Chair: Henrik Wegener, Wolfgang Witte

18.00-18.20 Summary of the day along the public health aspects
Richard Wise

18.45 Transport to Schloss Diedersdorf

19.30-21.30 Dinner in Diedersdorf
21.30 approx. Transport to hotel

Tuesday 11th November 2003

8.00 Departure from hotel Steglitz International to BfR Marienfelde

Session IV (continued): Risk Characterization - Food and Public Health Aspects
Chair: Henrik Wegener, Wolfgang Witte

What do we know: Reports on conclusions and activities of previous expert groups

08.30-08.45 Microbial Threat - The Copenhagen Recommendations-Initiative of the EU Chief Medical Officers
Niels Frimodt Møller
08.45-09.00 EU Scientific Steering Commitee
Reinhard Fries
09.00-09.15 Codex Alimentarius Commission
Selma Doyran
09.15-09.30 World Organization for Animal Health (OIE)
Patrick Dehaumont
09.30-09.45 World Health Organization (WHO)
Peter Braam

09.45-10.00 Discussion

10.00-10.05 Technical remarks for working groups, *Reiner Helmuth*

10.05-10.30 Coffee break

10.30-12.30 Working in Groups on Session I to IV under Chairmen leaderships

12.30-14.00 Lunch break

Session V: Management options and measures - What can be done?
Chair: Christian Grugel, Andreas Hensel

14.00-14.20 Report from Group I: Hazard Identification
John Threlfall, Stefan Schwarz

14.20-14.40 Report from Group II: Hazard Characterization
Linda Tollefson, Helmuth Tschäpe

14.40-15.00 Report from Group III: Exposure Assessment
Fred Angulo, Fernando Baquero

15.00-15.20 Report from Group IV: Risk Characterization
Henrik Wegener, Wolfgang Witte

15.20-15.45 Coffee break

15.45-16.05 The FDA position
Linda Tollefson

16.05-16.25 Risk management measures
Christian Grugel

16.25-16.45 Alternatives to antimicrobials and perspectives after the meeting
Andreas Hensel

16.45-16.55 Summary and closure
Reiner Helmuth

16.55 End of Meeting - Departure

Abstracts

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Towards a rational risk analysis of antimicrobial resistance

David Vose
Risk Media Ltd (Les Leches/France)

Risk analysis is the systematic, science-based evaluation of possible risk management measures to control an identified risk. It should seek to estimate the total change in the outcome of interest (e.g. human health risk, animal health risk) if the risk management action were to be taken, and thereby determine the most effective action or combination of actions to control the risk. Current microbial food safety risk analysis methods most closely approach the needs of antimicrobial risk analysis but with several important distinctions.

First, the antimicrobial hazard is a resistance determinant rather than a micro-organism. Use of similar antimicrobials in animal and human healthcare, co-selection, multi-resistant bacteria, transfer of resistance and commensal organisms add layers of complexity not observed in microbial food risk assessment. This makes the attribution of risk to different possible selection pressures for the resistance determinant difficult. *Second*, the human health effect of resistance is less easily measured than for microbial risk: there are, for example, ongoing discussions as to whether acquisition of resistance brings changes in virulence or pathogenicity. If not, the human health effect is only apparent when there is a treatment failure, which is also difficult to determine. *Third*, little data have been collected on the proportion of resistant to susceptible bacteria in the exposure environment leading to over-simplified characterisation of the bacterial populations. This is particularly relevant for non-pathogenic organisms which have not been of human health interest but may now be a reservoir of resistance determinants. *Fourth*: the issue of legacy. Once a resistant population of pathogens has emerged, it may remain long after selection pressure has been removed, and it will have a health impact that endures as long as the commercial life of the corresponding antimicrobial.

A small number of quantitative microbial risk analyses have been completed, but few of these have been useful in risk management and the food safety risk analysis community is beginning to realize that it has over-sold the value of full quantitative risk analysis. Microbial risk analysis is in its infancy, which international guidelines on microbial risk analysis have proven to be too restrictive and adherence to guidelines has over-shadowed the use of common sense. A very few antimicrobial risk analyses have been completed so far, and have by necessity concentrated on the simplest issues.

This presentation describes some of the lessons we have learned from microbial and anti-microbial risk analysis, discusses some improvements in data collection methods and reporting that would make antimicrobial risk analyses more feasible, and suggests some simpler, decision-focused (rather than modelling-focused) approaches to conducting broader antimicrobial risk analysis.

Session I: Hazard Identification
Chair: JohnThrelfall, Stefan Schwarz

Spread of antibiotic resistance determinants

Patrice Courvalin
Unité des Agents Antibactériens, Institut Pasteur (Paris/France)

The development of bacterial resistance, including multidrug resistance, is inevitable because it represents a particular facet of the general evolution of bacteria. Resistance to antibiotics can result from mutations in structural or regulatory house keeping genes that are passed vertically from one generation to the next. Alternatively, it may result from horizontal acquisition of foreign genetic information from bacteria of the same genus or from different genera. The two phenomena are not mutually exclusive and together may result in the emergence and more efficient dissemination of resistance. Bacteria are particularly adept at gathering resistance genes, whether isolated or grouped in operons, that mediate resistance to antimicrobials. Association of genetic structures ensures stability and vertical inheritance as well as horizontal spread of antibiotic resistance genes in phylogenetically remote bacteria genera. In contrast to cross-resistance, in which a single biochemical mechanism confers resistance to a single class of drugs (thus use of a given antibiotic can select resistance to other members of the group but not to drugs belonging to other classes), co-resistance is due to the presence, in the same host, of several mechanisms, each conferring resistance to a given class of drugs. In addition, the corresponding genes are often adjacent (physically linked) and expressed in a coordinated fashion. One of the most efficient system of this type is represented by the intregrons in Gram-negative bacilli. Because of the genetic organization resulting in co-expression of the various genes, use of any antibiotic that is a substrate for one of the resistance mechanism will co-select for resistance to the others and thus for maintenance of the entire gene set. It thus appears that bacterial genetic tinkering can lead to resistance to every antimicrobial agent. These notions will be discussed taking *Listeria monocytogenes* as an example.

Molecular typing of antibiotic resistant pathogens

Trudy M. Wassenaar[1], M. Wittwer[2], A. Ridley[3]
[1] Molecular Microbiology and Genomics Consultants (Zotzenheim/Germany)
[2] Bundesamt für Veterinärwesen (Bern/Switzerland)
[3] Veterinary Laboratory Agency (Weybridge/UK)

Molecular typing has been a highly valuable tool in molecular epidemiology of pathogens. Typing of sub-populations resistant or sensitive to antimicrobials, however, is hampered by a number of complications. Molecular typing is the grouping of isolates based on their genetic characterizations. Ideally, this grouping correlates with important phenotypic characteristics, such as virulence, host specificity, and resistance patterns. This is not always the case because (i) antibiotic resistance genes are frequently present on mobile elements and mobility disturbs clonal relationship (ii) antibiotic resistance due to point mutations is frequently re-invented and thus does not correlate to genetic back ground; (iii) multiple resistance can result from various events with different genetic mechanisms. Thus, the success story of some highly clonal pathogens can not be taken as a blue print for other species that may be less clonal. These difficulties will be discussed and the practicalities of molecular typing of resistant sub-populations will be illustrated with *Campylobacter jejuni.* Findings with this weakly clonal pathogen will be compared and contrasted to those of *Salmonella enterica* serovars that are of public health importance.

Session II: Hazard Characterization
Chair: Linda Tollefson, Helmuth Tschäpe

Veterinary use of antimicrobials and emergence of resistance in zoonotic and sentinel bacteria in EU countries.

Robin Bywater,
Bywater Consultancy (Shropshire/England)

Most bacteria causing antimicrobial resistance problems in humans appear unrelated to animal sources. A questionnaire completed by senior clinical microbiologists was used in an attempt to identify the organisms seen as important to the human problem, and to assess the perceived contribution of animal sources[1]. The results confirmed that methicillin resistant *Staphylococcus aureus* (MRSA) was the organism of greatest concern, and suggested that animal sources were seen as contributing less than 4% of the total human resistance problem, and that the hazard, such as it was, lay largely with the zoonotic microorganisms.

In characterising this hazard, there is some information on resistance among zoonotic organisms in EU countries, but existing national surveys use varying collection and assessment methods, and so are difficult to compare. The European Animal Health Study Center (CEESA), has carried out a surveillance study in *E.coli* (n=2118), *Salmonella* spp. (n=271) and *Campylobacter* spp. (n= 1326), isolated at slaughter from chickens, pigs (period 1999-2000) and cattle (period 2000-2001) in four countries per host. Sampling, isolation and MIC testing (the latter carried out in a central laboratory) used consistent and standardised methods. Antimicrobials tested (chosen as significant in human use) were ampicillin, cefepime, cefotaxime, ciprofloxacin, chloramphenicol, gentamicin, streptomycin, tetracycline, trimethoprim/sulfamethoxazole, nalidixic acid and erythromycin.

Results showed considerable variation among countries, hosts and antimicrobials, although low numbers of salmonellas hindered (and often precluded) comparison for this species. For chickens[2], isolates of *E. coli* from Sweden had the lowest, and France the highest levels of resistance; for *Campylobacter* spp Swedish isolates from chickens showed no resistance, France and Netherlands had higher resistance. For pigs[3], isolates of *E. coli* from Sweden showed low resistance, with higher resistance in isolates from elsewhere, particularly Spain, while for isolates of *Campylobacter*, resistance to nalidixic acid and ciprofloxacin was unexpectedly high in Swedish isolates compared with the other countries sampled. For cattle[4], isolates of *E.coli* showed generally lower resistance than for the other hosts, and was low or absent to the cephalosporins and ciprofloxacin.

It is suggested that the variations seen among zoonotic organisms and *E.coli* may reflect amounts or mode of antimicrobial usage, but that the resistance to modern compounds (and the consequent hazard) remains relatively low. However prudent and conservative antimicrobial use remains crucial in both humans and animals.

References

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Spread of resistant bacteria and resistance genes from animals to humans

Kåre Mølbak
Department of Epidemiology, Statens Serum Institut (Copenhagen/Denmark)

Several lines of evidence link antimicrobial-resistant pathogens in humans to animal reservoirs. These include outbreak investigations, analytical epidemiological studies of sporadic infections of foodborne illness, ecological studies (temporal evidence of the emergence of resistance and trends of drug resistance in foodborne pathogens), and subtyping of isolates collected from different sources. Microbiological studies of farmers, their families, and other exposed persons have furthermore supported these observations. The evidence is most obvious for the foodborne infections, but there are also examples of transfer of resistant organisms of lower or opportunistic pathogenicity.

Under the selective pressure from antimicrobial use, commensal bacteria such *Escherichia coli*, *Klebsiella* spp., *Enterobacter*, enterococci, or *Bacteriodes* spp. may become reservoirs of antimicrobial resistance genes. Some of these resistance elements may be transferred to gastrointestinal as well as other human pathogens. The extent to which transfer of mobile genetic elements takes place *in vivo* and the public health dimensions of the genetic exchange is more difficult to demonstrate than the transmission of resistant food-borne pathogens from farm-to-fork.

My presentation will focus on the public health implications of resistance in the foodborne pathogens *Campylobacter* and *Salmonella*. Data for infection with these bacteria suggest that infections with drug-resistant bacteria may be associated with severe illness. This has been measured in terms of duration of illness, rates of admission to hospital, risk of invasive illness, and case-fatality. Several mechanisms may explain these findings, including increased morbidity and transmission among subsets of patients exposed to antibiotics for other reasons, reduced efficacy of early empirical treatment, and possibly increased virulence of the pathogen.

In a recent, yet unpublished, analysis of 1,346 Danish patients with *Salmonella* Typhimurium infection, 6.8% of 103 patients with nalidixic acid (quinolone) resistant isolates experienced invasive illness or died, compared with 2.8% of 1,243 patients infected with pansusceptible isolates. Patients with nalidixic acid resistant isolates were 11.6 times more likely to experience invasive illness or death, following adjustment for comorbidity, age and gender ($p=0.0002$). The demonstration of this hazard to public health corroborate that the use of fluoroquinolones in food animals should be discontinued. In Denmark, infections with quinolone resistant salmonella are frequently associated with imported foods or travel to certain destinations, and therefore the initiatives to ban the use of fluoroquinolones for food animals should be carried out both nationally and internationally.

Hazard characterization in practice. Examples from human medicine

Uwe Frank
Freiburg University Hospital (Freiburg/Germany)

Veterinary use of antimicrobials which are important in human therapy may represent a public health risk by the transfer of resistant zoonotic pathogens or resistance genes from animals to humans. Resistant bacteria can diminish the effectiveness of antibiotics and demand the use of more expensive or less safe alternatives.

Most investigations on the transfer of resistant bacteria from animals to humans concern food-borne infections caused by *Salmonella* spp., *Campylobacter* spp., and *Yersinia* spp. Humans become infected with the zoonotic pathogens through the food chain and/or by direct contact. Although the horizontal transfer of resistance genes from the animal bacterial flora to pathogenic bacteria and the human intestinal flora has been well-documented in several instances, the importance of the indirect path of resistance gene transfer is less clear than for the direct transfer of resistant zoonotic organisms.

Examples of contemporary problems (1)

Origins and consequences of antimicrobial-resistant nontyphoidal Samonella: implications for the use of fluoroquinolones in food animals

Fred Angulo, R. Tauxe, M. Cohen
Foodborne and Diarrheal Diseases Branch; Centers for Disease Control and Prevention (Atlanta/USA)

Human Salmonella infections are common; most infections are self-limiting, however severe disease may occur. Antimicrobial agents, while not essential for the treatment of Salmonella gastroenteritis, are essential for the treatment of thousands of patients each year with invasive infections. Fluoroquinolones and third-generation cephalosporins are the drugs-of-choice for invasive Salmonella infections in humans; alternative antimicrobial choices are limited by increasing antimicrobial resistance, limited efficacy, and less desirable pharmacodynamic properties. Antimicrobial-resistant Salmonella results from the use of antimicrobial agents in food animals, and these antimicrobial resistant Salmonella are subsequently transmitted to humans, usually through the food supply. The antimicrobial resistance patterns of isolates collected from persons with Salmonella infections show more resistance to antimicrobial agents used in agriculture than to, antimicrobial agents used for the treatment of Salmonella infections in humans. Because of the adverse health consequences in humans and animals associated with the increasing prevalence of antimicrobial-resistant Salmonella, there is an urgent need to emphasize non-antimicrobial infection control strategies, such as improved sanitation and hygiene, to develop guidelines for the prudent usage of antimicrobial agents, and establishment of adequate public health safeguards to minimize the development and dissemination of antimicrobial resistance and dissemination of Salmonella resistant to these agents.

Examples of contemporary problems (2)

Glycopeptide resistant Staphylococcus

Wolfgang Witte
Robert Koch Institute (Wernigerode/Germany)

S. aureus with reduced susceptibility to glycopeptides (GISA):
That this species can be "trained" to vancomycin non susceptibility be stepwise in vitro selection using increasing concentrations has already been described in 1990 (1). First clinical isolates of GISA were reported in 1997 from Japan (2) and later in several countries; nevertheless the emergence of GISA seems to be relatively rare (only 12 strains described until now (for review see [3]; all of them have been MRSA). Heteroresistant GISA (hGISA) are obviously more common, and there are indications on treatment failure of glycopeptides in deep-seated infections (4). The emergence of the hGISA-phenotype in MRSA resistant to all antibiotics besides linezolid and fosfomycin in 2 French hospitals needs special attention (5).

The GISA phenotype is obviously based on extremely thick cell walls with incomplete cross linking of peptidoglycan chains (6) which exerts a trapping effect for glycopeptides. Although the majority of French GISA and also of GISA found in local outbreak in Germany have been evolved from one particular epidemic MRSA (multilocus type ST247, [7, 8]), other GISA exhibit MLST-types as known from different clonal lineages of MRSA (M. Enright, personal communication).

Phenotypically different from the above mentioned GISA are MRSA with resistance to teicoplanin but susceptible to vancomycin (at first described [9]) for a clinical case finally successfully treated with vancomycin and recently also found in Germany associated with a small clinical outbreak of infections with MRSA of MLST-type ST45 (10).

*Van*A-mediated glycopeptide resistance in *S. aureus*:
After the report on in vitro transfer of the *van*A gene cluster to *S. aureus* in 1992 (11) the emergence of natural *van*A coded full vancomycin resistance in *S. aureus* had been expected with fear.
This became true with an MRSA from an exit infection in a dialysis patient in the US in summer 2002 who also had a mixed infection with a *van*A containing *E. faecalis* (12). Shortly later a second independent case was reported from another diabetic. In both cases the *van*A containing MRSA belonged to a widely epidemic strain with the *van*A-cluster integrated into a conjugative plasmid (13).
The emergence of the *van*A gene cluster in clinical MRSA underlines the significance of glycopeptide resistant enterococci as a potential reservoir. The decline of glycopeptide resistance in *E. faecium* after the ban of avoparcin in animals as well as in humans in the community (14) also reduces the risk for further transfer of glycopeptide resistance in *S. aureus*.

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Session III: Exposure Assessment
Chair: Fred Angulo, Fernando Baquero

Consumption of antimicrobial agents in the EU

Thomas R. Shryock
International Federation of Animal Health in Europe (Brussels/Belgium)

Data on the amounts of antibiotic used in either the human or the animal sector in the EU have been difficult to obtain. Participants at the 2001 Microbial Threat 2 meeting in Visby, Sweden, provided information that many countries were just beginning to initiate national programs, but there were many obstacles. Human non-hospital antibiotic use data were obtained from a commercial source (IMS) and reported in the ATC DDD system by Cars et al. (1), then subsequently used by others. The CVMP issued a report (2) in 1999 on animal antibiotic usage, based in part, on data provided by the animal health trade association FEDESA (re-aligned later as IFAH Europe). FEDESA undertook a member survey in 1997 and 1999 via an external consultant (to preserve proprietary data and assure independence) to estimate the total amounts of antibiotics used in animals (food and companion combined). Member companies (16 of 19) responded and provided an estimate (at 100% potency) of the kilogram amounts of their products sold in the EU and Switzerland. The consultant applied an extrapolation factor to these amounts to adjust upward for non-member companies with similar product lines (note: coccidiostats were excluded). IMS human use data were used for comparison purposes.

1997 to 1999 Change in Antibiotic Use Volume (tonnes and percentage)

TOTAL	Human Use	Vet. Rx.	Growth Promotion
1997: 12,752 100%	7659 60%	3494 27.5%	1599 12.5%
1999: 13,152 100%	8525 65%	3827 29%	800 6%
1999:1997 +10%	+11.3%	+9.5%	-50%

Both human and veterinary therapeutic antibiotic use increased by about the same percentage over the 2 year survey period, whereas the 50% decrease for growth promotion was attributed to the July 1, 1999 implementation of the ban on use of five antibiotics with such claims. In 1999, the breakout by class for total animal use was as follows: tetracyclines, 41%; macrolides, 11%; penicillins, 10%, sulphas, 9%, aminoglycosides, 5%; other therapeutics, 6%; and fluoroquinolones, 1%. A per country estimate of animal antibiotic use showed the countries with more animal production (e.g. Spain, Germany, France, Italy) used more antibiotic than did the smaller countries (Austria, Switzerland) or the Nordic countries (Finland, Sweden, Denmark). A breakout by class for each country was not available. Comparison to the human data on a country-specific basis was therefore not possible.

Although antibiotic usage data collection programs in the EU, for both human and animal use, suffer from the same limitations of lack of standardized data, specific knowledge of treatment applications, and comprehensiveness, general trends might be temporally associated with clinical observations of susceptibility surveillance programs. This would enable focused epidemiological studies to be designed to explore the reasons for changes in a particular type of use. Additionally, antibiotic

usage data should be useful for estimating the degree of selective pressure in a given population of animals or patients.

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Monitoring antimicrobial resistance – Principles and limitations

Frank Møller Aarestrup
Danish Veterinary Institute (Copenhagen/Denmark)

Antimicrobial agents are in the production of food animals used for therapy and prophylactics of bacterial infections and in feed to promote growth. The use of antimicrobial agents causes problems in the therapy of infections through the selection for resistance among bacteria pathogenic for animals or humans. Current knowledge regarding the occurrence of antimicrobial resistance in food animals, the quantitative impact of the use of different antimicrobial agents on selection for resistance and the most appropriate treatment regimes to limit the development of resistance is incomplete. Programmes monitoring the occurrence and development of resistance are essential to determine the most important areas for intervention and to monitor the effects of interventions.

When designing a monitoring programme it is important to decide on the purpose of the programme. Thus, there are major differences between programmes designed to detect changes in a national population, individual herds or groups of animals. In addition, programmes have to be designed differently according to whether the aim is to determine changes in resistance for all antimicrobial agents or only the antimicrobial agents considered most important in relation to treatment of humans.

In 1995 a continuos surveillance for antimicrobial resistance among bacteria isolated from food animals was established in Denmark. Three categories of bacteria, indicator bacteria, zoonotic bacteria and animal pathogens are continuously isolated from broilers, cattle and pigs and tested for susceptibility to antimicrobial agents used for therapy and growth promotion by disc diffusion or MIC-determinations. This programme will only detect changes on a national level. However, isolating the bacteria and testing for several antimicrobial agents will enable us to determine the effect of linkage of resistance.

Since 1995 major differences in the consumption pattern of different antimicrobial agents have occurred in Denmark. The Danish monitoring programme has enabled us to determine the effect of these changes on the occurrence of resistance. The Danish monitoring is however, not suited to determine changes on a herd-level or to detect emergence of new types of resistance only occurring at a low level.

Presentations from monitoring programmes and their consequences, USA

Paula J. Fedorka-Cray
USDA-ARS-Antimicrobial Resistance Research Unit (Athens/USA)

Recognizing the potential utility of antimicrobial susceptibility testing for monitoring trends in antimicrobial resistance development and because of the public health concerns associated with the use of antimicrobials in food-producing animals, an antimicrobial resistance monitoring program was proposed by the Food and Drug Administration Center for Veterinary Medicine (FDA). This program was developed particularly as a post-marketing activity to help ensure the continued safety and efficacy of veterinary antimicrobials, especially fluoroquinolones. In 1996, the FDA, USDA, and CDC initiated the National Antimicrobial Resistance Monitoring System (NARMS; referred to in previous publications as the National Antimicrobial Susceptibility Monitoring Program and subsequently changed to NARMS-Enteric Bacteria) to prospectively monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal diagnostic specimens, from healthy farm animals, and from raw product collected from federally inspected slaughter and processing plants. Non-typhoid *Salmonella* was selected as the sentinel organism. Additional organisms were added to the program, and in 2001, NARMS monitored antimicrobial susceptibility in non-typhoid *Salmonella*, *Escherichia coli*, *Campylobacter*, and Enterococcus in humans and animals. *Salmonella* Typhi, and Listeria, Vibrio and Shigella isolates collected from humans are also tested. The program has also expanded to included testing of isolates from retail meat. The animal arm of NARMS is resides at the USDA-ARS laboratory in Athens, GA while the human arm resides at the CDC in Atlanta, GA and the retail arm resides at the FDA-OR in Laurel, MD.

The goals and objectives of the monitoring program are to 1) provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from the human and animal populations; 2) facilitate the identification of resistance in humans and animals as it arises; 3) provide timely information to veterinarians and physicians; 4) prolong the life span of approved drugs by promoting the prudent and judicious use of antimicrobials; and 5) identify areas for more detailed investigation. Program information is available to the public and may be accessed at www.fda.gov/cvm/index/narms/narms_pg.htm. Additional information on results from the animal isolate testing, including percent resistance by animal species for each year testing has been conducted, can be found at www.arru.saa.ars.usda.gov.

Use of the information will be targeted to redirecting drug use so as to diminish the development and spread of resistance over the short term, with directives involving long-term use developed in collaboration with the appropriate professional practitioner groups. As the information generated from any monitoring system is descriptive, outbreak investigations and field studies will be initiated as a result of major shifts or changes in resistance patterns in either animal or human isolates. Research will be needed/directed/requested to fill known information gaps and to clarify observational discrepancies. In addition, the NARMS isolates are invaluable for other research areas including development of diagnostic tests, the study of molecular mechanisms of resistance, gene flow and population genetics, and for virulence and *in vivo* colonization studies.

Presentations from monitoring programmes and their consequences EU

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During the nineties worldwide the increasing importance of antimicrobial resistance as public health threat was subject for discussion, both in human and in veterinary medicine. As a consequence, in 1998 the Chief Medical Officers of EU Member States organised the Microbial Threat meeting in Copenhagen, Denmark. The report of this conference, 'the Copenhagen Recommendations' was a basis for EU-policies to be developed.

Regarding monitoring programs it was recommended that the EU and member states should set up a European surveillance system of antimicrobial resistance and need to collect data on the supply and consumption of antimicrobial agents. For resistance surveillance guidance was given on methodologies, sampling strategies, inclusion of bacteria and antibiotic classes of importance and data handling. Based on these recommendations national resistance and usage monitoring programmes were developed in all member states to a certain extend. Well known examples are the Scandinavian programmes: DANMAP, SVARM/SVEDRES, NORM/NORMVET, FINNRES. In 2003 in The Netherlands the first reports were published, NETHMAP/MARAN.

In the EU-research programmes many applications for projects on resistance and usage monitoring including all members stated were made. Most of them failed to be approved.

However positive examples exist. The concerted action Antimicrobial Resistance in bacteria of Animal Origin (ARBAO) was approved in 1997 and run until 2001. This project resulted in detailed recommendations for EU-monitoring programmes in animals as reported in 2001. Subsequently ARBAO-II project was approved in 2002 focussing at harmonisation of test results, building a network of veterinary national reference laboratories, and webpages for input of surveillance data of comparable quality. Project aimed at antimicrobial consumption in animals failed approval by the EU.

In human medicine in 1998 already a EU-project on resistance surveillance was running, 'European Antimicrobial Resistance Surveillance System' (EARSS). This project started on two bacterial species important in human medicine (pneumococci and staphylococci) and was very successful. In 2000 *E. coli* and enterococci were included. The simplicity of the project was the basis for its success. In the past years the number of countries and laboratories have continuously increased. Also on antimicrobial consumption data a EU-project, 'European Surveillance of Antimicrobial Consumption', (ESAC) started in 2001 aiming to collect standardised, harmonised and comparable data on consumption of antimicrobial agents in human medicine.
In the autumn of 2003 the new 'zoonoses directive' has been approved. This means that after 2003 each EU member states will have to monitor resistance in zoonotic agents and other agents relevant to public health annually. Because of necessary coordination and control a Communatoir Reference Laboratory (CRL) for antimicrobial resistance will have to be designated including National reference Laboratories (NRL's). Although it is tempting to combine the CRL task for a specific bacterial species (eg. *Salmonella*) with the CRL task for resistance, it is essential that the latter CRL is a laboratory with sufficient expertise on antimicrobial resistance tensing methodologies.

Activities focussed at harmonisation and standardisation of susceptibility tests and its results are momentarily organised amongst others by WHO, the CRL for *Salmonella* and ARBAO-II. These activities are very important but they overlap and coordination is lacking.

It can be concluded that after 1998 a lot of national activities are developed regarding surveillance of resistance and usage data. On the human medical side coordination does exist in two EU-projects, although these projects do not entirely cover the field for surveillance. In the veterinary medical side, in spite of many attempts made, coordination at the EU-level is lacking. The new 'zoonoses directive' may be the trigger for a future coordination of the national activities.

Short presentation on the situation in Germany: Humans

Klaus Huppertz, B. Wiedemann and the GENARS-group (Bonn/Germany)

Due to the establishment of the GENARS-project (***Ge***rman ***N***etwork for ***A***ntimicrobial ***R***esistance ***S***urveillance) in 2001, reports on the current status of antimicrobial resistance in Germany are available at any time. In contrast to most other surveillance programs the GENARS-project uses the every day routine data of laboratories of medical microbiology for surveillance. Therefore, the standard of the methods for identification and sensitivity testing had to be raised in these laboratories to meet to the standard of this surveillance study and include MIC-determination and identification to the species level.

Table 1 gives an overview on the current status (1st half of 2003) of the percentages of resistant strains for some selected species and antibiotics in Germany.

	Ampicillin	Penicillin	Oxacillin	Ceftazidime	Piperacillin	Pip / Taz	Ciprofloxacin	Meropenem	Gentamicin	Erythromycin
E. coli	42,0	-	-	0,6	25,4	2,1	10,7	0,0	4,9	-
P. aeruginosa	-	-	-	6,3	8,8	6,9	13,9	2,6	19,3	-
S. aureus	-	58,2	10,8	-	-	-	17,3	-	6,6	21,1
S. pneumoniae	-	0,0	-	-	-	-	-	0,0	-	6,7

Table 1: Percentages of resistant strains for the 1st half of 2003 in Germany

Since the GENARS-project started in 2001 trends on the development of antimicrobial resistance by GENARS-data are not yet meaningful. Therefore, data presented for trends on antimicrobial resistance in Germany are taken from the study group “resistance” of the Paul-Ehrlich-Society. Based on these data a strong increase in the resistance of *P. aeruginosa* to Ceftazidime and Piperacillin could be observed for the last 13 years. Also remarkable is the continuous increase of resistant strains of *S. aureus* to Oxacillin from 1.7 % in 1990 up to 20.7 % in 2001. However, not only increasing resistance rates could be detected, but also decreasing rates as can be seen in *S. aureus* resistant to Doxycycline (1990: 8,9 %; 2001: 0,5 %).

With the establishment of the GENARS-project a continuous surveillance of antimicrobial resistance of human pathogens started. This project which is based on a high quality method and on every day data from the laboratory routine will not only improve resistance surveillance in Germany but will also be advantageous for the patients who benefit from more reliable test results and better hospital epidemiology.

Short presentation on the situation in Germany: Animals (1)

Resistance of Salmonella isolates in Germany

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The National Veterinary Reference Laboratory for Salmonella in Germany types between 3000 - 5000 salmonella isolates from animals, food, feed and the environment per year. They are submitted by public health laboratories of the 16 Federal Länder all over Germany, from universities, zoos, private companies and veterinarians.

In 2000 - 2002 fifty three percent of all isolates (11738) stemmed from animals, 30 % from food, 10 % from feed and 7 % from the environment. In the category animal (6220), over 73 % of the Salmonella isolates were from food producing animals, 13 % from wild animals, 9 % from zoo-animals and 5 % from domestic animals. The salmonella isolates from food producing animals (4490) originate to 46 % from poultry, 28 % from cattle, 24 % from pig and 2 % from other sources.

MIC determinations are performed according to the NCCLS guidelines (M7-A5, M31-A) using the microdilution broth method and the breakpoints from NCCLS and DANMAP 2001. Currently 17 different antimicrobial agents are tested.

Despite an overall reduction of resistant salmonella isolates from 79 % (2000) to 45 % (2002) the prevalence of resistance remains quite high. The overall decrease is mainly due to decreasing sulfamethoxazole resistance. Multiresistance is relatively stable over the three years (43 % in 2000, 40 % in 2001, 36 % in 2002).

The resistance level in Salmonellae from food producing animals like cattle and pigs is especially dominated by *Salmonella* Typhimurium (ST) phage type DT104. In 2002 over half of all ST isolates belong to this phage type. Ninety-five percent of the DT104 isolates are multiresistant with five or more different resistant determinants. Forty-two percent of ST isolates from cattle- and pigmeat belong to DT104 and are multiresistant. This demonstrates the spread of this phage type along the food chain.
The resistance level in Salmonellae from poultry (75 % in 2000, 63 % in 2001, 44 % in 2002) is influenced by serotypes, which differ from those in cattle and pig. Especially in poultry isolates an increasing quinolone resistance from 7 % (2001) to 27 % (2002) can be observed. In isolates from poultrymeat the nalidixic acid resistance level is stable and high over the time period (29 % 2000, 23 % 2001, 25 % 2002). One of the main poultry serotypes with high prevalence to nalidixic acid resistance is *S*. Paratyphi B d-tartrate positive. Over 40 % of the 238 isolate from poultry and poultry meat in 2000/2001 had MIC values > 128 µg/ml. Comparable results were published by van Pelt et al. (Eurosurveillance 2003; 8:31-5) for the Netherlands. In this serotype a profound shift towards higher MIC's to ciprofloxacin could be observed. Thirteen percent of the isolates had MIC's >=2 and belonged to Salmonellae with reduced susceptibility, which can cause serious health problems in humans.

Short presentation on the situation in Germany: Animals (2)

Antimicrobial resistance in *Campylobacter* spp. in animals: situation in Germany

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Campylobacterioses are zoonotic diseases. Domestic animals such as poultry, pigs and cattle may act as reservoirs for *Campylobacter* (C.) spp. As these may be transferred from animals to humans via food, the emergence of antimicrobial resistance in enteric C.spp. due to the use of antimicrobial agents in husbandry is a matter of concern. The studies were conducted in order to compare the occurrence of antimicrobial resistance among C.spp. strains isolated from different food animals and from humans.

We analysed 143 *C.* spp. strains isolated at slaughterhouse level from broilers (n=58), pigs (n=51), beef cattle (n=34) and turkey (n=158) for their susceptibility to erythromycin, gentamicin, ampicillin and ampicillin+sulbactam, ciprofloxacin, nalidixic acid and tetracycline. Additionally, 37 isolates from cases of human campylobacteriosis were tested. In addition, the susceptibilities of 257 *C.* spp strains from retail market chicken and turkey products and from men isolated in the same regional and time frame were tested. Antimicrobial susceptibility was determined by broth microdilution (see Luber et al.(2003), J. Clin. Microbiol., 41, 1062-1068).

C. spp from slaughtered pigs, chicken broilers and cattle displayed origin specific resistance rates. Isolates from pigs were significantly ($p<0.001$) more often resistant to erythromycin (37.3%) and tetracycline (60.8%), than those from broilers or cattle. Broiler isolates were significantly more often resistant to ampicillin (37.9%), nalidixic acid and ciprofloxacin (each 55.2%). Turkey isolates revealed a high resistance to ampicillin (51.9%), ciprofloxacin (36.1%) and nalidixic acid (36.1%). 10.8% of C. spp. from human stool samples were resistant to erythromycin, 5.4% were resistant to the chinolones nalidixic acid and ciproflocaxin, 10.8% to ampicillin and 13.5% were resistant to tetracycline. Multiresistance was found in 5.9% of bovine, 15.7% of porcine and in 29.3% of avian isolates, but in none of the human strains.

The *C.* spp isolates recovered in 2001-2002 from retail market poultry and from men revealed no differences in the resistance rates to ciprofloxacin. Chicken products isolates displayed significant less resistance to tetracycline than those of turkey or human origin.

In conclusion, high resistance rates in *C*. spp. originating from pigs, chicken broilers, turkey and cattle demonstrate the importance of animal foods as sources for resistant strains. Moreover, origin specific resistance rates suggested the development of resistance in *C*. spp. during therapeutically antimicrobial treatment in food animals. The discrepancies in the antimicrobial resistance rates among isolates originating from poultry and humans in different time frames support the hypothesis that at least some of the resistant Campylobacter strains causing infections in humans come from sources other than poultry products.

Short presentation on the situation in Germany: Animals (3)

Endangering potential by antibiotic resistant commensals like enterococci

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Enterococci belong to the natural flora of the gastrointestinal tract in animal and in man. *Enterococcus (E.) faecalis* and *E. faecium* are at present the most important species and responsible for more than 80% (*E. faecalis*) and 10-20% (*E. faecium*) of enterococcal infections in humans. The quantity of infections caused by enterococci, in particular *E. faecalis* and *E. faecium*, has been increasing in the field of human medicine within the last years. Resistances to important antimicrobial agents have increased in this genus simultaneously. A link with the application of antimicrobial agents in livestock farming is supposed. Enterococci are usually considered as bacteria of low level pathogenity, which predominantly infect patients with prenounced predisposition. They are able to cause different infections, e.g. of the urinary tract and of the bile trays and are also responsible for severe lifethreatening diseases as bacteremia or endocarditis. Today, enterococci are accepted as important pathogens of nosocomial infections. Currently they are in second or third place of bacteria, that cause such infections and they are one of the most important of the Gram-positive bacteria (Klare and Witte, 1998).
The natural resistance to different antibiotic classes includes cephalosporines, aminoglycosides (low-level type), lincosamides, streptogramines (*E. faecalis*) and polymyxins. Enterococci are also frequently resistant against quinolones. Additionally, this bacterial genus can acquire antibiotic resistance to ampicillin (*E. faecium*), macrolides and tetracyclines. Furthermore enterococci can process genes that mediate resistance to chloramphenicol, glycopeptides, trimethoprim/sulphonamides and high-level resistance to aminoglycosides.
Cattle and pigs seem to be of little importance as a reservoir of enterococci with resistances to ampicillin, gentamicin and the glycopeptide antibiotics, which are the agents of choice for the treatment of enterococcal infections in human medicine. The risk for the consumer to acquire such resistant enterococci via the food chain seems to be small. In comparison to this the resistance rates against the recently approved antimicrobial agent quinupristin/dalfopristin are rather high in *E. faecium* isolated from cattle, pigs and food. This problem is probably caused by the former use of the antimicrobial growth promoter virginiamycin in conventional animal fattening. Virginiamycin causes cross-resistances to quinupristin/dalfopristin in enterococci and has been banned in the EU since 1999. This ban probably adds to a decrease of resistance against quinupristin/ dalfopristin.
Poultry seems to have a mayor impact on enterococcal resistance to penicillin. In contrast to the findings for cattle and pigs quinupristin/dalfopristin resistance in enterococci species remains below 10%.
Resistances to antimicrobial agents, which have importance for veterinary and human medicine but only a low significance in the treatment of enterococcal infections, e.g. tetracycline or erythromycin, were partly found quite frequently.
A transfer of resistance genes to other genera of bacteria cannot be excluded. On the one hand this may imply a risk for the consumers, but on the other hand the use of a certain quantity of antimicrobial active agents for the treatment of bacterial infections in farm animals seems to be indispensable.

In general the risk for the consumers to acquire enterococci, which are resistant to the agents of choice for the treatment of enterococcal infections, via the food chain seems to be very small.

Short presentations on the situation in Germany: Animals (4)

Antibiotic resistance monitoring in veterinary pathogens from sick food-producing animals: the German national program

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Objectives: Against the backdrop of a steady increase in the problem of antibiotic resistance development and spread, the Federal Office of Consumer Protection and Food Safety (BVL) has begun implementing a nationwide resistance monitoring program for bacteria from sick food-producing animals species with due consideration of the recommendations of national and international bodies. For the first time in Germany, representative monitoring was undertaken in 2001 in sick fattening pigs (respiratory diseases) and dairy cows (mastitis). Based on the data collected and evaluated from the pilot study 2001, in 2002 the BVL started the second national monitoring study on the resistance of bacterial pathogens from sick food-producing animals with an extended selection of clinical indications.
Methods: To guarantee representation of the bacterial strains to be examined for the defined scale of the study, the cooperating institutions involved in sample collection and bacterial isolation were given the selection of bacterial isolates in a random sampling plan. For each animal herd/flock only one corresponding bacterial strain was included in the study. It was ensured that bacteria were provided from many animal husbandry locations (regional distribution using the animal population figures in the adminstrative districts). The first sampling period was restricted to seven months and the second sampling period to one year. In the planning phase for the national resistance monitoring to determine the current level of antibiotic resistance, model calculations were performed which describe the influence of the random sample size on the reliability of test results. The model calculations were undertaken with a significance level of $\alpha = 0.05$ and a power of $1-\beta = 0.80$. Due to these calculations, at least 300 bacterial strains per bacterial species/genus per indication as well as per animal species and year should be included in the studies. The susceptibility of the bacteria was determined using the 2-fold microbroth dilution method in accordance to instructions M31 A2 of the National Committee for Clinical Laboratory Standards (NCCLS).
Results: 39 official laboratories from 13 German federal Länder took part in the nationwide monitoring study and 1,058 bacterial strains were included 2001 and 2,031 bacterial strains 2002/2003 in the susceptibility assessment. The quantitative susceptibility results (MIC) from the tested bacterial species from the defined clinical indications have clearly shown lower resistance values in comparison to data published from Germany so far.
Conclusions: Initial experience from a representative monitoring study conducted for the first time in Germany to determine the antimicrobial susceptibility of animal pathogenic bacteria in food-producing animals has shown that the necessary structures for a resistance monitoring system can be implemented in a federal system. Experience from this study reveals the urgent need to pursue an interdisciplinary approach when tackling the problem of resistance together with human medicine. This can be done by communicating the epidemiological data on resistance development and spread. The conclusions could then be used for further assessment of the need for action on a validated scientific basis in human and veterinary medicine. Altogether, our data provide valuable insights into the epidemiology of bacterial resistance in animal pathogens. Our future goal will be to investigate an extended selection of animal species and also bacterial specimens from private and university diagnostic laboratories.

Session IV: Risk Characterization - Food and Public Health Aspects
Chair: Henrik Wegener, Wolfgang Witte

What do we know: Reports on conclusions and activities of previous expert groups (1)

Microbial Threat – The Copenhagen Recommendations-Initiative of the EU

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The Conference was initiated by the EU Chief Medical Officers at their Luxembourg meeting Oct. 1997. the initial intiative was taken by the Danish CMO, Einar Krag, who later hosted the conference. The background for action was the increasing resistance to antibiotics, where inappropriate use was of major causal importance, and effective mechanisms to limit emerging problem of drug resistant microbes seemed not yet in place. This would have considerable implications for quality of health and health care.
Before the Conference, preparatory meetings with experts/CMO´s defined specific questions for debate. Two days prior to the conference, participants adjourned in 5 workshops, which provided basic material for the conference. At the Conference the Workshops presented papers for discussion and modification, whereafter the programme committee prepared recommendations. These were discussed and modified on thelfinal day of the Conference.
The five Workshops encompassed the following themes:
1.Human health implications of the increasing resistance,
2.Surveillance of data on microorganisms resistant to antimicrobial agents (a.a.)
3.Recording of a) clinical use of a.a. in human and veterinary medicine, and b) other use of a.a. including animal feeding practices in the EU
4.Elements of good practice in the use of a.a.
5.Framework for development of guidelines to prevent the emergence and spread of antimicrobial resistant microorganisms.

Participants included the following: Presidency: Ministers of Health and of Food, Ariculture and Fisheries. Vice-presidency: EU Commission for PHSW, E.Krag CMO, DK. General rapporteur: Richard Smith, BMJ, UK. Country delegations of experts and other authorities from all EU members and Czech Rep., Estonia, Hungary, Iceland, Latvia, Lithuania, Norway, Slovak Rep., Slovenia, Switzerland, USA. Oganizations: Pharmaceutical Industry, Fefasa, Fedesa, Pharmacy org., Veterinary org., Medical org. EU Commission, WHO and professional journals

The recommendations agreed upon for the EU were:

- -The EU must recognise that antimicrobial resistance is a major problem
- -review progress with these recommendations pharmaceutical companies encouraged to develop new drugs, but these will not solve the problem
- -EU should set up surveillance system of resistance
- -the EU need to collect data on consumption of antimicrobial agents
- -the EU should encourage prudent use of antimicrobial agents
- -the EU should make coordinated research on resistance high priority

What do we know: Reports on Conclusions and Activities of Previous Expert Groups (2)

EU Scientific Steering Committee

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In 1997, the European Commission set up several Scientific Committees in order to get scientific advice in the field of consumer health and food safety. In 1998, a mandate was given to the Scientific Steering Committee to evaluate the problem of antibiotic resistance and to make recommendations for controlling the spread of resistance. The working party consisted of 12 members. The report (Opinion) consisting of 119 pages was adopted by the Scientific Steering Committee on the 28th of May 1999.

In particular the mandate given by the commission reads as follows:

- Evaluate the current prevalence and development of resistance
- Examine its implication for human and animal health
- Evaluate factors contributing to the etiology of the present situation
- Examine means of influencing/controlling the development
- Make recommendations based on scientific evidence
- Advice on the monitoring of the outcome of measures which the working group might recommend.

The working group identified four areas of major concern:

- Treatment and prevention of disease in humans
- Treatment and prevention of disease in animals
- Improvement of animal production (feed additive use)
- Plant protection and the overall effects of antimicrobials in the environment.

The group focused to issues surrounding antibacterial therapy. Antimicrobials which are active against viruses, fungi or protozoa were not considered, also assessment of individual products was not done.

In general, the opinion in its structure reflects mainly this scope, which is as follows:

- The basis of resistance to antimicrobials,
- Prevalence of resistance in pathogens,
- Amounts of antimicrobials used
- Relationship of the use to resistance and its transfer between ecosystems
- Options for the control and containment of resistance
- Areas for further research
- Conclusions and recommendations.

Regarding *"control and containment"*, the improvement of prescription use, ways of reducing the need for antimicrobials, providing of new antimicrobials as well as educating of prescribers and users were identified as major issues.

In the field of *"further research"*, the gathering of valid data, the mechanism of selection pressure and transfer of resistance genes, ways of measuring the impact of resistance, prudent use, infection control and more rapid diagnosis for bacterial infections were stressed.

Finally four "areas of action" were proposed: Prudent use of antimicrobials, prevention of infection and containment of resistant organisms, new modalities of prevention and infection treatment, and the establishing of monitoring the effect of intervention. The SSC recommended also an EU-wide cooperation.

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What do we know: Reports on Conclusions and Activities of Previous Expert Groups (3)

Activities of the Codex Alimentarius Commission related to antibiotic resistance

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The question of antimicrobial resistance has been discussed from different point of views in the framework of Codex, directly as regards food hygiene and veterinary drugs or indirectly as regards pesticides. For the moment it is under discussion but there are still a number of questions to be solved in order to decide how to proceed and whether to undertake specific work in this area, as the Codex Alimentarius Commission is a standard setting organization that develops standards, codes of practice and related texts that provide guidance to member countries on food safety issues. Following initial discussions in specialized Committee, the Executive Committee of the Codex Alimentarius Commission recommended to use a multi-disciplinary approach to this complex issue.

Antibiotic resistance is related to some major areas of food safety activities in Codex, especially microbiological contamination. The Codex Committee on Food Hygiene therefore considered antibiotic resistance from the perspective of the food chain and developed a risk profile, including the factors that contribute to antibiotic resistance in the food chain, the implications for human health and the risk management options. The options put forward may be summarized in two main categories: prevention of contamination through the food chain, in order to reduce the presence of both resistant and non-resistant bacteria; and prudent use of antibiotics and antimicrobials in humans and in food producing animals. As regards the aspects related to microbiological contamination, more specific risk assessment concerning some specific food/pathogen/antimicrobial combinations may be required in the future, in the framework of current FAO/WHO activities on microbiological risk assessment. Following the establishment of the risk profile in 2001, the Committee on Food Hygiene did not take further action as it was recognized that scientific advice was necessary before any further work was initiated, and the results of the FAO/OIE,/WHO Expert Consultations will provide the necessary guidance for further action in the framework of Codex.

As regards the aspects related to the administration of veterinary drugs, the Codex Committee on Residues of Veterinary Drugs is currently developing a Code of Practice to Minimize and Contain Antimicrobial Resistance that will supplement the current Recommended International Code of Practice for Control of the Use of Veterinary Drugs (CAC/RCP 38-1993).

As to the issue of antibiotics in plant protection, there is no consensus in the Codex Committee on Pesticide Residues on the need to address antibiotics used in agriculture and consideration of this question was deferred until scientific advice became available on antibiotic resistance as a whole. It is therefore expected that the results of the FAO/OIE/WHO Expert consultation will provide guidance to determine the need for specific work in the framework of Codex.

What do we know: Reports on conclusions and activities of previous expert groups(4)

World Organization for Animal Health (OIE)
Patrick Dehaumont
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Introduction :

Huge concerns are developing regarding antimicrobial resistance and its potential consequence for human health and animal health as well.
Any use of antimicrobial agents should be done very carefully whatever use it is (human, animal, plants, food processing)
Even though the respective responsibilities are not perfectly identified to explain the phenomenon, OIE initiated international scientific activities in this field in order to better protect public health and animal health and welfare.
Basically, OIE aims at strengthening the safety of international trade of animals and animal products through sanitary rules, recommendations and information that may be implemented by the governments of countries belonging to OIE. Consistently with the above mentioned objectives, OIE developed international standards on antimicrobial resistance : "Resistance surveillance programs", "Surveillance of antimicrobial consumption in animal husbandry", "Prudent use and contaminant of antimicrobial resistance", "Laboratories methodologies for bacterial antimicrobial susceptibility testing", "Risk analysis and antimicrobial resistance". This communication summarizes the process that led to the elaboration of these guidelines, their state of play and the perspectives for the future.

1. What has been done so far

In 1997, considering the growing importance of antimicrobial resistance at a world wide level, the Regional Commission for Europe of OIE requested a specific report to the OIE collaborating centre with the view to decide whether an action plan should be implemented. The report was delivered during the 1998 international session of OIE. On that basis, and after a wide exchange of view and assessment of the challenges, the international committee of OIE decide to :

- create an ad hoc expert group
- define the mandate and terms of reference to be followed by the group.

This international experts committee proposed a work plan to elaborate 5 guidelines

Resistance surveillance programs,
Surveillance of antimicrobial consumption in animal husbandry,
Prudent use and contaminant of antimicrobial resistance,
Laboratories methodologies for bacterial antimicrobial susceptibility testing
Risk analysis and antimicrobial resistance,

After preparation of the 5 scientific documents, an international consultation was set up from 15 June to 15 September 2000 that enabled the final adoption by the group in November 2000 of the scientific documents and recommendations.

The next milestone was the 2nd OIE international conference on antimicrobial resistance organised from 2 to 4 October 2001 aiming at :

- diffusing and promoting recommendations of the OIE expert group
- developing international cooperation in the considered field
- proposing new goals and meeting new challenges

As a result of all that efforts from the experts and all OIE members, 4 out of 5 guidelines were finally adopted during the last annual session of OIE in May 2003.

2. The guidelines – Scope and objectives

2.1. GL for the harmonization of antimicrobial resistance surveillance and monitoring programs.

Purpose :

- follow trends in antimicrobial resistance in bacteria
- detect the emergence of new antimicrobial resistance mechanisms
- provide the data necessary for conducting risk analysis with relevance for human and animal health
- provide a basis for policy recommendations for animal and public health
- provide information for prescribing practices and prudent use recommendations

Recommendation and strategy :

- Necessity of a survey and monitoring at regular intervals of prevalence changes of bacteria of animal, food, environmental and human origin.
- Necessity of a consistent, representative and robust sampling strategy
- Necessity of a consistent strategy for strains to be considering and antimicrobial in susceptibility testing to be used
- Necessity of high quality reporting methodology

2.2. Guidelines for the monitoring of the quantities of antimicrobials used in animal husbandry

Purpose :

- to describe an approach for the monitoring of quantities of antimicrobial used in animal husbandry based on an objective and quantitative methodology

Recommendation and strategy :

- It is mainly proposed to develop standardized monitoring system based on the quality and reliability of sources of information, of datas collected on antimicrobial use, of classes of antimicrobials monitored. Moreover the issue of sustainable systems for the follow up of the conditions of use of antimicrobials is considered.

2.3. Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine

Purpose :

- these guidelines provide a guidance for the responsible and prudent use of antimicrobial agents in veterinary medicine with specific attention to public health and animal health as well.
- responsibilities of all stakeholders are taken into consideration.
- the main objectives of the guidelines are to maintain the efficacy of antimicrobials and limit or reduce the resistance phenomenon.

Even though public health is of huge concern, it must be kept in mind that ethical and economic needs lead to keep animals in good health and welfare. Consequently the use of antimicrobial agents in veterinary medicine and rearing is essential.

Recommendations and strategy :

The main strategy is to share the responsibilities between the different stakeholders, and to encourage each of them to consider, as far as they are concerned, what they should do at each step of research, development, use and monitoring of veterinary medicines.

As a consequence, the following responsibilities are considered :
- Public authorities, at both pre marketing and post marketing level
- Responsabilities of pharmaceutical industry, at research, development, and marketing level
- Responsabilities of Pharmacists
- Responsabilities of Veterinarians
- Responsabilities of Livestock producers

2.4. Laboratories methodologies for bacterial antimicrobial susceptibility testing

Purpose :

- the purpose of this guideline is to propose robust and reproductible criteria for antimicrobial susceptibility testing (AST)

Recommandation and strategy :

In order to achieve standardization of AST, requirements are proposed for :
- The conditions in which the tests should be conducted
- AST methodologies
- Criteria for selection of AST

Moreover three test methods are proposed : disk diffusion, broth dilution and Agar dilution. For each of them a cost/benefit analysis is proposed to help choose the relevant one.
Rules for interpretation and guarantee of the reliability of results are then detailed.
In this field the importance of quality control, quality assurance and external proficiency testing is emphasized.

2.5. Guideline on development of an appropriate risk analysis methodology for the potential impact on public health of antimicribial resistant bacteria of animal origin.

This guideline has not been completed so far and is still in process.

The purpose and objectives are mainly to conduct transparent consistent risk analysis and to identify the factors to be used in each following steps :

- ♦ of the risk assessment
- Hazard identification
- Hazard characterization
- Exposure assessment
- Risk characterization
  - ♦ of the risk management
- Risk management policy
- Risk evaluation
- Risk reduction strategy
- Monitoring and review
  - ♦ of the risk communication, essential between all stakeholders and decisions markers

3. Guidelines status

During the last international OIE session 4 out of 5 guidelines were adopted.
Guideline 1, 2 and 3 were incorporated in the terrestrial Animal health code.
Guideline 4 was incorporated in the manual of diagnostic tests and vaccines for terrestrial animals.
The 5th one is still under discussion and should be presented hopefully to the next international session in 2004.

4. Perspectives and new goals

Antimicrobial resistance is a multidisciplinary issue and a worldwide issue.
Consistent to its habits, OIE develops close contact with all organizations concerned such as WHO and FAO, and governments of numerous countries (164 countries are currently members of OIE).

Having written that it's obvious that the OIE's goals can only be achieved with the WHO and FAO organisations which are currently also working on the issue of antimicrobial resistance.
This close cooperation is actively developed to get benefits of synergies, to avoid contradictory standards and to address gaps which may exist among current standards.

Two concrete experiences may be reminded as encouraging examples :

- The close cooperation above mentioned enabled the Codex Alimentarius committee for residues of veterinary drugs in food to develop a Codex Alimentarius guideline for the prudent use of antimicrobial agents fundamentally based on the OIE guideline
- A world wide consultation of experts has been recently launched by WHO, FAO and OIE with the view to gather all available scientific datas and to prepare a common action plan for the future

What do we know: Reports on conclusions and activities of previous expert groups (5)

Antimicrobial resistance due to non-human antimicrobial usage

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The continuing emergence of pathogenic organisms that are resistant to antimicrobials is a cause of increasing concern. Although mechanisms by which organisms acquire resistance are well understood, the precise impact of drug usage in selection of drug resistance has not yet been fully elucidated. Nonetheless there is evidence that prudent use of antibiotics in human, veterinary practice, animal husbandry and agriculture could make a significant impact on the emergence of resistant microorganisms pathogenic to man. Antimicrobial use in animals select for resistance in zoonotic pathogens and commensal flora, and these resistant bacteria can be transmitted to humans through contact with animals or food (and a multitude of other avenues), and they can infect humans and cause diseases which can be more severe and/or longer lasting than non resistant infections.

In countries where data are available, as much as 50% or greater of the total volume of antimicrobials produced in these counties is administered to animals. Of this volume, a significant proportion is used in food animals to increase growth rate or weight gain (growth promoter) or to prevent diseases (disease prophylactic). It is clear that antimicrobial resistance is an international problem: resistant bacteria can easily be carried between countries by travellers, animals, food and other carriers. However most potential solutions of the problem are national or local in scope because they involve government regulation or changes in prevailing farming practices.

The consequences of selective pressure include i) the increased risk for resistant pathogens to be transferred to humans by direct contact with animals or through the consumption of contaminated food and water and ii) the transfer of resistance genes from animal to human bacterial flora. Increasingly, data suggest that inappropriate use of antimicrobials, especially of first-line drugs, for treatment, prophylaxis and growth promotion, poses a real public health risk.
It is well recognized that the issues of antimicrobial use and misuse in the food chain are of global concern. International interdisciplinary cooperation is essential. WHO has organized a number of consultations to address the issues related to the complex antimicrobial use at the different steps of the food chain, the emergence of resistant pathogens and the associated human public health problem.

Documents:

WHO Consultation on The Medical impact of the Use of Antimicrobials in Food Animals (Berlin, Germany, 13-17 October 1997) - WHO/EMC/ZOO/97.4

WHO Consultation on Use of Quinolones in Food Animals and Potential Impact on Human Health (Geneva, Switzerland, 2-5 June 1998) - WHO/EMC/ZDI/98.10

WHO Global Principles for the Containment of antimicrobial Resistance in Animals intended for Food (Geneva, Switzerland, June 2000) - WHO/CDS/CSR/APH/2000/4

Website:
http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm

WHO Global strategy for Containment of Antimicrobial Resistance - WHO/CDS/CSR/DRS/2001/2

WHO Consultation on Monitoring antimicrobial usage in food animals for the protection of human health (Oslo, Norway, 10-13 September 2001) - WHO/CDS/CSR/EPH/2002.11

Antimicrobial resistance : http://www.who.int/emc/diseases/zoo/vphpublications/antimicrobial_resistance.html

WHO Global Salm-Surv: Network on foodborne disease surveillance including antimicrobial resistance:
Link to : http://www.who.int/salmsurv/en/

Planned: A Joint FAO/WHO/OIE Expert Consultation on Non-human Antimicrobial Usage and Antimicrobial Resistance (Geneva, 1-5 December 2003)

Session V: Management options and measures - What can be done?
Chair: Christian Grugel, Andreas Hensel

Management Options to Minimize and Control Antimicrobial Resistance The U.S. Food and Drug Administration Position

Linda Tollefson
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On October 23, the United States Food and Drug Administration published the final version of a document titled “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern.” This document outlines a pathway drug sponsors can use to address concerns about antimicrobial resistance. The guidance balances the need for antimicrobials to treat livestock and poultry with the need to protect human health by considering the importance of drugs in human medicine. It includes a ranking of antimicrobial drugs in regard to their importance in human medicine.

The document applies to therapeutic and non-therapeutic antimicrobial drugs intended for use in food-producing animals. It will also lead to a review of all existing approvals. The process uses a qualitative risk assessment approach to assess the potential of the intended use of a product to develop resistance in bacteria that may harm humans. The risk assessment has three components: the Release Assessment, which is the probability that bacteria that are resistant to an antimicrobial would be present in an animal treated with the antimicrobial; the Exposure Estimate, which estimates the probability that humans would ingest the resistant bacteria; and the Consequence Assessment, which assesses the likelihood that human exposure to the resistant bacteria would result in a human health consequence. A human health consequence is defined as a situation in which a physician would have difficulty treating a person with an antimicrobial drug because the bacteria infecting the human had acquired resistance to the drug and that resistance came from use of the drug in animals.

The level of risk determines the level of risk management that is required for the drug to be used. FDA has the option of not approving a drug if the risk of a public health consequence were too high.

Working Groups on Session I to IV under Chairmen leaderships

Room D 145	Lecture Hall left	Lecture Hall right	Room D 146
WG I: Hazard Identification	**WG II: Hazard Characterization**	**WG III: Exposure Assessment**	**WG IV: Risk Characterization**
Schwarz	***Tollefson***	***Angulo***	***Wegener***
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			Wise
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International Symposium

Towards a Risk Analysis of Antibiotic Resistance

Berlin 9 - 11 November 2003

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