Tackling Foodborne Antimicrobial Resistance Globally Through Integrated Surveillance

Report of the 3rd Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance

14 - 17 June 2011

Oslo, Norway

AGISAR 3

World Health Organization

Tackling Foodborne Antimicrobial Resistance Globally Through Integrated Surveillance

Report of the 3rd Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance

14 - 17 June 2011

Oslo, Norway

AGISAR 3

World Health Organization

WHO Library Cataloguing-in-Publication Data

Report of the 3rd meeting of the WHO advisory group on integrated surveillance of antimicrobial resistance, 14-17 June 2011, Oslo, Norway

1.Anti-infective agents - classification. 2.Anti-infective agents - adverse effects. 3.Drug resistance, microbial - drug effects. 4.Risk management. 5.Humans. I.World Health Organization. II.Title: AGISAR 3.

ISBN 978 92 4 150401 0 (NLM classification: QV 250)

Contents

List of Tables

List of Figures

List of Abbreviations

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial resistance
CCRVDF	*Codex* Committee on Residues of Veterinary Drugs in Foods (Codex – FAO)
CCFFP	*Codex* Committee on Fish and Fishery Products (Codex – FAO)
CCFH	*Codex* Committee on Food Hygiene (Codex – FAO)
CCPR	*Codex* Committee on Pesticide Residues (Codex – FAO)
CDC	Centers for Disease Control and Prevention (United States of America)
CIA	Critically important antimicrobials
Codex	*Codex Alimentarius* (FAO)
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DG	Director General (WHO)
ECDC	European Centres for Disease Control and Prevention (Europe)
ESAC	European Surveillance of Antimicrobial Consumption project
ESBL	Extended spectrum beta-lactamase
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (United States of America)
FSIS	Food Safety and Inspection Service (USDA)
GAP	Good aquaculture practices
GFN	Global Food Network
JECFA	Joint Expert Committee on Food Additives (FAO, WHO)
MDR	Multidrug-resistant bacteria defined as: “acquired non-susceptibility to at least one agent in three or more antimicrobial categories” (from ECDC)
NARMS	National Antimicrobial Resistance Monitoring System (CDC, FDA, USDA)
NDM-1	New Delhi metallo-beta-lactamase 1 (also suggested by some to be renamed PCM: plasmid encoding carbapenem-resistant metallo-beta-lactamase 1)
OIE	World Organisation for Animal Health

PDR	Pandrug resistant bacteria defined as: “non-susceptibility to all agents in all antimicrobial categories.” (from ECDC)
TFAF	Intergovernmental Task Force on Animal Feeding (Codex – FAO)
TFAMR	Intergovernmental Task Force on Antimicrobial Resistance (Codex – FAO)
USDA	United States Department of Agriculture
USDA-ARS	USDA - Agricultural Research Service
WHA	World Health Assembly
WHD	World Health Day
WHO	World Health Organization
WHONET	Database and analytical software package
XDR	Extensively drug-resistant bacteria defined as: “as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories)” (from ECDC)

1 Acknowledgements

The Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland, wishes to express its sincere thanks to all those who contributed to the success of the meeting. We would like to thank the AGISAR members as well as the resource advisers and other FAO, OIE and WHO representatives for their valuable technical input; we are particularly grateful to Kari Grave and Peter Collignon for chairing Parts I and II, respectively, and to H. Morgan Scott for rapporteuring during the meetings. Finally we wish to express our sincere gratitude to the WHO Collaborating Centre for Drug Statistics Methodology at the Norwegian Institute of Public Health for hosting our meeting.

2 Executive Summary and Recommendations

The rates of antimicrobial resistant in bacteria causing serious and life-threatening infections are rapidly rising. Antimicrobials were the miracle drugs of the 20th century. Unfortunately because of this rapidly rising resistance many people around the world are now back in the "pre-antibiotic" era if they develop serious bacterial infections. This results not only in increasing deaths but also more complications from infections and morbidity, including prolonged hospital stays. This is particularly a problem in developing countries, where rates of resistance are now very high in many common bacteria. Many infections are now effectively untreatable because these bacteria are resistant to all affordable and/or accessible antimicrobials available for large proportions of the population.

With time, antimicrobial resistance develops whenever antimicrobial are used. The more antimicrobials are used, the more resistance eventually develops and spreads. Spread of these resistant bacteria to people can occur by many routes but the more important ways are via water, foods and by person to person contact.

Antimicrobials are used widely in agriculture. This includes non-therapeutic use such as for growth promotion. It also includes use as prophylaxis to try to prevent infections developing in food animals and therapeutic use to treat sick animals. However, this use also includes using agents defined by WHO as "critically important" for human medicine.

Antimicrobial agents are "critically important" when they are the sole, or one of limited available therapy, to treat serious human disease. It is of prime importance that the utility of such antibacterial agents should be preserved, as loss of efficacy in these drugs due to emergence of resistance would have an important impact on human health, especially for those with life threatening infections.

Bacteria (including those resistant to antimicrobials) that commonly transfer to people from food animals are *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp. More recently, emerging evidence has shown that *Staphylococcus aureus* (including MRSA) and *Clostridium difficile* also occur in food animals and can later be found in food products and environments shared with humans.

Resistant Gram negative bacteria (e.g., *E. coli*) have become a major and rapidly increasing problem. There are no new classes of antimicrobials in the pipeline and so it is unlikely that any new classes of effective antimicrobials will be available for 10 years or more to treat infections caused by resistant Gram negative bacteria.

Recently, we have seen the development and spread of bacteria carrying metallo-betalactamase genes that are resistant to carbapenems (and all beta-lactams). One of the most concerning aspects is the recent intercontinental spread of a multi-resistant strain of *E.coli* (New Delhi metallo-betalactamase, or NDM strain) which is resistant to carbapenems and nearly all other antimicrobials (including non-betalactam classes). These types of multi-resistant bacteria have caused infections not only in hospitals, but also in the community. They have now also been found in Canada, Britain, the U.S., Australia, and elsewhere. The

genes encoding for the metallo-betalactamases have been transferred to many other genera of bacteria (e.g., *Klebsiella*, *Vibrio* and *Providentia*). These increasingly commonly isolated bacterial isolates have necessitated using therapy with intravenous polymyxin; which, as an "old" antimicrobial had previously been discarded from systemic clinical use because of toxicity and other problems. In many cases it is now the only agent with proven activity against many of these multi-resistant isolates. Notwithstanding this, some bacterial strains carrying the NDM gene are resistant to all antimicrobials, including the polymyxins. The end of the age of the miracle drug may indeed be upon us.

In The Netherlands the same genes encoding for ESBL (extended spectrum beta-lactamases) in *E. coli* isolates are found in both food animal isolates (especially poultry) and in those causing serious infections in people. On a global scale, *E. coli* is the most important human pathogen and causes substantially many more infections than *Salmonella* and *Campylobacter* combined. Thus, the importance of resistance in *E. coli*, typically considered a benign commensal, should not be underestimated.

In this 3rd revision of the WHO "critically important" antimicrobial list, the following drugs and classes were shifted for the following reasons:

- Over the last few years there have been dramatic increases in multi-resistant Gram negative infections both in the community and in hospitals. Therapy of many of these Gram negative infections (e.g. with multi-resistant *E. coli*) have become much more limited and agents such as colistin (a polymyxin) are now being used as often are no other alternatives. Thus classes of drugs active against Gram negatives such as phosphonic acid derivatives (e.g., fosfomycin), polymyxins (e.g., colistin) and monobactams (e.g., aztreonam) have been reclassified as "Critically Important".
- In contrast, for Gram positive infections more antimicrobials have become available (e.g., lipopeptides, oxazolidinones and additional glycopeptides). Thus, streptogramins that were previously classified as Critically Important are now classified as "Highly Important" as there are more effective agents that cause less side effects now available to treat these infections.
- Tetracyclines are re-categorised now as "Highly Important". In the previous edition they were reclassified as "critically important" because tetracyclines are the main therapy for *Brucella* infections which are most often acquired by people from animals. However, there are many countries where *Brucella* infections have been eradicated from food animals. However, in areas of the world where *Brucella* species are still likely to be transmitted from food production animals, tetracyclines should continue to be classified as "critically important."

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that critically important antimicrobials are used prudently both in human and veterinary medicine.

Of special importance, risk managers should carefully consider that fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been categorized as being of highest priority for risk management among those antimicrobials.

Carbapenems, lipopeptides and oxazolidinones currently have no veterinary equivalent. This WHO advisory group (AGISAR) recommends that these classes as well as any new class of antimicrobial developed for human therapy should not be used in animals, plants, or in aquaculture recommendations from AGISAR

Recommendations from AGISAR

- When a new class of antimicrobials comes on the market, it should be considered "critically important" from the outset unless strong evidence suggests otherwise
- Existing drugs that are already classified as "critically important" antimicrobials but which are not currently used in food production such as carbapenems, oxazolidinones (linezolid), and lipopeptides (daptomycin), should not be used in the future in food animal production
- In regions of the world where at least one criterion for critically important status is met, and limited alternative therapies are available for a given condition, then the class should by default be considered critically important
- Within two years, each country establishes Antimicrobial Resistance (AMR) testing of foods in the domestic market, as well as those being introduced into international trade.
- Monitoring of country progress in achieving program elements, and recognition of successes (e.g., via certification or membership in an advisory capacity to others). Provide incentives to laboratories for participating in AMR activities.
- In a guidance document, develop more complete definitions of integrated surveillance/monitoring of usage and resistance, potentially allowing for integrated analysis. Include in the guidance document a list of what is needed to accomplish adequate testing in all three sectors (human, animal, meat products).
- Competent authorities in member countries make provisions for the collection and reporting of national level antimicrobial sales and usage data in humans and animals; including, if necessary, development of appropriate enabling legislation. In the case of data from animals, ensure that this is consistent with the World Organisation for Animal Health (OIE) Terrestrial Code.
- Applicants for pilot projects should consider incorporation of some or all of the antimicrobial use protocols into new project proposals in order to facilitate capacity building and provide information for refinement of protocols.
- Future pilot projects should be further developed, implemented and expanded in their scope through the inclusion of antimicrobial use data in veterinary and human medicine and pilot projects should include in their proposals and protocols a well-defined dissemination strategy for the project results to be shared with relevant stakeholders

- WHO should encourage countries and their laboratories to adopt the WHONET software. Global Food Network (GFN) should incorporate software training into educational workshops. WHO should facilitate training in developing countries and WHONET should be integrated into country pilot sites/studies. Participating countries and their laboratories should include denominator data (e.g., sample numbers and not just isolates) along with antimicrobial resistance and use data. Tutorials/self-teaching/technical support should be provided as a necessary adjunct to software training sessions.

3 Preamble

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was established in December 2008 to support WHO efforts to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals. In particular, the Advisory Group mandate is to assist WHO on matters related to the integrated surveillance of antimicrobial resistance and the containment of food-related antimicrobial resistance. Annual meetings have previously been held in Copenhagen, Denmark (AGISAR I – June, 2009) and Guelph, Canada (AGISAR II – June 2010). The Terms of Reference of WHO-AGISAR as outlined in the AGISAR I report are as follows:

- Develop harmonized schemes for monitoring antimicrobial resistance in zoonotic and enteric bacteria. This should include appropriate sampling.
- Support WHO capacity-building activities in Member countries for antimicrobial resistance monitoring by developing Antimicrobial Resistance (AMR) training modules for Global Foodborne Infections Network (GFN) training courses.
- Promote information sharing on AMR.
- Provide expert advice to the WHO on containment of antimicrobial resistance, with a particular focus on Critically Important Antimicrobials (CIA) for human medicine.
- Support and advise the WHO on the selection of sentinel sites and the design of pilot projects for conducting integrated surveillance of antimicrobial resistance.
- Support WHO capacity-building activities in Member countries for antimicrobial usage monitoring.

WHO-AGISAR comprises over 20 internationally-recognized experts in a broad range of disciplines relevant to antimicrobial resistance, appointed following a web-published call for advisers, and following a transparent selection process. The membership has remained relatively constant over the past three meetings, with some substitutions, particularly among the resource advisors. WHO-AGISAR holds quarterly telephone conferences and annual face-to-face meetings, with subcommittees often meeting more regularly.

WHO convened the third meeting of AGISAR in Oslo, Norway, from 14 to 17 June 2011. Welcoming and opening remarks were delivered by Hanne Strøm of the WHO Collaborating

Centre for Drug Statistic Methodology (Norway) and Camilla Stoltenberg of the Norwegian Institute of Public Health. Awa Aidara-Kane of the World Health Organization opened the meeting with welcoming remarks, followed by a list of objectives and proposed outputs from the meeting. Among the latter, an AGISAR 3 report, updated WHO List of Critically Important Antimicrobials – 3rd Revision, and a series of guidance documents from the four AGISAR subcommittees were expected.

Following this, Kari Grave of the Norwegian School of Veterinary Science was elected chair for Part I of the meeting, while Peter Collignon of the Australian National University was elected chair for Parts II and III of the meeting. Additionally, H. Morgan Scott of Kansas State University (United States) was elected as rapporteur.

The first part of the meeting was organized to take stock of relevant international, regional, and national initiatives concerning antimicrobial usage and resistance, with special emphasis on the 2011 World Health Day focus on antimicrobial resistance and resolutions from the WHO, Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE). The four subcommittees that were first commissioned at AGISAR II then broke out to finalize their draft reports from the 2010 meeting, and to discuss ongoing and future activities, data integration across consumption and resistance surveillance, and communication tools and strategies. Plenary sessions were devoted largely to whole group discussions concerning the integration of consumption and resistance data, data management, capacity building, and communications and risk management strategies.

The second part of the meeting was devoted to considering worldwide updates on issues concerning critically important antimicrobials (CIA), and to revising the CIA list for the third time, with special emphasis on how the list should be used for risk management and communication, and in consideration of recent developments.

The third part of the meeting (not formally included as part of this report) concerned input from AGISAR members on two WHO initiatives: 1) the Joint FAO/WHO Expert Committee on Food Additives (JECFA) request for data concerning the evaluation or re-evaluation of substances considered as veterinary residues in food, and 2) a focus group discussion on exploring better ways to share food safety data and information.

The meeting agenda and list of participants and their affiliations may be found in Annex 1 and 2, respectively.

4 Meeting Objectives

The AGISAR III meeting objectives were as follows:

1) Discuss ongoing international/ regional/national initiatives on antimicrobial usage monitoring and integrated surveillance of antimicrobial resistance,
2) Discuss current and future activities of the four WHO-AGISAR subcommittees (Usage monitoring; AMR surveillance; Capacity building, country pilot study and focused projects; Software development and data management), and
3) Review and update the WHO list of Critically Important Antimicrobials for Human Medicine.

The expected outputs for the meeting were as follows:

1) AGISAR III meeting report, including short summaries of presentations from the plenary sessions,
2) WHO List of Critically Important Antimicrobials – 3rd Revision, and
3) Guidance documents from the four AGISAR subcommittees.

5 Part 1. Taking Stock and Subcommittee Report Deliberations

5.1 Taking Stock: International Initiatives

The World Health Organization (WHO):

Antimicrobial resistance was the sole focus of this year's World Health Day (April 7, 2011). On that day, the WHO Director General (DG) (Dr. Margaret Chan) launched a six policy package asking WHO member states to:

1) Commit to a comprehensive, financed national plan with accountability and civil society engagement,
2) Strengthen surveillance and laboratory capacity,
3) Ensure uninterrupted access to quality essential medicines,
4) Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care,
5) Enhance infection prevention and control, and
6) Foster innovations, research and development of new tools to combat infections.

In addition, on World Health Day the WHO-DG led a high-level panel at WHO headquarters in Geneva, on which both the OIE and FAO participated. Following WHD 2011, the WHO began the establishment of an AMR coordinating unit whose objective is to reduce the emergence and spread of resistance through elimination of inappropriate use in all sectors and implementation of effective surveillance and containment strategies.

The Food and Agriculture Organization of the United Nations (FAO):

FAO's activities on AMR are undertaken by the Veterinary Public Health (VPH) team that involves the Animal Health and Production Division, the Food Safety and Nutrition Division, and the Fisheries and Aquaculture Division and all contribute to the work of the Codex Alimentarius Commission. These activities are undertaken within the context of the FAO mission and mandate: to lead international efforts to reduce world hunger.

FAO's work on AMR is mostly focused on combating resistance in developing countries, where national policies and the necessary systems for regulation, surveillance and monitoring of antimicrobial usage, resistance and residues in food are either weak or do not exist. The aim is to strengthen national/regional policies, systems and capacities in these areas and to promote the prudent and responsible use of antimicrobial drugs. This will help to ensure that veterinary antimicrobial drugs remain valuable tools for treatment of animal diseases and thereby continue to support the livelihoods of livestock owners and the economies of countries, all the while ensuring that associated risks to human health are minimized.

Collaboration with international partners such as WHO and OIE is important for a holistic approach to addressing AMR. FAO therefore welcomes the WHO-AGISAR initiative. In the last year FAO has established collaborations with WHO on a pilot project in Kenya, which it is hoped will be the first of many similar joint activities, and will be a template to be

disseminated to other countries. A brief listing of some of FAO's ongoing AMR activities follows:

1. FAO contribution to the Kenya pilot project:

The Kenya pilot project includes microbiological analysis and antimicrobial susceptibility testing of *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus* spp. in all stages of the production to consumption continuum of the poultry, beef animal and pig value chains, and monitoring of antimicrobial used in these species. It also involves assessment of national policies and legislative framework and gender analysis.

The expected outputs from the Kenya project include policy guidance and enforcement guidance and guidance on prudent use of antimicrobials.

2. Aquaculture and AMR:

FAO activities in this arena are largely focused on the promotion of good aquaculture practices (GAP) that emphasize the need to minimize the use of antimicrobials in aquaculture. This is achieved by raising awareness on the public health impacts of antimicrobials use in aquaculture, developing site-specific GAPs, and development of technical guidelines for aquaculture certification. These emphasize minimal and responsible use of antimicrobials. Finally, FAO is undertaking international surveys on the use of veterinary medicines in aquaculture to better understand the scope and scale of the situation.

3. FAO contribution to the work of Codex Alimentarius Commission:

FAO provides support to the Committee on Residues of Veterinary Drugs in Foods (CCRVDF), the *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance (TFAMR), the *ad hoc* Codex Intergovernmental Task Force on Animal Feeding (TFAF), and the Codex Committees on Food Hygiene (CCFH), Pesticide Residues (CCPR) and Fish and Fishery Products (CCFFP).

The Codex Task Force on Antimicrobial Resistance (TFAMR):

FAO/OIE/WHO expert consultations on non-human antimicrobial usage and antimicrobial resistance (AMR) recommended the establishment of a Codex Alimentarius Task Force on Antimicrobial Resistance (TFAMR). This task force was established in 2006 to draft guidelines on assessing and managing risks associated with antimicrobial resistance (AMR) in the food chain arising from the use of antimicrobials in animals and plants. At the last meeting, October 2010, these guidelines were finalized and were to be submitted to the Codex Commission for adoption as a Codex standard during the summer of 2011 (http://www.codexalimentarius.net/download/report/746/REP11_AMe.pdf).

These guidelines provide a structured format (Figure 1) for risk analysis of AMR arising from the food chain and have the following main components: 1) general principles for foodborne AMR risk analysis, 2) a framework for foodborne AMR risk analysis, 3) preliminary foodborne AMR risk management activities, 4) foodborne AMR risk assessment, 5)

foodborne AMR risk management, 6) surveillance of use of antimicrobial agents and AMR microorganisms and determinants, and 7) foodborne AMR risk communication.

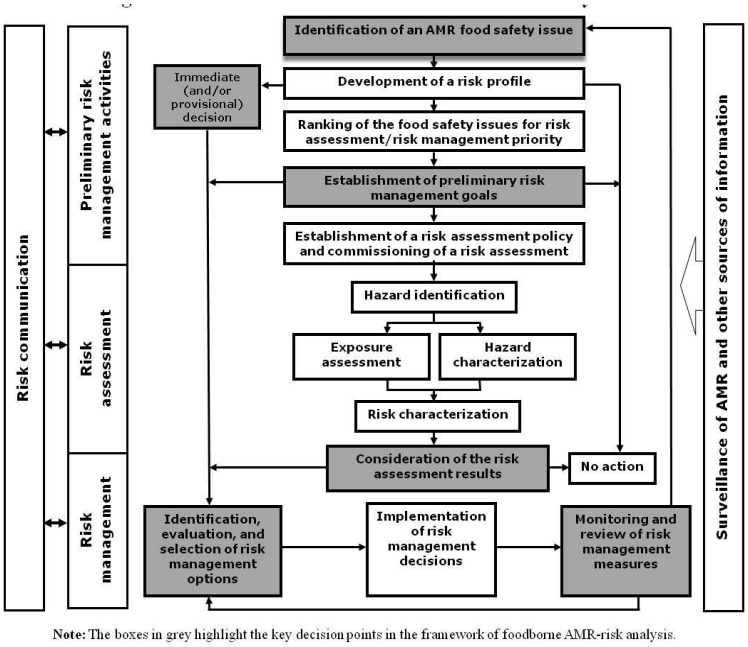


Figure 1. Framework for Foodborne AMR Risk Analysis

One novel aspect of this risk analysis framework is the emphasis on surveillance of antimicrobial use and resistance throughout, highlighting the necessity for good quality surveillance data. The appendices provide detachable working 'tools' for the collection of suggested information for risk profiling and risk assessment and examples of methods for deriving qualitative risk estimates. Also, there is a table which identifies risk management options that are specifically related to AMR.

<u>The World Organisation for Animal Health (OIE):</u>

The OIE has developed a coherent strategy for its activities in the area of veterinary drugs that pays specific attention not only to the responsible and prudent use of antimicrobials, but also to improvements in governance related to veterinary medicinal products. These latter improvements cover all the steps from production, distribution and on to use, each adapted to the needs of its 178 Member States.

OIE activities are based on several complementary approaches:

1) The development and regular updating of international standards and guidelines within the mandate of the OIE as the standard-setting body for animal health and zoonotic diseases, as recognized by the World Trade Organization (WTO).

The OIE is currently (July, 2011) working on the elaboration of guidelines on antimicrobial resistance related to aquaculture. A first standard for the responsible and prudent use of antimicrobial agents in aquatic animals was adopted at the 79 General Session in May 2011 for inclusion in the Aquatic Animal Health Code as Chapter 6.3.

The existing chapters in the OIE Terrestrial Animal Health Code and Manual of Diagnostic Tests and Vaccines in Terrestrial Animals, related to antimicrobial resistance, are also in the process of being updated with the participation of WHO and FAO experts. This includes chapters 6.7: Harmonization of national antimicrobial resistance surveillance and monitoring programs, 6.8: Monitoring of the quantities of antimicrobials used in animal husbandry, 6.9: Responsible and prudent use of antimicrobial agents in veterinary medicine, and 6.1: Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals. The latter will take into account the outcome of the Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance, to which the OIE has actively contributed.

OIE has also established a list of veterinary critical important antimicrobials that has been published on the OIE Website; plans are underway to update the list in 2012.

2) The provision of permanent support to Veterinary Services and laboratories to enable OIE Members to implement the published standards.

The evaluation of the performance of Veterinary Services is supported by the OIE PVS tool, which is based on a qualitative assessment of the performance and the compliance of Veterinary Services with the OIE international standards.

The OIE Laboratory Twinning Program, launched in 2006, creates opportunities for developing and in-transition countries to develop laboratory diagnostic methods and scientific knowledge based on the OIE Standards. Three OIE Collaborating Centers related to Veterinary Medicinal Products (France, Japan and US-FDA on Veterinary Drug Registration programs) and a Reference Laboratory on antimicrobial resistance, support OIE's activities in the area.

3) The modernization or updating of national legislation, including marketing approval and control of veterinary products.

As an associated Member of the VICH (International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products), OIE is actively promoting the need for harmonization in the approval and registration process for veterinary medicinal products.

4) Capacity building

OIE has undertaken a number of initiatives specifically directed to veterinary medicinal products to enhance awareness of the need for responsible and prudent use of veterinary drugs. In 2008 and 2009, OIE organized two regional conferences (Africa and Middle East) specifically dedicated to veterinary medicinal products.

To further enhance awareness, the OIE has started to organize regional training workshops for OIE National Focal Points on veterinary products that were designated by the OIE Delegates. Training workshops took place in Europe (July 2010), the Americas (September 2010), Africa (November 2010), and in the Asia-Pacific region (June 2011). The WHO

participates in those training activities that specifically address the issue of antimicrobial resistance.

5) Collaboration with relevant international organizations.

5.2 WHO Essential Medicines and the Rational Use of Antimicrobials

Essential medicines arose in the mid-1970s from the concept that a limited range of carefully selected medicines leads to better health care, drug management, and lower costs. Essential medicines are defined as "…those [medicines] that satisfy the priority health care needs of the population" (WHO Executive Board, 2002). The essential medicines concept is implemented through national lists of essential medicines, which are usually based on the WHO Model List of Essential Medicines. The principle of Essential Medicines Lists (EMLs) has been implemented in 156 developed and developing countries.

Irrational use of medicines is widespread and irrational use of antimicrobials a very large component of this. In addition to the irrational use by the prescribers, widespread indiscriminate use of antimicrobials by consumers/patients in the community is common. Well regulated pharmacies dispensing antimicrobials on prescription are the exception rather than the rule in a large proportion of the developing countries. Such use has enormous consequences and costs for the health care system, individuals, and the community.

It is not entirely clear whether the majority of use of antimicrobials is in developing or developed countries, nor is it obvious in which settings (hospital or community) the majority of irrational use occurs. There is considerable evidence that countries with comprehensive health care systems such as in northern Europe have advantages in countering resistance with respect to understanding antimicrobial use and resistance, and by regulation. However such comprehensive health care systems are the exception rather than the rule in the developing world; thus managing antimicrobial resistance in the developing world is not only managing prescribers but also one of dealing with the inadequacies of the health care system. The problem is far more prevalent in the profit-driven private sector than in the state health care services.

WHO efforts in this area are longstanding; however, implementation of suggested strategies is worldwide has been very patchy. The WHO 2001 Global Strategy for Containment of Antimicrobial Resistance was very comprehensive, but not implemented by either WHO or member countries in its entirety. Subsequent initiatives (e.g., World Health Assembly resolutions on rational use, Patient Safety Programme) have likewise thus far not had a significant effect. This year the World Health Day theme was on combating antimicrobial resistance and it acknowledged several additional fronts that also must be faced such as: 1) managing rather than fighting resistance would be a tacit recognition that "cost" of a use of an antimicrobial includes some resistance, 2) it will require a wide and deep involvement of a multitude of stakeholders to tackle the issue, 3) such efforts must proceed with urgency and with acknowledgement that the drug pipeline for new classes of antimicrobial is empty, and

4) a parallel focus on diagnostics (and non-antimicrobial therapies) is also needed to improve specificity of treatment and reduce selection pressures.

The six-fold WHO Policy Package to Combat Antimicrobial Resistance (WHA – April 7, 2011) is as follows:

- Commit to a comprehensive, financed national plan with accountability and civil society engagement
- Strengthen surveillance and laboratory capacity
- Ensure uninterrupted access to essential medicines of assured quality
- Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care
- Enhance infection prevention and control (IPC)
- Foster innovations and research and development for new tools

The Policy Package is a fresh start in combating antimicrobial resistance; this time with the accumulated experience as well as the urgency it may be the beginning of a journey towards a solution.

Use of Critically Important Antimicrobials in Food-Producing Animals in the United States

AMR among pathogenic and commensal enteric bacteria of food-animal origin has continued to serve as a focus of fierce debate in national and international scientific and political circles. Available evidence supports theories suggesting that the use of antimicrobials in animal agriculture leads to the selection of resistant strains of bacteria within treated animals and within aggregated groups of treated animals (as it also does in human medicine). However, the 'measurable' effect applies largely to periods animals are being treated, and for short periods thereafter. Poorly understood are the longer-term effects reflecting the cumulative impacts of multiple uses in many animals, pens/barns, and farms over extended periods of time.

In terms of the critically important antimicrobials, as listed by the WHO 2nd revision, the top three are of relevance to U.S. agricultural producers since their use spans all four categories as listed above. In general, the products approved in the U.S. as fluoroquinolones are limited to enrofloxacin and this product approval was revoked for use in poultry in 2005. Thus, it is used almost exclusively for therapeutic purposes in individual animals and rarely in large groups of animals. For 3rd and 4th generation cephalosporins, the product approved at this time in the U.S. is ceftiofur, available in short-, medium-, and long-acting formulations for injection. These facilitate use as therapeutic, metaphylactic and prophylactic situations under a 'control' label for some indications. This product was under review by the FDA and they have now ruled to prohibit some types of extra-label use in agriculture (e.g., in ovo injections in poultry). In addition, it is apparent that resistance co-selection with tetracycline has a large influence on ceftiofur resistance in cattle. The third product on the top 3 listing is macrolides. The dominant macrolide in use in the U.S. is tylosin, which while available in both parenteral and oral formulations is largely believed to be used in feed grade formulations; for example,

for control of liver abscesses in feeder cattle. Other products such as tilmicosin and tulathromycin are seeing use for both metaphylaxis and therapy.

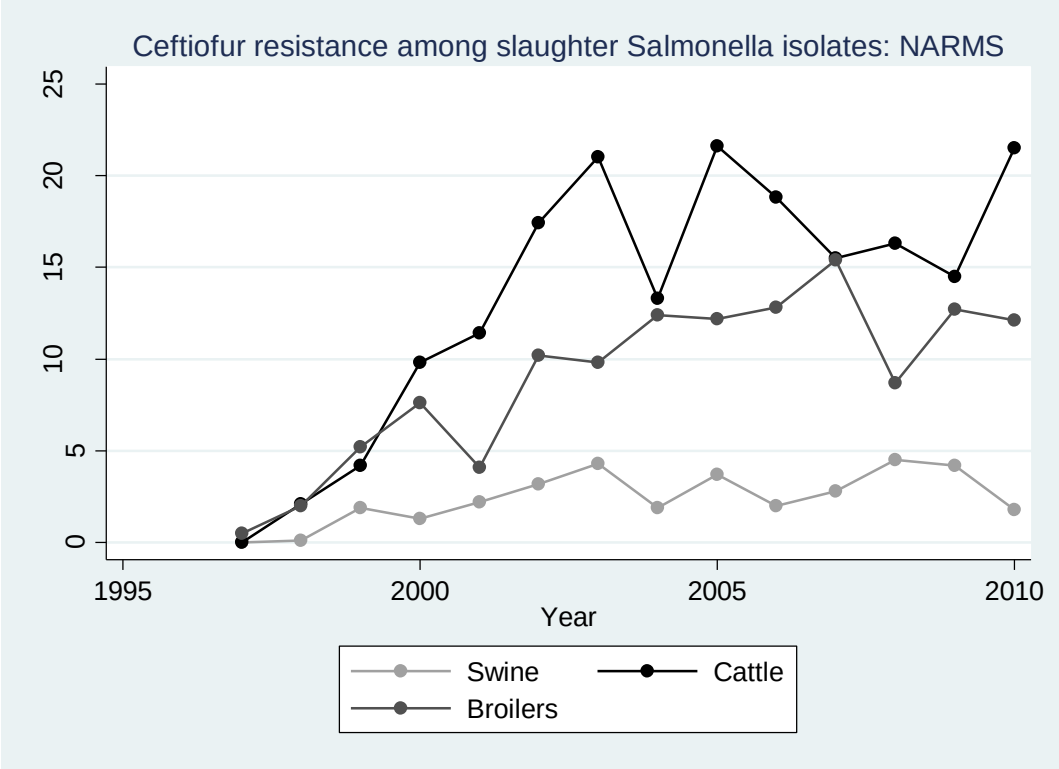
In terms of *Salmonella enterica*, information adapted from the NARMS website (USDA, 2011) and the 2008 NARMS Animal Arm Report (USDA, 2010) has been presented in annual reports (see Figure 2). Ceftiofur resistance differences among cattle, broilers and swine in the U.S. are readily illustrated. This antimicrobial class is currently listed as number 2 in importance on the WHO critically important list. The difference in levels of resistance may well relate to levels of historical use in cattle and broilers versus swine. However, it is just as likely to be lower in swine as a simple function of dominant serovar (see Table 1). It is well recognized that many resistance phenotypes are serovar-dependant among *Salmonella* (a trend usually not seen with commensal *E. coli*). Thus, cattle levels have recently been dominated by the Newport serovar while broilers have instead been affected by Kentucky and Heidelberg. Among pigs, Derby and Infantis show relatively low levels of resistance to ceftiofur. The resistance levels among *Salmonella* of animal origin to fluoroquinolones remain a relative success, with low levels of resistance in the U.S. at least. In all three hosts (cattle, broilers, pigs) there is virtually no fluoroquinolones resistance detected using NARMS sampling protocols. This is not to say the resistance is not out there, but levels are prevalent below the detection limit for NARMS. In other countries, particularly in the developing world, fluoroquinolones resistance is high and climbing among *Salmonella*, *Campylobacter* and other bacteria.

Table 1 Top ten Salmonella enterica serovars isolated from cattle, broilers and pigs at slaughter in 2008. Adapted from NARMS 2008 report data available on website (USDA, 2011).

Cattle	**No.**	**%**	**Broiler**	**No.**	**%**	**Pigs**	**No.**	**%**
Montevideo	104	23.5	Kentucky*	219	35.1	Derby	25	22.5
Newport*	53	12.0	Enteriditis	116	18.6	Infantis	15	13.5
Dublin*	31	7.0	Heidelberg*	94	15.1	Agona*	6	5.4
Anatum	27	6.1	Typhimurium v 5-*	39	6.3	London	6	5.4
Cerro	27	6.1	Typhimurium*	31	5.0	Saintpaul	6	5.4
Typhimurium*	25	5.6	I 4,[5],12:i:-	23	3.7	Typhimurium v 5-	6	5.4
Kentucky	22	5.0	Infantis	14	2.2	Anatum*	5	4.5
Muenster	18	4.1	Montevideo	13	2.1	Johannesburg	5	4.5
Agona*	17	3.8	Schwarzengrund	7	1.1	Ohio	4	3.6
Representing:	**324**	**73.1**	**Representing:**	**556**	**89.1**	**Representing:**	**78**	**70.3**
Out of:	**443**	**100**	**Out of:**	**624**	**100**	**Out of:**	**111**	**100**

*Moderate to strong association with ceftiofur resistance

Figure 2: Trend of ceftiofur resistance among *Salmonella enterica* isolated from slaughter samples (1998 – 2010) collected by the USDA Food Safety and Inspection Service (FSIS) for cattle (black line, black circles: cannot discern beef from dairy), broilers (dark grey line, dark grey circles) and pigs (light grey line, light grey circles) and submitted to the National Antimicrobial Resistance Monitoring System (NARMS) for phenotypic analysis. Adapted from NARMS data supplied on website (USDA, 2011).



Dissemination of CTX-M in Western Africa

Very few studies in Africa are devoted to the burden caused by Enterobacteria resistant to third generation cephalosporins, and particularly to those carrying genes of the CTX-M family which are spreading widely in most of the world. However, one study (Ruppe et al. 2009), although performed in a small number of subjects, strongly suggested that CTX-M15 genes carried on multi-drug-resistance regions, very similar to those described in other parts of the world, were present in fecal *E. coli* from 10% of healthy children from a highly isolated Senegalese village where antimicrobial selective pressure was thought to be minimal. Another study by Woerther et al. (2011, in press) showed that the rate of colonisation by such *E. coli* was as high as 20% in malnourished children admitted to a re-nutrition centre in Niger. In addition, 100% of those children became carriers of ESBL bacteria at the time of discharge, stressing the need to carefully review antimicrobial and hygiene practices during the care of such children. Such levels of carriage are worrisome because there is accumulating evidence that this carriage may lead to generalized infections in some patients and that such multidrug resistance is an independent risk factor for increased mortality (Gudiol et al. 2011). Although data were acquired in western Europe instead of Africa, evidence is emerging that the CTX-M MDR regions, as well as the plasmids on which they are carried, are often found in *E. coli* strains that have caused infections in humans and also

been shown to be identical to those found in poultry (Leverstein-van Hall et al. 2011). This suggests that the food chain can be a likely source of resistance and further justifies efforts to control antimicrobial exposure in the food-chain production.

The Gulf Cooperation Council Center for Infection Control (GCC-CIC):

The GCC-CIC was established in 2005 under the umbrella of King Abdulaziz Medical Center (KAMC) of the Saudi National Guard. Members included are: Kuwait, Saudi Arabia, Oman, UAE, Qatar and Bahrain. KAMC has also been recognized as a WHO Collaborating Center for Infection Control in 2009. The Center has aimed to improve the quality of infection control in the Gulf countries and establish a network of expertise to support such activities. A major achievement of the Center was the establishment and standardization of an infection control manual for the practices of infection control in the healthcare environment. The manual includes over 60 policies relevant to the infection control. In 2007, Saudi Arabia lead the collaboration between the gulf countries and the WHO for the "Clean Care is Safer Care" initiative. In addition, the development of a unified surveillance manual with a focus on device related infections was achieved. An intense training program was initiated in 2011 for infection prevention specialists in the region. The Center has also collaborated with the WHO to developed Arabic translations of WHO Guidelines on Hand Hygiene, and has participated in the Regional Expert Consultation for the Development of the Patient Safety Friendly Hospital Initiative (PSFHI) Improvement Toolkit.

During the 5 year planning for the Center's activities in 2010, antimicrobial resistance was considered a high priority. Some of the countries such as Kuwait have already initiated a national stewardship program and other countries such as Saudi Arabia and Qatar are following the same steps. Guidelines for the proper use of antimicrobial agents are being developed in the countries based on specific epidemiological features of resistance in each country. The Center has been able to share tools used for standardization of the measurement of antimicrobial use according to WHO and CDC standards. Proper auditing tools will be developed and tested for implementation in 2012 and 2013.

The Center has also focused on coordinating educational activities at the regional and international levels. The most recent symposium carried out in Riyadh 2010 was specifically designed to address antimicrobial resistance with more than five hundred (500) healthcare workers and participants in attendance.

Finally, the Center has been internationally recognized at the Fifth Decennial International Conference on Healthcare-Associated Infections, the Society for Healthcare Epidemiology of America (SHEA) and the Association for Professionals in Infection Control and Epidemiology (APIC) and was awarded their first "SHEA-APIC Partnership Award" to National Guard Health Affairs in Saudi Arabia. The Award was created to recognize and celebrate the efforts of multidisciplinary teams working together to champion infection prevention efforts within their healthcare organization.

Regional Initiatives

The European Food Safety Authority (EFSA):

Resistance to commonly used antimicrobials, such as tetracycline, ampicillin and sulfonamides were frequently found among the isolates tested by 25 Member States of the European Union. For some antimicrobials, large differences in the occurrence of resistance were observed between Member States. The reported high occurrence of fluoroquinolone resistance in *Salmonella* isolates from poultry and in *Campylobacter* isolates from poultry, pigs and cattle, as well as from broiler meat, is of particular concern, since fluoroquinolones are defined as critically important antimicrobials in human medicine.

A European Union-wide baseline survey on methicillin-resistant *Staphylococcus aureus* (MRSA) was conducted in 2008 in holdings with breeding pigs. A total of 1,600 holdings housing and selling mainly breeding pigs (breeding holdings), and 3,473 holdings housing breeding pigs and selling mainly pigs for fattening or slaughter (production holdings) from 24 Member States and two other European countries were included in the survey. The survey results indicate that MRSA was commonly detected in holdings with breeding pigs in some Member States, while in others the prevalence was low or not detected (holdings from seven States). The European Union-wide prevalence of MRSA positive breeding holdings was 14.0%, and the prevalence ranged from 0% to 46.0% among the Member States. The within-holding prevalence was 26.9%, and ranged from 0% to 51.2%. MRSA CC398 was the predominant MRSA lineage identified, covering 92.5% of the MRSA isolates.

Risk of MRSA increased with population size and at country-level a strong positive association between the prevalence of MRSA-positive breeding holdings and MRSA-positive production holdings was found, suggesting vertical dissemination of MRSA.

The European Food Safety Authority (EFSA) asked its Panel on Biological Hazards to deliver a scientific opinion on the assessment of the public health significance of methicillin resistant *Staphylococcus aureus* (MRSA). In brief, the opinion states that CC398 is the MRSA lineage most often associated with asymptomatic carriage in intensively reared food-producing animals. Livestock-associated MRSA (LA-MRSA) represent only a small proportion of the total number of reports of MRSA infections in the EU, however, in some countries with a low prevalence of human MRSA infection, CC398 is a major contributor to the overall MRSA burden. CC398 has, albeit rarely, been associated with deep-seated infections of skin and soft tissue, pneumonia and septicemia in humans. Where CC398 prevalence is high in food-producing animals, people in contact with these live animals (especially farmers and veterinarians, and their families) are at greater risk of colonization and infection than the general population. Food may be contaminated by MRSA (including CC398): eating and handling contaminated food is a potential vehicle for transmission. There is currently no evidence for increased risk of human colonization or infection following contact or consumption of food contaminated by CC398, both in the community and in hospital. The potential for CC398-colonised humans to contribute to the spread of MRSA in hospitals currently seems to be far less than for hospital-associated MRSA strains.

World Health Organization Regional Office for Europe (WHO-EURO):

Antimicrobial resistance has become an international public health problem that urgently requires attention. The magnitude of the problem is illustrated by the fact that more than 25,000 people in the European Union die each year from infections caused by antimicrobial-resistant bacteria. Overuse of antimicrobials in food animals has important consequences for public health, as it promotes the development of antimicrobial-resistant bacteria and resistance genes that can be passed on to people, usually through the food chain. To protect public health, all antimicrobial growth promoters in animal agriculture have been withdrawn in the European Union since 2006. Discontinuing the use of antimicrobial growth promoters has reduced the risk to human health without harming animal health or the economics of animal production. In aquaculture, improved management of fish farms and the introduction of effective vaccines also can significantly reduce the usage of antimicrobials.

Tackling antimicrobial resistance requires a holistic, inter-sector and multifaceted approach with effective coordination of action and exchange of information among the agricultural, food, veterinary and health sectors. The WHO Regional Office for Europe is developing a strategy on antimicrobial resistance, and addressing antimicrobial resistance in the food-chain is one of the key objectives of this strategy. In connection with the World Health Day 2011, whose theme was antimicrobial resistance, the WHO Regional Office for Europe launched a booklet: 'Tackling antibiotic resistance from a food safety perspective in Europe". This publication explores the options for prevention and containment of antimicrobial resistance in the food-chain through national coordination and international cooperation; this includes the regulation and reduction of antimicrobial use in food animals, training and capacity building, surveillance of resistance trends and antimicrobial usage, promotion of knowledge and research, and advocacy and communication to raise awareness of the issues. The publication is primarily intended for policy-makers and authorities working in the public health, agriculture, food production and veterinary sectors, and offers to them ways to take a holistic, inter-sector, and multifaceted approach to this growing problem.

More specifically, the booklet calls for the establishment of a formal mechanism of interaction at the national level between the health ministry and other relevant ministries and authorities to address antimicrobial resistance in the food-chain. It is suggested that national veterinary, agricultural and pharmaceutical authorities, among others, consider: 1) eliminating the use of antimicrobials as growth promoters, 2) requiring that antimicrobials be administered to animals only when prescribed by a veterinarian, and 3) requiring that antimicrobials identified as critically important in human medicine – especially fluoroquinolones and third- and fourth-generation cephalosporins – only be used in food animals when their use is highly justified. Furthermore, countries should aim for: 1) reducing the need for antimicrobials in animal husbandry by improving animal health through biosecurity measures, disease prevention (including the introduction of effective vaccines), and good hygienic and management practices, and 2) eliminating any economic incentives that facilitate the inappropriate prescription of antimicrobials. It is suggested that public health, veterinary and food authorities consider: 1) establishing a system for monitoring the usage of antimicrobials in people and food animals, and 2) establishing an integrated (among

the public health, food and veterinary sectors) surveillance system to monitor antimicrobial resistance in selected foodborne bacteria. Also, it is suggested that veterinary, agriculture and food authorities consider developing guidelines on the prudent use of antimicrobials in food animals, taking a multidisciplinary approach. Such guidelines should especially cover antimicrobials categorized as critically important for human medicine. The authorities should also provide the training needed to implement the guidelines.

5.3 Taking Stock: National Initiatives

Denmark:

One hundred and twenty (120) tonnes of non-therapeutic uses of antimicrobials (NTA) were phased out of production in Denmark during the period from 1995 to 2000. The single largest reduction in the use of therapeutic antimicrobials was seen in 1995 when restrictions on direct sales from veterinarians to farmers were introduced. In 2010, additional new initiatives to reduce the use of antimicrobials in pig production were put in place due to a measured increase in antimicrobial consumption for pigs in recent years. These included: 1) a voluntary discontinuation of the use of cephalosporins in Danish pig production was launched by the Danish pig industry, 2) veterinary advisory service contract agreement requirements (details below) were renewed, 3) a 'yellow card' system (based on deviations from average antimicrobial use) was introduced in June 2010, and 4) new treatment guidelines were launched in May 2010 and introduced in May 2011.

In October 2010, a number of farmers received a 'yellow card' and were asked to reduce their consumption of antimicrobial agents. So far, these initiatives have resulted in: 1) a large reduction in the use of cephalosporins in 2010 (due to the voluntary discontinuation of cephalosporin use in the second half of the year), and 2) a reduction in the total consumption for pigs to the about same level as in 2008, with the highest decrease occurring in the second half of 2010.

The renewed veterinary advisory service contact agreements are mandatory for all larger pig and cattle farms and are drawn up between each farm owner and their veterinarian. The agreements focus on 1) health and production (e.g. animals at risk, reasons for high mortality), 2) antimicrobial consumption, resistance and zoonosis (e.g., instructions in use of medicine), 3) herd diagnosis and treatment guidelines, and 4) animal welfare (e.g., audits of 'self control', transport ability).

New evidence-based prudent-use guidelines for antimicrobial treatment of swine in Denmark have been developed with stakeholders from both research institutions and industry. The treatment guidelines categorize the antimicrobial agents based on four criteria: 1) efficacy of the antimicrobial drug, 2) susceptibility of the target bacterium towards the antimicrobial, 3) the human importance of the class of drug and, 4) pharmacokinetics. The guidelines are specific to the pathogens in question and divide the antimicrobials into three categories: 1) antimicrobial agents that should preferably be used (marked with green color), 2) those that can be used with care and attention (yellow), 3) and those that should be used rarely, or not at all (red).

The Netherlands:

In the Netherlands, discussions about the use of antimicrobials in veterinary medicine have been ongoing for several decades. In 1997, the Dutch Health Council (advisory body for the Minister of Health) recommended to ban the use of growth promoters (GP). In concordance with the European regulations, the ban became effective in 2006. From 1997 to 2006 there was an annual increase in sales of antimicrobials for therapeutic use in veterinary medicine. Despite reports and discussions on the veterinary use of antimicrobials, the Netherlands showed the highest sales of veterinary antimicrobials per kg biomass of major food animals in a European survey of 10 countries. In direct contrast, the use of antimicrobials for humans in the Netherlands is very low compared to other European countries. This difference has driven discussions between veterinarians and medical doctors about the need for reductions in veterinary use.

Recent findings that the resistant bacterium LA-MRSA (Livestock Associated MRSA) and ESBL-producing Gram-negative bacteria are widely spread among Dutch food-producing animals have led to public awareness and questions of the parliament to the Minister of Agriculture and the Minister of Public Health. The presence of MRSA in pigs and veal calves has had a direct impact for the farmers: the Dutch ''Search and Destroy'' policy to control MRSA in hospitals identified farmers as a risk group for MRSA carriage. Therefore, in some hospitals they have been asked to show up only at the end of the day. Other measures experienced by farmers were equally as stigmatizing. In former days, antimicrobial resistance was perceived by farmers as not being a real problem; however, MRSA has had the dramatic effect of making farmers very aware of the problem. More recently, it has also become clear that extended spectrum beta-lactamase producing bacteria (ESBLs) are highly prevalent in the Dutch broiler production system. Consequently, the meat at retail level is often contaminated with ESBLs. Studies have shown that 20% of human ESBLs are genetically indistinguishable from poultry isolates, suggesting a transmission from poultry to humans. Although not yet proven, the use of cephalosporins in the poultry chain may very well have been a factor that contributed to the emergence, spread, and proliferation of ESBLs in the broiler production system.

In 2007, the Ministers of Agriculture and Public Health informed the Parliament about their vision concerning the transparency of veterinary drug prescription and use, and the responsibility of the different actors in food production chain. A working group was created to prepare a 'covenant' – an agreement between the ministries, production sectors, drug sellers, and consumers. Their plans were presented in 2008 and adopted in 2010. The adoption in 2010 was a response to the request of the Minister of Agriculture to ensure that the targets for reduction of usage (20% in 2012, and 50% in 2013) as presented early in 2010 by the Ministry of Agriculture, will be met. The Royal Dutch Society for Veterinary Medicine (representing veterinarians) strongly supported the designation of an independent Veterinary Drug Authority (VDA) in the Netherlands. This VDA was installed in 2011.

The current status (as of June 2011) in the Netherlands is that: 1) veterinarians and farmers are obliged to provide their usage data to the Veterinary Drug Authority (VDA) allowing

benchmarking of these data, 2) the VDA has the mandate to set norms for usage in different animal sectors as a reference for the benchmarking, 3) the Ministry of Agriculture is responsible for increased enforcement of regulations, and 4) the targets for reductions in usage in 2012 and 2013 (20% and 50%, respectively) must be met.

It can be concluded that public opinion has been a strong driver behind the recent changes in the policy of veterinary antimicrobial usage. The responsibility and the leadership of the production sectors have led to the implementation of measures. The fact that the presence of LA-MRSA has directly impacted the farmers themselves in their private lives (including their families), has no doubt helped influence the willingness of farmers to support these changes.

Lebanon:

An epidemiological survey of foodborne diseases and foodborne outbreaks in Lebanon provided by the Epidemiological Surveillance Unit at the Ministry of Health (ESUMOH) highlighted: 1) the number of foodborne episodes in 2010, 2) the products and bacterial agents responsible for food poisoning, and 3) prominent symptoms reported by clinically affected humans. In Lebanon, the agro-food sector is the most important sector of Lebanese industry economy and accounts for 20% of industrial enterprises. While Lebanon has taken some steps forward in food safety, it is still lagging behind other developed countries in this area due mainly to 1) gaps, and sometimes overlaps, in responsibilities that hinder progress, and 2) the lack of a food safety surveillance system; specifically, the lack of information on the magnitude and severity of dietary exposure of the population to food toxicants. With respect to food safety as related to antimicrobial resistance, in Lebanon and several other Arab countries highlights multiple research projects tackling the issue of food safety, while others focus more on antimicrobial resistance. Bacteria under study include: *Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus aureus* and *Salmonella* spp.

Recently, Lebanon undertook steps to ensure a safer food supply by consolidating food safety into a single agency called the "Lebanese Association for Food Safety (LAFS)", with connections to all relevant ministries. The association was established at the end of 2010 by a group of young and dedicated scientists with the aim to: 1) develop customized consumer-awareness educational materials and promote an internet-accessible (e.g., via website, social networking sites) campaign via media, the food sector, academia, and through workshops, 2) develop and maintain a database with essential information on food safety, food borne illness cases and relevant regulatory requirements for consumers and industry members, 3) serve as a link between the consumer, food sector and governmental authorities to ensure complaints and action are taken seriously, 4) collaborate with national authorities and other stakeholders regarding food safety and relevant regulatory matters, and 5) provide service and carry out targeted research based on identified needs and gaps.

Kenya:

An integrated surveillance study of antimicrobial resistance has recently been undertaken in Kenya. The overall objective of the study was to undertake baseline integrated antimicrobial resistance surveillance among several zoonotic bacteria from healthy food animals, retail

meat outlets, as well as from human clinical specimens in selected sites in Kenya. The specific aims of the study were: 1) to determine the prevalence of *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp. in carcasses and retail meats as well as from human clinical specimens in selected regions in Kenya, 2) to determine the antimicrobial susceptibility patterns of these foodborne pathogens to five commonly available classes of antimicrobials – tetracyclines, chloramphenicol, sulphonamides, β-lactams and quinolones, and 3) to investigate *in vitro* the transferability of antimicrobial resistance determinants in *E. coli* and *Enterococcus* spp (indicator organisms) isolated from animals and meat products.

At all abattoirs and slaughter slabs the scientists collected rectal swabs from live animals, carcass swabs as well as effluent at the point of killing, dressing and exit into wastewater discharge, for bacteriological analysis. For the on-farm samples, a detailed questionnaire was administered to obtain information on general management, feeding and treatment practices on the farm. The clinical specimens came from children with diarrhea (< 5 years of age) attending health facility close to samplings sites.

Among the isolates from animal sources, resistance levels tested by disk diffusion technique were highest for isolates from pigs and poultry in comparison to cattle, and especially high for resistance to ampicillin, tetracycline, cotrimoxazole and streptomycin. However, isolates from all animals were fully susceptible or showed <5% resistance to gentamicin, kanamycin, ceftrixazone and ciprofloxacin. Among the isolates from pigs and poultry, 2.5% resistance to ciprofloxacin and correspondingly higher rates of resistance to nalidixic acid (10% in cattle and 26% in poultry) were observed. Levels of resistance among *E. coli* clinical isolates from children were significantly higher than for animal isolates, especially to ampicillin (averaging 72%), and co-trimoxazole (averaging 52%). In farmer interviews and follow-up studies it was observed that the four most frequently used antimicrobial classes by farmers, i.e., tetracyclines, penicillins, sulfonamides and streptomycin were also among the four to which bacteria were most resistant. For instance, in beef animals resistance was highest for penicillins followed by streptomycin, while in chickens, levels of resistance were highest against tetracyclines, sulfonamides, penicillins and streptomycin. In pigs, high levels of resistance among enteric bacteria were observed against streptomycin, penicillins, tetracyclines and sulfonamides.

These results indicate that although antimicrobials are not used as growth promoters in Kenya, indiscriminate use of antimicrobials for therapeutic and prophylactic purposes may have promoted the emergence and propagation of antimicrobial resistance in livestock. This could be attributed to misuse of antimicrobials by the end users (either farmers or animal health professionals).

5.4 AGISAR Subcommittee Reports

5.4.1 Antimicrobial Resistance Monitoring Subcommittee:

Goals of the resistance monitoring subcommittee:

The goals of the subcommittee are as follows: 1) to provide guidance on surveillance and monitoring priorities, and minimum requirements for integrated monitoring systems and for AGISAR pilot monitoring projects, 2) to provide guidance on sampling strategies, 3) to develop recommendations for international harmonization of integrated antimicrobial resistance monitoring systems for foodborne bacteria, including both pathogenic and commensal organisms, 4) to disseminate guidelines and standards on laboratory testing methods and quality assurance, 5) to propose components of reporting and information sharing that permit regional and international comparison of findings, and 6) to communicate recommendations through Global Foodborne Infections Network (GFN) training courses, AGISAR pilot projects, and through other partnerships.

Issues that were considered during the resistance monitoring subcommittee sessions:

The guidance document on AMR monitoring that was circulated during the past year was finalized during the Oslo meetings. In particular, there was agreement as to the need to merge with it information (particularly on harmonization) from the first meeting of AGISAR (Copenhagen, 2009), which preceded the subcommittee's existence, and to increase the level of detail in the subcommittee guidance document to be suitably comprehensive. This latter point included (for example): 1) the need to distinguish Typhi and Paratyphi serovars in reporting Salmonella susceptibilities, 2) a desire to see hospital-acquired strains distinguished from community-acquired strains in reporting from human arms of integrated surveillance systems, 3) that readers be directed to expert rules when discussing quality control issues (e.g., for discordant AST results such as for naladixic acid and quinolones, and criteria for necessitating repeat testing), and 4) that a list of drugs to be tested and direction on how multiple resistance types best be reported both in terms of raw data and in aggregate, be provided to the reader.

In the working group sessions it was also discussed that while earlier drafts of the guidance document necessarily focused on immature systems (getting going), important aspects of more 'mature' systems should be expanded. These include: 1) striving for real-time monitoring/surveillance and reporting, 2) emphasizing greater epidemiologic involvement, 3) carrying out research to support surveillance where warranted, 4) exploring genetic epidemiology, and 5) inclusion of strain typing data (e.g., pulsed-field gel electrophoresis (PFGE), whole-genome sequencing (WGS), multi-locus sequence typing (MLST)).

Despite the general worldwide movement of AMR monitoring systems away from use of passive data from veterinary diagnostic laboratories, the subcommittee saw potential advantages in occasionally comparing isolates from clinical veterinary sources with those from on-farm, slaughter and retail meat (presumed healthy animal sources) for both *E. coli* and *Salmonella.* Clinical veterinary isolates may provide surrogate indicators of drivers of resistance, such as antimicrobial use, and also early warning of what could eventually enter

the food supply in larger numbers from healthy animals. The value of resistance surveillance of diagnostic laboratory isolates was recognized to be controversial; however, it was generally agreed that such isolates may later be shown to predict emergence of novel food-borne strains in human clinical cases.

Additional suggestions made by the subcommittee were to: 1) add a glossary and a list of abbreviations to the guidance document, include a unifying and workable definition of multi-drug resistance (MDR; with possible reference to a forthcoming CLSI document), 2) include discussion of unique aspects of aquaculture monitoring in the document, 3) include communication tools and strategies making better use of the AGISAR home page in particular, 4) include (and update regularly) contacts to support those seeking to improve and change their monitoring systems (e.g., among partners and WHO collaborating centers), and 5) add links to consensus standard documents such as published by CLSI and EUCAST.

The last major point of discussion among the subcommittee was with respect to ultimately promoting data integration across both consumption and resistance data monitoring systems. The subcommittee discussed the limits and constraints likely to be faced in attempting to address correlation of drug use and resistance data.

Resistance monitoring subcommittee recommendations:

- A more complete definition of integrated surveillance/monitoring of usage and resistance, potentially allowing for integrated analysis, is needed at the start of the guidance document, as well as a listing what is needed to accomplish adequate testing in all three sectors (human, animal, meat products; perhaps by adding a figure).

- Monitor country progress in achieving program elements, and recognize them for successes (e.g., via certification or membership in an advisory capacity to others). Incentivize laboratories for participating in AMR activities. Discussions are ongoing at WHO regarding this subject and mapping of individual countries' AMR monitoring is a possibility.

- AGISAR should recommend that, within two years, each country would establish the AMR microbiological testing of foods in the domestic market, as well as those being introduced into international trade. This is to ensure that countries do not ignore their domestic markets and public health needs by instead focusing only on their exports and access to international markets.

- It is expected that the final version of the resistance subcommittee guidelines will be available on the WHO-AGISAR web page in 2012 (at: www.agisar.org).

5.4.2 Usage Monitoring Subcommittee:

Goals of the usage monitoring subcommittee:

The major aim of the usage subcommittee is to support and promote the collection of standardized data on the usage of antimicrobial agents for humans and animals, including aquatic species, at regional/national levels. The subcommittee is also exploring ways to support and promote the analysis and reporting of antimicrobial agent usage and will develop an action plan (e.g., guidelines, capacity building) to that effect.

Issues that were considered during the usage monitoring subcommittee sessions:

The subcommittee furthered its work to develop a series of protocols for the collection of antimicrobial sales and usage data. It completed its "*Guidance for the collection of data on overall sales of antimicrobial agents*." The subcommittee also discussed elements of a protocol for collection of usage data at the farm level.

The document: "Guidance for the collection of data on overall sales of antimicrobial agents" will be ready for posting on the AGISAR website by late 2011. The subcommittee also plans by that time to post a first draft of additional information concerning procedures to be used for reporting overall animal use by species. The next step will be to finalize guidance for collection of community and hospital data (for humans) and end-use data (for animals / farms). This will require the development of protocols for collection of point-prevalence and longitudinal data for both human and animal sectors in different settings. A further step will be development of guidance for analysis and reporting of antimicrobial use data from animals. Such guidance is already available for data from humans and appropriate references will be provided on the website.

Usage monitoring subcommittee recommendations:

- Competent authorities in member countries make provisions for the collection and reporting of national level antimicrobial sales and usage data in humans and animals; including, if necessary, development of appropriate enabling legislation. In the case of data from animals, this is consistent with the OIE Terrestrial Code.

- Applicants for pilot projects consider incorporation of some or all of the antimicrobial use protocols into new project proposals in order to facilitate capacity building and provide information for refinement of protocols.

5.4.3 Data Management and Software Development Subcommittee:

Goals of the data management and software development subcommittee:

The major purpose of the subcommittee is to guide the development and subsequent implementation of software specifications to support the use of WHONET software by appropriate agencies; specifically, in the case of AGISAR to meet the AMR monitoring needs of public health, veterinary, food science, and environmental microbiology laboratories.

The subcommittee's work is supported through the identification of existing surveillance collaborations in these areas, and the review of existing documentation and reports from these

groups, with discussions with coordinators of these networks about their data needs. Primary areas of relevance to database and analytical software development include: 1) recommended, desirable, versus optional data fields, 2) data analysis capabilities, 3) report formats, and 4) data exchange (interfaces) with surveillance networks.

Issues that were considered during the data management and software development monitoring subcommittee sessions:

Significant analytical capabilities have been added to the WHONET software package in recent years in response to subcommittee deliberations, interaction with other subcommittees (particularly, usage and resistance monitoring) and end-users. In addition, further advances in WHONET's alert features have been made including: 1) microbiological alerts of public health or quality assurance importance and, 2) statistical alerts for automated outbreak detection; both in hospital (e.g., publication based on work from a Boston-area hospital), and in community settings (e.g., laboratory-based detection of outbreaks of shigellosis in Argentina as a collaborative project with the Malbrán Institute in Buenos Aires). In collaboration with the European Centre for Disease Prevention and Control (ECDC), the ECDC-proposed multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant bacteria definitions have been incorporated into WHONET and these have subsequently been evaluated against three databases from countries with high, medium, and low levels of resistance, respectively. From a July 2011 article in the journal *Clinical Microbiology and Infection*: "MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and PDR was defined as non-susceptibility to all agents in all antimicrobial categories."

In addition to analysis options, another priority is the development of data/file export formats and interface capabilities to facilitate submission of data to the "country database" maintained by the Danish National Food Institute (DTU) on the behalf of the Global Foodborne Infections Network (GFN). At present, data contributors manually enter summary statistics concerning the top 15 *Salmonella* serotypes into a web-based interface. Discussions with DTU staff have suggested three areas in which WHONET software enhancements could provide additional value to GFN participants: 1) data reporting format for WHONET's "isolate listing summary" analysis could be expanded to specific *Salmonella* serotypes which would permit electronic data submissions to the existing table structure of the GFN country database, 2) development of a new reporting format for GFN to cover percent antimicrobial-resistant, intermediate, or susceptible (%RIS) summary statistics; and 3) exploration of the possibility of hosting isolate-level record sets of original data from GFN participants, authors publishing in the Journal of Infection in Developing Countries, and from other interested partners.

The core of the work to support antimicrobial use surveillance in human and food animal populations is based on recommendations from the WHO AGISAR Usage Monitoring Subcommittee, which are to a large degree based on the experiences and protocols of the

European Surveillance of Antimicrobial Consumption project (ESAC) and the WHO Collaborating Centre for Drug Statistics Methodology in Oslo. The documents focus on two types of surveillance: 1) aggregate quantitative statistics of drug use in both animal and human settings (in:"*Guidance for the collection of data on overall sales of antimicrobial agents*") –has been accomplished through adaptation of the existing ABC Calc software to include veterinary agents (DDDs for veterinary usages have not yet been formally defined), and 2) qualitative indicators concerning the use of antimicrobials in hospitalized patients – have been developed through an MS Access database modeled on the surveys included in the second AGISAR report (June 2010). The usage subcommittee report for the in-hospital usage has not yet been completed.

Finally, discussion was solicited from the other working groups and included: 1) when samples are part of an identified outbreak, that these be clearly identified in the database, 2) that all *Salmonella* and other isolates be captured, not only those which are antimicrobial resistant (recognition that tracking of susceptible isolates is also critical) and therefore the estimates of the overall burden of foodborne disease due to each bacteria species and subtype (whether resistant or not) can be sustained.

Data management and software development subcommittee recommendations:

There were several overarching recommendations from the subcommittee:

- WHO should encourage countries and their laboratories to adopt the software,
- GFN should incorporate software training into educational workshops,
- WHO should facilitate training in developing countries,
- WHONET should be integrated into pilot sites/studies,
- Participating countries and their laboratories should include denominator data (i.e., sample numbers and not just isolates) along with antimicrobial resistance and use data, and
- Tutorials/self-teaching/technical support should be provided.

5.4.4 Capacity Building, Country Pilot Studies and Focused Research Projects Subcommittee:

Goals of the capacity building. country pilot studies, and focused research projects subcommittee:

The terms of reference for capacity building are as follows: to facilitate capacity building through GFN for the integrated surveillance of resistance among both food borne pathogens and commensal enteric bacteria as well as antimicrobial drug usage across sectors (animal, food, human), particularly in developing countries. The terms of reference for the pilot projects are: to facilitate pilot studies focusing on integrated surveillance of resistance among food borne pathogens and commensal enteric bacteria as well as antimicrobial drug use, with an emphasis on appropriate interventions in one or more developing countries. In particular, the objectives of the pilot projects include:

- Supplement the work of AGISAR by providing data from additional parts of the world, particularly from developing countries.
- Contribute to strengthening the capacities of countries to establish their own programs on integrated surveillance of AMR and antimicrobial drug use.
- Foster communication and collaboration between animal, food and health sectors, thereby contributing to better prevention and control of foodborne diseases (including those caused by resistant bacteria) all along the entire food chain.
- Increase awareness and commitment among countries to implement strategies for prevention and control of foodborne diseases and containment of AMR.
- Use the competencies built through pilot studies to monitor effectiveness of control strategies.

Issues that were considered during the capacity building. country pilot studies, and focused research projects subcommittee sessions:

Building on the successes of the initial pilot projects, the committee discussed extension and expansion of the scope of future projects through the inclusion of antimicrobial use data in veterinary and human medicine. Pilot projects in the future were requested to include in their proposals and protocols a well-defined dissemination strategy for the project results to be shared with relevant stakeholders. Members of other AGISAR subcommittees would be welcomed to be included in the development of criteria for calls for project proposals as well as in the reviewing process of future proposals submitted for pilot project funding. In order to strengthen the review process for pilot project applications, the committee further offered specific recommendations as to pilot project proposal requirements.

Capacity building. country pilot studies, and focused research projects subcommittee recommendations:

- AGISAR should develop detailed proposal guidance and a common template for the applicants to follow (e.g., length of proposal, format, budget limits)
- AGISAR should develop guidance for reviewers of the proposals to ensure a uniform and fair scoring system
- Calls for proposals should be posted on the AGISAR website and be publicized through the GFN training forums
- Resources from OIE, WHO, FAO and other partners should be posted on the AGISAR website to help countries in their design of proposals and analysis of data
- Mentorship programs for developing countries (e.g., through GFN training) should be facilitated by AGISAR so that participants can be guided through process of developing fundable project proposals.

5.4.5 AGISAR Communication Tools and Strategies:

Risk communication is an important consideration for AGISAR. The risk analysis framework, promoted by WHO and FAO, to address hazards in the food supply, utilizes three essential components: risk assessment, risk management and risk communication. Risk communication is broadly defined as the interactive exchange of information and opinions concerning risk and risk management among risk assessors, risk managers, consumers and other interested parties.

In addressing risk communication with consumers, expert communicators utilize specific tools and strategies that are essential to providing appropriate consumer information during a food safety event on what foods should be avoided without triggering an overreaction by consumers, who sometimes avoid purchasing food items long after the event is over. Effective risk communication is the result of careful planning and a strong scientific understanding of the pathogens, and their public health impact.

The data collection function of AGISAR will generate information of interest to multiple stakeholders, including government risk managers, the food industry, retailers and consumers. Producers may be concerned about disclosure of information about practices that they are not equipped to address. Consumers may be concerned that the results demonstrate that their food is potentially contaminated. Risk managers must be prepared to address concerns of stakeholders at any point during the data collection process.

WHO and FAO have convened a number of expert panels to describe the interaction between risk assessors and risk managers that are relevant to the AGISAR process. Importantly, experts found that transparency is a key objective and its importance cannot be overemphasized. In addition, the panels recommended that risk communication with a broad variety of stakeholders should be considered at all stages of developing a food safety program or policy. Therefore, in furthering recommendations for foodborne antimicrobial resistance surveillance, AGISAR should anticipate the needs of risk managers in the area of risk communication

Risk evaluation is an important step in risk communication. During this stage, some core questions for designing communication include: How controllable is the risk by consumers or producers? Are actions in one part of the food chain increasing the risk for others along the food chain? Are benefits and risks of a particular technology shared equally, or only by one segment of stakeholders? Are alternative production methods available to producers? What background information will be essential in advising the public and other stakeholders during a food crisis?

Anticipating the risk management and risk communication aspects of the AGISAR's project are appropriate next steps in the work plan, according to the risk analysis framework. In developing the platform for collection of information from the field, AGISAR members should consider and anticipate the information needs of risk managers in the countries and discuss outcomes that could emerge from the data gathered through the project. Risk managers should be equipped with information that describes various scenarios and

stakeholder response, considers risk management options, and provides relevant points for communicating with stakeholders.

6 Part II –WHO List of Critically Important Antimicrobials

6.1 Introduction

Use of antimicrobials in food animals can create an important source of antimicrobial resistant bacteria that can spread to humans through the food supply. Improved management of antimicrobial use in food animals, particularly in reducing those "critically important" for human medicine, is an important step towards preserving the benefits of antimicrobials for people. The WHO has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine.

6.2 History of the current document

The 1st WHO Expert Meeting on Critically Important Antimicrobials (CIA) for Human Health was held in Canberra, Australia, in 2005. During that meeting, participants considered the list of all antimicrobial classes used in human medicine and categorized antimicrobials into three groups: *critically important*, *highly important*, and *important*, based on criteria developed at the meeting.

The 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark, in May 2007. During the second meeting, participants reviewed the two criteria and re-examined the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. Participants were also requested to prioritize agents within the critically important category in order to allow allocation of resources towards the agents for which management of the risks from antimicrobial resistance are needed most urgently. These antimicrobial classes were fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides.

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was formed in 2009, following a worldwide solicitation of experts from a variety of relevant fields, including human health and veterinary medicine, to serve as members. One agenda item of the 1st AGISAR meeting held in Copenhagen, 2009 was a follow-up of the two previous expert consultations on critically important antimicrobials. Experts at the 2009 meeting reviewed the Copenhagen 2007 list of CIA (the 1st revision of the CIA list) and produced the 2nd revision of the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and new drugs.

The 3rd AGISAR meeting was held in Oslo, Norway, in June 2011, and a further revision of the list included not only new drug developments and scientific information, but also focused on consolidating the suggestions on how the list might best be used to manage risks associated with antimicrobial use. Additional substances were added to the list according to their ATC codes (per the WHO Collaborating Centre for Drug Statistics), to ensure a more

complete listing of products. Veterinary drugs falling in the same classes of antimicrobials as those in the human medicine list are now also listed in the tables to help risk managers more readily identify those drugs and classes that are analogous to human medicines and with greater potential to impact resistance among the critically important antimicrobials for human medicine.

6.2.1 Contemporary context

Antimicrobials are used widely in agriculture. This includes non-therapeutic use such as for growth promotion. It also includes use as prophylaxis to try to prevent infections developing in food animals and therapeutic use to treat sick animals. However, this use also includes using agents defined by WHO as "critically important" for human medicine.

Bacteria (including those resistant to antimicrobials) that commonly transfer to people from food animals are *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp. More recently, emerging evidence has shown that *Staphylococcus aureus* (including MRSA) and *Clostridium difficile* also occur in food animals and can later be found in food products and environments shared with humans. More details and background information can be found in the previous edition of the 1st AGISAR report at www.agisar.org.

Resistant Gram negative bacteria (e.g., *E. coli*) have become a major and rapidly increasing problem. There are no new classes of antimicrobials in the pipeline and so it is unlikely that any new classes of effective antimicrobials will be available for 10 years or more to treat infections caused by resistant Gram negative bacteria.

Recently, we have seen the development and spread of bacteria carrying metallo-betalactamase genes that are resistant to carbapenems (and all beta-lactams). One of the most concerning aspects is the recent intercontinental spread of a multi-resistant strain of E.coli (New Delhi metallo- betalactamase or NDM strain) which are resistant to carbapenems and nearly all other antimicrobials (including non-betalactam classes). These types of multi-resistant bacteria have caused infections not only in hospitals, but also in the community. They have also spread within hospitals in Britain and elsewhere. The genes encoding for the metallo-betalactamases have been transferred to many other genera of bacteria (e.g., *Klebsiella*, *Vibrio* and *Providentia*). These increasingly commonly isolated bacterial isolates have necessitated using therapy with intravenous polymyxin; which, as an "old" antimicrobial had previously been discarded from systemic clinical use because of toxicity and other problems. In many cases it is now the only agent with proven activity against many of these multi-resistant isolates. Notwithstanding this, some bacterial strains carrying the NDM gene are resistant to all antimicrobials, including the polymyxins. The end of the age of the miracle drug may indeed be upon us.

In The Netherlands the same genes encoding for ESBL (extended spectrum beta-lactamases) in *E. coli* isolates are found in both food animal isolates (especially poultry) and in those causing serious infections in people. On a global scale, *E. coli* is the most important human pathogen and causes substantially many more infections than *Salmonella* and *Campylobacter*

combined. Thus, the importance of resistance in *E. coli*, typically considered a benign commensal, should not be underestimated.

6.3 Purpose

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that critically important antimicrobials are used prudently both in human and veterinary medicine.

Of special importance, risk managers should carefully consider that fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been categorized as being of highest priority for risk management among those antimicrobials.

Carbapenems, lipopeptides and oxazolidinones currently have no veterinary equivalent. WHO recommends that these classes as well as any new class of antimicrobial developed for human therapy should not be used in animals, plants, or in aquaculture.

6.4 Use of the document

The list of Critically Important Antimicrobials should be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance due to human and non-human antimicrobial use. Some examples of appropriate use of the document include:

- Prioritizing for most urgent development of risk management strategies those antimicrobials characterized as *critically important* in order to preserve their effectiveness in human medicine.
- Ensuring that critically important antimicrobials are included in antimicrobial susceptibility monitoring programmes.
- Refining and prioritizing risk profile and hazard analysis activities for interventions by species or by region.
- Developing risk management options such as restricted use, labelling, limiting or prohibiting extra-label use, and making antimicrobial agents available by prescription only.
- For the development of prudent use and treatment guidelines in humans and animals.
- To direct special research projects to address prevalence data gaps on existing or potential future CIAs.
- Communicating risks to the public

This list should not be considered as the sole source of information to guide a risk management approach; instead, there are some basic overarching principles that should guide future decisions regarding antimicrobials, including:

- when a new class of drug comes on the market, it should be considered critically important from the outset unless strong evidence suggests otherwise,
- existing drugs such as carbepenems, linezolid, and daptomycin, which are not currently used in food production, should likewise not be used in the future in animals, plants, or in aquaculture , and
- in regions of the world where at least one criterion for critically important status is met, and limited alternative therapies are available for a given condition, then the class should by default be considered critically important

6.5 The criteria

Criterion 1:

An antimicrobial agent which is the sole, or one of limited available therapy, to treat serious human disease.

Explanation: It is self-evident that antimicrobials that are the sole or one of few alternatives for treatment of serious infectious diseases in humans have an important place in human medicine. Serious disease refers to those illnesses which, if left untreated, are likely to result in irreversible morbidity or mortality. Seriousness of disease may relate to the site of infection or the host (e.g., pneumonia, meningitis). Multidrug resistance alone may or may not influence patient outcomes. For instance, multidrug resistance in *S. aureus* severely limits options in the treatment of invasive infections such as pneumonia and blood stream infections and alters the clinical outcome (increased morbidly and mortality). However for skin lesions such as abscesses, incision and drainage alone are often effective without the use of an antimicrobial. Nevertheless, antimicrobials are often used for early treatment of MRSA skin lesions so that they do not progress to abscess formation.

It is of prime importance that the utility of such antibacterial agents should be preserved, as loss of efficacy in these drugs due to emergence of resistance would have an important impact on human health, especially for those with life threatening infections. Participants have included in the *Comments* section of the table examples of the diseases for which the given antibacterial (or class of selected agents within a class) was considered one of the sole or limited therapies for specific infection(s). This criterion does not consider the likelihood that such pathogens may transmit, or have been proven to transmit, from non-human sources to humans.

Criterion 2:

Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted to humans from non-human sources or, (2) human diseases causes by organisms that may acquire resistance genes from non-human sources.

Explanation: Antimicrobial agents used to treat diseases caused by bacteria that may be transmitted to man from non-human sources are considered of higher importance because these are most amenable to risk-management strategies related to non-human antimicrobial use. The organisms that cause disease need not be drug-resistant at the present time; however, the potential for transmission shows the path for acquisition of resistance now or in the future. The evidence for a link between non-human sources and the potential to cause human disease is greatest for certain bacteria (e.g., *S. aureus*, *Enterococcus* spp., *E. coli*, *Campylobacter* spp. and *Salmonella* spp.). Commensal organisms from non-human sources (animals, water, food or the environment) also may transmit resistance determinants to human pathogens and the commensals themselves may also be pathogenic in immunosuppressed hosts. The *Comments* section of the table includes examples of the bacterial genera or species of concern. It is important to note that transmission of such organisms or their genes need not be demonstrated; rather, it is considered sufficient that the potential for such transmission exists.

6.6 Interpretation of categorization

Critically Important

Those antimicrobials which meet both Criterion 1 and Criterion 2 are termed: *critically important* for human medicine.

Highly Important

Those antimicrobials which meet either Criterion 1 or Criterion 2 are termed: *highly important* for human medicine.

Important

Those antimicrobials those which meet neither Criterion 1 nor Criterion 2 are termed: *important* for human medicine.

The list below is meant to show examples of members of each class of drugs, and is not meant to be inclusive of all drugs. Not all drugs listed in a given class have necessarily been proven safe and effective for the diseases listed.

Comments are included in the table when it is recognized that regional factors could affect the ranking; however, these comments are not meant to be exhaustive and other regional factors could be relevant in shifting an antimicrobial's importance. While countries or regions may choose to shift one drug, or class of drug, importance upwards (e.g., based on cost or availability); however, it is imperative that countries not elect to unilaterally move a

drug classification downwards. Only a WHO panel of experts are authorized to move drug classification in that direction.

In this 3rd revision of the WHO list, the following drugs and classes were shifted for the following reasons:

Over the last few years there have been dramatic increases in multi-resistant Gram negative infections both in the community and in hospitals. Therapy of many of these Gram negative infections (e.g. with multi-resistant *E. coli*) have become much more limited and agents such as colistin (a polymyxin) are now being used as often are no other alternatives. Thus classes of drugs active against Gram negatives such as phosphonic acid derivatives (e.g., fosfomycin), polymyxins (e.g., colistin) and monobactams (e.g., aztreonam) have been reclassified as "Critically Important".

In contrast, for Gram positive infections more antimicrobials have become available (e.g., lipopeptides, oxazolidinones and additional glycopeptides). Thus, streptogramins that were previously classified as Critically Important are now classified as "Highly Important" as there are more effective agents that cause less side effects now available to treat these infections. On the other hand, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals and the very serious consequences of treatment failures in such cases, this class was re-classified as being of highest priority in this revision of the List.

Tetracyclines are re-categorised now as "Highly Important". In the previous edition they were reclassified as "critically important" because tetracyclines are the main therapy for *Brucella* infections which are most often acquired by people from animals. However, there are many countries where *Brucella* infections have been eradicated from food animals. However, in areas of the world where *Brucella* species are still likely to be transmitted from food production animals, tetracyclines should continue to be classified as "critically important."

As sole therapy for certain conditions (e.g., endocarditis) and because cross resistance occurs, all aminoglycosides have been consolidated into the critically important category, including kanamycin and neomycin which were previously listed as highly important.

Lincosamides (e.g., clindamycin and lincomycin) have been moved to highly important because human infection may result from transmission of *Enterococcus* spp. and *Staphylococcus* aureus including MRSA from non-human sources.

Table 1. Listing and categorization of antimicrobials used in human medicine. Examples of veterinary use only drugs are listed at the end of each category for easy reference.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Aminoglycosides amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin sisomicin streptoduocin streptomycin tobramycin *Veterinary use only::* apramycin framycetin	Yes	Yes	(Criterion 1) Sole or limited therapy as part of treatment of enterococcal endocarditis and Multi-Drug Resistant (MDR) tuberculosis. (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources.
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR *Enterobacteriaceae*. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef *Veterinary use only:* cefovecin cefquinome ceftiofur	Yes	Yes	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children. Limited therapy for infections due to Multi-Drug Resistant *Enterobacteriaceae*, which are increasing in incidence worldwide. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.
Cyclic esters fosfomycin	Yes	Yes	(Criterion 1) Limited therapy for ESBL *E.coli* causing UTI. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Fluoro- and other quinolones	Yes	Yes	(Criterion 1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp. and MDR *Shigella* spp. infections. (Criterion 2) May result from transmission of *Campylobacter* spp. and Enterobacteriaceae including *E. coli* and *Salmonella* spp. from non-human sources.
cinoxacin ciprofloxacin enoxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin oxolinic acid pazufloxacin pefloxacin pipemidic acid piromidic acid prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin trovafloxacin *Veterinary use only:* danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin orbifloxacin			

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary use only:* Avoparcin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. And MRSA from non-human sources.
Glycylcyclines tigecycline	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR *Enterobacteriaceae*. Limited therapy for infections due to MRSA. (Criterion 2) May result from transmission of MRSA and *Enterobacteriaceae* from non-human sources.
Lipopeptides daptomycin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin *Veterinary use only:* gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin	Yes	Yes	(Criterion 1) Limited therapy for *Legionella*, *Campylobacter* and MDR *Salmonella* and *Shigella* infections. (Criterion 2) May result from transmission of *Campylobacter* spp. and *Salmonella* from non-human sources.
Monobactams aztreonam carumonam	Yes	Yes	(Criterion 1) Limited therapy for infections with MDR Gram negatives, especially with limited other options including for ESBLs. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Oxazolidinones linezolid	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin ampicillin azidocillin azlocillin bacampicillin carbenicillin carindacillin clometocillin epicillin hetacillin metampicillin meticillin mezlocillin penamecillin penicillin G (=benzylpenicillin) penicillin V (=phenoxymethylpenicillin) pheneticillin piperacillin pivampicillin propicillin sulbenicillin sultamicillin talampicillin temocillin ticarcillin *Veterinary use only:* penethamate hydroiodide	Yes	Yes	(Criterion 1) Limited therapy for syphilis (natural penicillins) *Listeria, Enterococcus* spp. *(aminopenicillins)* and MDR *Pseudomonas* spp. *(antipseudomonal)*. (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* including *E. coli* as well as *Pseudomonas aeruginosa* from non-human sources.
Polymyxins colistin polymyxin B	Yes	Yes	(Criterion 1) Limited therapy for infections with MDR *Enterobacteriaceae* (e.g. *Klebsiella* spp., *E. coli, Acinetobacter, Pseudomonas* spp.). (Criterion 2) May result from transmission of *Enterobacteriaceae* from non-human sources.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Rifamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	Yes	Yes	(Criterion 1) Limited therapy as part of treatment of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance. (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources and multi-drug resistant *Staphylococcus aureus* through the food chain.
Drugs used solely to treat tuberculosis or other mycobacterial diseases calcium aminosalicylate capreomycin cycloserine ethambutol ethionamide isoniazid morinamide para-aminosalicylic acid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	Yes	Yes	(Criterion 1) Limited therapy for tuberculosis and other *Mycobacterium* spp. disease and for many of these drugs, single drug therapy may select for resistance. (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Amdinopenicillins mecillinam pivmecillinam	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MDR *Shigella* spp. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Amphenicols chloramphenicol thiamphenicol *Veterinary use only:* florfenicol	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, Criterion 1 may be met: the class may represent one of the limited therapies for acute bacterial meningitis, typhoid and non-typhoid fever and respiratory infections. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* from non-human sources.
Cephalosporins (1st and 2nd generation) and cephamycins cefaclor cefacetrile cefadroxil cefaloridine cefalexin cefalotin cefamandole cefapirin cefatrizine cefazedone cefazolin cefbuperazone cefmetazole cefminox cefonicid ceforanide cefotetan cefotiam cefoxitin cefprozil cefradine cefroxadine ceftezole cefuroxime flomoxef loracarbef *Veterinary use only:* cefalonium	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Lincosamides clindamycin lincomycin *Veterinary use only:* pirlimycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus* including MRSA from non-human sources.
Penicillins (Antistaphylococcal) cloxacilllin dicloxacillin flucloxacillin oxacillin nafcillin	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for staphylococcal infections (*S. aureus*). (Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources.
Pleuromutilins retapamulin	No	Yes	(Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources.
Pseudomonic acids mupirocin	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for topical *Staphylococcus aureus* infections. (Criterion 2) May result from transmission of MRSA from non-human sources.
Riminofenazines clofazimine	Yes	No	(Criterion 1) Limited therapy for leprosy.
Steroid antibacterials fusidic acid	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MRSA. (Criterion 2) May result from transmission of MRSA from non-human sources.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Streptogramins quinupristin/dalfopristin pristinamycin *Veterinary use only:* virginiamycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources
Sulfonamides, Dihydrofolate reductase inhibitors and combinations brodimoprim iclaprim pyrimethamine sulfadiazine sulfadimethoxine sulfadimidine sulfafurazole (=sulfisoxazole) sulfaisodimidine sulfalene sulfamazone sulfamerazine sulfamethizole sulfamethoxazole sulfamethoxypyridazine sulfametomidine sulfametoxydiazine sulfametrole sulfamoxole sulfanilamide sulfaperin sulfaphenazole sulfapyridine sulfathiazole sulfathiourea tetroxoprim trimethoprim *Veterinary use only:* ormosulfathiazole phthalylsulfathiazole	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, systemic non-typhoidal salmonella infections and other infections. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Sulfones dapsone aldesulfone	Yes	No	(Criterion 1) Limited therapy for leprosy.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Tetracyclines chlortetracycline clomocycline demeclocycline doxycycline lymecycline metacycline minocycline penimepicycline rolitetracycline oxytetracycline tetracycline	Yes	^No	(Criterion 1) Limited therapy for infections due to *Brucella*, *Chlamydia* spp. and *Rickettsia* spp. (Criterion 2^) Transmission of *Brucella* spp. from non-human sources. ^Countries where human brucellosis is common should consider making tetracycline a critical antibiotic, as there is considerable concern regarding the availability of effective products where *Brucella spp*. are endemic

IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Aminocyclitols spectinomycin	No	No^	(Criterion 2^) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources. No demonstrated transmission from *E. coli to Gonococcus*
Cyclic polypeptides bacitracin	No	No	
Nitrofurantoins furazolidone nitrofurantoin nifurtoinol nitrofural *Veterinary use only:* furaltadone	No	No	
Nitroimidazoles metronidazole tinidazole ornidazole	No[#]	No	(Criterion 1[#]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for anaerobic infections including *C. difficile*.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

6.7 Prioritization within the Critically Important category

Given the mandate to prioritize agents within the *Critically Important* category, the Copenhagen panel (2007) focused on the two criteria developed by the Canberra panel (2005) to prioritize agents within the *critically important* category. As a result of this prioritization, the list was re-examined during the 1st AGISAR meeting (Copenhagen, 2009) and then further re-categorized during the Oslo (2011) meeting.

Focusing Criterion 1:

Sole therapy or one of few alternatives to treat serious human disease

- Application 1.1 – High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few alternatives to treat serious human disease.
- Application 1.2 – High frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance.

Explanation: In order to apply Criterion 1 in a focused manner, the panel developed two applications, both of which related to volume of antimicrobial usage. Increased volume of usage directly relates to development of resistance and therefore poses a greater threat to their utility as sole therapies. Furthermore, humans receiving antimicrobials for any indication have a greater susceptibility to acquiring infection by a foodborne pathogen resistant to those antimicrobial agents.

Focusing Criterion 2:

Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

- Application 2.1 – Greater degree of confidence that there are non-human sources that result in transmission of resistant bacteria (*Campylobacter* spp.), or their resistance genes, to humans (high for *Salmonella* spp., *Escherichia* coli and *Enterococcus* spp.).

Explanation: In order to apply Criterion 2 in a focused manner, the panel developed one application. Risk-management strategies are most urgently needed in situations where evidence suggests that transmission of resistant bacteria from non-human sources is already occurring, or has occurred previously.

Table 2. Prioritization of antimicrobials categorized as *Critically Important* in human medicine. Examples of veterinary use only drugs are listed at the end of each category for easy reference.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Aminoglycosides amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin sisomicin streptoduocin streptomycin tobramycin *Veterinary use only:* apramycin framycetin	No	No	Yes	(Application 2.1) Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources.
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef *Veterinary use only:* cefovecin cefquinome ceftiofur	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.
Cyclic esters fosfomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Fluoro- and other quinolones	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of *Campylobacter* spp. and Enterobacteriaceae including *E. coli* and *Salmonella* spp. from non-human sources
cinoxacin ciprofloxacin enoxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin oxolinic acid pazufloxacin pefloxacin pipemidic acid piromidic acid prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin trovafloxacin *Veterinary use only:* danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin orbifloxacin				

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary use only:* avoparcin	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of vancomycin resistant enterococcus (VRE) has occurred in past when avoparcin was used in food animals.
Glycylcyclines tigecycline	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Lipopeptides daptomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin *Veterinary use only:* gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of *Campylobacter* spp. from non-human sources.
Monobactams aztreonam carumonam	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Oxazolidinones linezolid	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin ampicillin azidocillin azlocillin bacampicillin carbenicillin carindacillin clometocillin epicillin hetacillin metampicillin meticillin mezlocillin penamecillin penicillin G (=benzylpenicillin) penicillin V (=phenoxymethylpenicillin) pheneticillin piperacillin pivampicillin propicillin sulbenicillin sultamicillin talampicillin temocillin ticarcillin *Veterinary use only:* penethamate hydroiodide	No[#]	Yes	Yes	(Application 1.1[#]) In certain geographic settings, application 1.1 may be met: there may be a high absolute number of people affected by all disease for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine. (Application 2.1) Transmission of *Enterococcus* spp. and *Enterobacteriaceae* (including *Salmonella spp* and *Escherichia coli*)
Polymyxins colistin polymyxin B	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Rifamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine.
Drugs used solely to treat tuberculosis or other mycobacterial diseases calcium aminosalicylate capreomycin cycloserine ethambutol ethionamide isoniazid morinamide para-aminosalicylic acid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of use in human medicine.

**This list does not necessarily include all drugs in a class used in human medicine; however, the major examples are included here*

6.8 Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (1.1, 1.2 and 2.1): Fluoroquinolones, 3rd and 4th generation cephalosporins, Macrolides, and Glycopeptides.

Fluoroquinolones are known to select for fluoroquinolone-resistant *Salmonella* spp. and *E.coli* in animals. At the same time, fluoroquinolones are one of few available therapies for serious *Salmonella* spp. and *E.coli* infections. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

3rd and 4th generation cephalosporins are known to select for cephalosporin-resistant *Salmonella* spp. and *E. coli* in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella and *E. coli* infections, particularly in children. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

Macrolides are known to select for macrolide-resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., especially *Campylobacter jejuni*, the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptides-resistant *Enterococcus* spp. in food animals (e.g., when avoparcin was used as a growth promoter, vancomycin resistant enterococcus (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals and the very serious consequences of treatment failures in such cases, this class was re-classified as being of highest priority in the 3rd revision of the List.

7 ANNEX 1: List of Participants

Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR – by WHO Regional Office

AFRO

Samuel KARIUKI
Centre for Microbiology Research,
KEMRI
Kenyatta Hospital Compound
PO Box 43640
Nairobi - 00100
KENYA
Tel: +254-202-718247
Fax: +254-202-711673
Mobile: +254-722-232467
Email: skariuki@kemri.org

Eric MITEMA
Faculty of Veterinary Medicine
Department of Public Health,
Pharmacology and Toxicology
University of Nairobi
P.O. Box 29053
Nairobi
KENYA
Tel: +254 20 631277
Fax: +254 2 631325
Email: esmitema@uonbi.ac.ke

AMRO

Paula J. FEDORKA CRAY
Research Leader Bacterial Epidemiology and Antimicrobial Resistance Research Unit
Richard Russell Research Center
905 College Station Rd
Athens, GA 30605
USA
Tel: +1 706 546-3685
Fax: +1 706 546-3066
Email: paula.cray@ars.usda.gov

Heriberto FERNÁNDEZ
Institute of Clinical Microbiology
Universidad Austral de Chile
Edificio de Ciencias Biomédicas 2° Piso
Campus Isla Teja
PO box 567
Valdivia
CHILE
Tel: +56 63 214377
Fax: +56 63 293300
Email: hfernand@uach.cl
Email: hfernandezjaramillo@gmail.com

Rebecca IRWIN
Veterinary Epidemiologist
Director, Antimicrobial Resistance Program (VM-05)
Laboratory for Foodborne Zoonoses,
Public Health Agency of Canada
R.R. # 6,
Guelph, Ontario - N1H 6J3
CANADA
Tel: +1 519 826-2183
Email: rebecca_irwin@phac-aspc.gc.ca

Scott A. MCEWEN
Professor & Graduate Coordinator
Department of Population Medicine
Ontario Veterinary College
University of Guelph
Guelph, Ontario - N1G 2W1
CANADA
Tel: +519-824-4120 ext 54751
Fax: +519-763-3117
Email: smcewen@uoguelph.ca

Patrick MCDERMOTT
Director
U.S. National Antimicrobial Resistance Monitoring System
Center for Veterinary Medicine
U.S. Food & Drug Administration
8401 Muirkirk Rd, Mod 2
Laurel, MD 20708
USA
Tel: +1 301-210-4213
Fax: +1 301-210-4298
Email: Patrick.mcdermott@fda.hhs.gov

Tom O'BRIEN
Co-Director
WHO Collaborating Centre for Surveillance of Antimicrobial Resistance
Brigham and Women's Hospital
Microbiology Laboratory
75 Francis Street
Boston, Massachusetts 02115
USA
Email: tobrien@rics.bwh.harvard.edu

Richard REID-SMITH
Veterinary Epidemiologist
Canadian Integrated Program for Antimicrobial Resistance Surveillance
Antimicrobial Resistance Surveillance Unit
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada
& Adjunct Professor
Depts. of Population Medicine & Pathobiology
University of Guelph
Public Health Agency of Canada
160 Research Lane - Unit 103
Guelph, Ontario - N1G 5B2
CANADA
Tel: +1 519 826-2203
Fax: +1 519 826-2255
Email: richard_reid-smith@phac-aspc.gc.ca

H. Morgan SCOTT
Professor, Epidemiology
Department of Diagnostic Medicine / Pathobiology
332 Coles Hall, 1600 Denison Avenue
College of Veterinary Medicine, Kansas State University
Manhattan, Kansas, 66506-5705
USA
Tel: +1-785-532-4602
Fax: +1-785-532-4851
Email: hmscott@vet.k-state.edu

Caroline SMITH DEWAAL
Director
Food Safety Program
Center for Science in the Public Interest (CSPI)
1875 Connecticut Ave. NW Suite 300
Washington, D.C. 20009
USA
Tel: +1 202 777 8366
Fax: +1 202 265 4954
Email: cdewaal@cspinet.org

John STELLING
Co-Director
WHO Collaborating Centre for Surveillance of Antimicrobial Resistance
Brigham and Women's Hospital
Microbiology Laboratory
75 Francis Street
Boston, Massachusetts 02115
USA
Email: jstelling@whonet.org

EMRO

Hanan BALKHY
MD. MMed. FAAP. CIC.
Director WHO Collaborating Center for Infection Control
Director, GCC Center for Infection Control
Executive Director, Infection Prevention and Control Department- 2134
King Saud Bin Abdulaziz University for Health Sciences
P.O.Box 22490
Riyadh 11426
KINGDOM OF SAUDI ARABIA
Tel: +96612520088-43720/13250
Fax: +96612520772
Email: balkhyh@ngha.med.sa
Email: balkhyh@hotmail.com (preferred)

EURO

Jacques ACAR
22, Rue Emeriau
75015 Paris
FRANCE
Email: jfacar7@hotmail.com / jfacar7@wanadoo.fr

Kari GRAVE
Norwegian School of Veterinary Science
P.O. Box 8146 Dep.
N-0033 Oslo
NORWAY
Tel: +47 22 96 49 88
Mobile: +47 95 81 54 48
Fax: +47 22 96 47 52
Email: kari.grave@veths.no

Christina GREKO
Strama VL
Dept of Animal Health and Antimicrobial Strategies
National Veterinary Institute (SVA)
SE-751 89 Uppsala
SWEDEN
Tel: +46 18 67 43 47,
Mobile: +46 705 46 37 43
Email: christina.greko@sva.se

Rene Sjøgren HENDRIKSEN
National Food Institute "DTU-Food"
Technical University of Denmark
Dept. of Microbiology and Risk Assessment.
Research group on
Antimicrobial Resistance and Molecular Epidemiology
Kemitorvet, Building 204ST
DK-2800 Kgs. Lyngby
DENMARK
Tel: +45 72346288
Mobile: +45 22450763
Fax: +45 72346001
Email: rshe@food.dtu.dk

Gérard MOULIN
Deputy Director of the National Agency for Veterinary medicinal products
AFSSA / ANMV
La Haute Marche
BP 90203
35302 FOUGERES
FRANCE
Tel: +33 2 99 94 78 78
Fax: +33 2 99 94 78 99
Email: g.moulin@afssa.fr

Hege SALVESEN BLIX
WHO Collaborating Centre for Drug Statistic Methodology
Norwegian Institute of Public Health
P.O. Box 4404 Nydalen
Marcus Thranes gt.6
N-0403 Oslo
NORWAY
Tel: +47 21078163
Email: hege.salvesen.blix@fhi.no

WPRO

Peter COLLIGNON
Infectious Diseases Physician and Microbiologist
Director Infectious Diseases Unit and Microbiology Department
The Canberra Hospital
Professor, School of Clinical Medicine
Australian National University
PO Box 11
Woden ACT. 2607
AUSTRALIA
Tel: +61 2 6244 2105
Fax: +61 2 6244 4646
Email: peter.collignon@act.gov.au

Hyo-Sun KWAK
Deputy Director, Food Microbiology Division
Korea Food & Drug Administration
194 Tongilro, Eunpyeong-gu, Seoul 122-704
REPUBLIC OF KOREA
Tel: +822-380-1682
Email: kwakhyos@korea.kr

Haruo WATANABE
Deputy Director General
National Institute of Infectious Diseases (NIID)
1-23-1 Toyama, Shinjuku-ku
Tokyo 162-8640
JAPAN
Tel: +81-3-5285-1337
Fax: +81-3-5285-1193
Email: haruwata@nih.go.jp

Gun-Jo WOO
Professor, Department of Food Bioscience & Technology
College of Life Science & Biotechnology
Korea University
Anam-Dong, Seongbuk-Gu, Seoul 136-701
REPUBLIC OF KOREA
Tel: +82-2-3290-3021
Email: visionkorea@korea.ac.kr

FAO REPRESENTATIVE

Patrick OTTO
Animal Health Officer (Veterinary Public Health)
Food and Agriculture Organisation of the United Nations
Viale delle Terme di Caracalla
00153 Rome
ITALY
Tel: +39 06 570 53088
Email: patrick.otto@fao.org

OIE REPRESENTATIVE

Elisabeth ERLACHER-VINDEL
Adjointe au Chef du Service Scientifique et Technique
Deputy Head of Scientific and Technical Department
Jefe adjunta del Departamento Cientifico y Técnico
Organisation Mondiale de la Santé Animale
World Organisation for Animal Health
12, rue de Prony
75017 Paris
FRANCE
Email: e.erlacher-vindel@oie.int
Tel: +33 -1 44 15 19 08 (standard: +33 -1 44 15 18 88)
Fax: +33 -1 42 67 09 87
Website: www.oie.int

EFSA REPRESENTATIVE

Stef BRONZWAER
Deputy Head of Scientific Cooperation Unit
European Food Safety Authority (EFSA)
Largo N. Palli 5/A
43100 Parma
ITALY
Tel: +39.0521.036.669
Fax: +39.0521.036.0.669
www.efsa.europa.eu
Email: stef.bronzwaer@efsa.europa.eu

RESOURCE ADVISERS

Yvonne AGERSØ
Senior scientist
Department of Microbiology and Risk Assessment
DTU Food
Technical University of Denmark
National Food Institute
Kemitorvet
Building 204st
2800 Lyngby
DENMARK
Tel: +45 35886273
Email: yvoa@food.dtu.dk
www.food.dtu.dk

Antoine ANDREMONT
Laboratoire de bactériologie
Hôpital Bichat Claude-Bernard
46, rue Henri Huchard
75018 Paris
FRANCE
Tel: +33 (0)1 40 25 85 00
Fax: +33 (0)1 40 25 85 81
Email: antoine.andremont@bch.aphp.fr

Sandrine BLANCHEMANCHE
Director
Met@ Risk - Food Risk Analysis Methodologies Unit
Institut national de la recherche agronomique - Paris (INRA)
16, rue Claude Bernard
75231 Paris Cedex 05
FRANCE
Tel : +33 1 44 08 86 12
Fax : +33 1 44 08 72 76
Email : sandrine.blanchemanche@paris.inra.fr

Hidemasa IZUMIYA
Chief, Laboratory of Unit II (Enteric Infection)
Department of Bacteriology I
National Institute of Infectious Diseases
Toyama 1-23-1, Shinjuku-ku
Tokyo 162-8640
JAPAN
Tel: +81-3-5285-1111
Fax: +81-3-5285-1163
Email: izumiya@nih.go.jp

Beth E. KARP
DVM, MPH, DACVPM
Senior Veterinary Epidemiologist
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Rd, MS-D63
Atlanta, GA 30333
USA
Tel: +1 404 639-5097
Email:bkarp@cdc.gov

Ghassan M. MATAR
Professor
Dept. of Microbiology & Immunology
Faculty of Medicine
American University of Beirut
Beirut
LEBANON
Email: gmatar@aub.edu.lb

Jaap A. WAGENAAR
DVM PhD
Dept Infectious Diseases and Immunology
Faculty of Veterinary Medicine
Utrecht University
Central Veterinary Institute
Lelystad
NETHERLANDS
Email: j.wagenaar@uu.nl

WHO SECRETARIAT

Awa AIDARA-KANE
Scientist
Department of Food Safety, Zoonoses and Foodborne Diseases
Health Security and Environment
World Health Organization
20, Avenue Appia
1211, Geneva 27
SWITZERLAND
Tel: +41 22 791 24 03
Fax: +41 22 791 48 07
Email: aidarakanea@who.int

Hilde KRUSE
World Health Organization
Europe Regional Office
Division of Health Programmes
Non-communicable Diseases and Environment
Rome
ITALY
Tel: +39 064877525
Email: kruseh@who.int

Danilo LO FO WONG
Scientist
Department of Food Safety and Zoonoses
World Health Organization
20, avenue Appia
CH-1211 Geneva 27
SWITZERLAND
Tel: +41 22 791 38.82
Email: lofowongd@who.int

Enrique PEREZ-GUTIERREZ
Health Surveillance, Disease Prevention and Control (HSD)
VPH/PANAFTOSA
Tel: 55-21-36619030
Fax: 55-21-36619027
Email: pereze@pan.ops-oms.org

Krisantha WEERASURIYA
World Health Organization
Health Systems and Services
Essential Medicines & Pharmaceutical Policies
Rational use of medicines
Geneva
SWITZERLAND
Tel: +41 22 791.23.57
Email: weerasuriyak@who.int

ANNEX 2: Agenda

Time	Tuesday 14 June 2011	Speaker
10.00 – 10.30	**SESSION I: Opening** • Welcome and opening remarks	Hanne Strøm, WHO Collaborating Centre for Drug Statistic Methodology
		Camilla Stoltenberg, Norwegian Institute of Public Health
	• Election of Chairperson • Appointment of Rapporteur • Adoption of the agenda	Awa Aidara-Kane
10.30 – 11.00	**SESSION II - WHO Introduction** • Update on WHO AMR activities - objectives and expected outcome of the meeting	Awa Aidara-Kane
	Updates from FAO and OIE • FAO • OIE	Patrick Otto Elisabeth Erlarcher Vindel
11.00 – 13.00	**SESSION III: Management of Antimicrobial Resistance from a Food Safety Perspective** **International Initiatives:** • Codex Guidelines on Risk Analysis of Foodborne Antimicrobial Resistance	Rebecca Irwin
	Regional Initiatives: • EFSA AMR Risk Assessment in Zoonotic and Foodborne Bacteria • Tackling AMR from a food safety perspective in Europe	Stef Bronzwaer Hilde Kruse

13.00 – 14.00	Lunch	
14.00 – 15.30	**SESSION III (cont): Management of Antimicrobial Resistance from a Food Safety Perspective** **National initiatives :** • Denmark • The Netherlands • Lebanon	Yvonne Agersø Jaap Wagenaar Ghassan Matar
15.30 – 16.00	Coffee break	
16.00 – 18.00	**SESSION IV: Sub-committee (SC) Working Groups** • Discuss ongoing /future activities • Discuss data integration across consumption and resistance • Discuss communication tools and strategies	Usage Monitoring Antimicrobial Resistance Monitoring Country Pilot projects & Capacity Building Data Management &Software Development

Time	**Wednesday , 15 June 2011**	
08.30 – 10.00	**Session IV (cont): SC Working Groups** • Discuss ongoing /future activities • Discuss data integration across consumption and resistance • Discuss communication tools and strategies	Usage Monitoring Antimicrobial Resistance Monitoring Country Pilot projects & Capacity Building Data Management &Software Development
10.00 – 10.30	Coffee break	

10.30 – 11.30	**Session IV: Plenary (cont): Reports from WGs** *AMR Monitoring* • International Harmonization of AMR Monitoring Systems - Recent developments • AGISAR Guidance Document on AMR Monitoring: Report from the SC Working Group and discussion	Patrick McDermott
11.30 – 12.30	**Session IV: Plenary (cont): Reports from WGs** *Country Pilot Projects & Focussed Research Projects* • FAO/WHO Kenya Project • Latin American Projects Report from the SC WG and discussion	Sam Kariuki Enrique Perez
12.30 – 13.30	Lunch	
13.30 – 14.30	**Session IV: Plenary (cont): Reports from WGs** *Usage Monitoring* • AGISAR Guidance Document on Usage Monitoring : Report from the SC WG and discussion	Kari Grave
14.30 – 15.30	**Session V: Plenary: Reports from WGs** *Data Management &Software Development* • Update on AGISAR Software Development • Risk Communication- Communication tools and strategies Report from the SC WG and discussion	John Stelling Caroline Smith De Waal

15.30 – 16.00	Coffee break	
16.00 – 17.30	Report finalization and adoption Conclusions -Next steps	
19.30	Diner provided by the WHO Collaborating Centre for Drug Statistic Methodology, Norwegian Institute of Public Health	

Time	**Thursday 16 June 2010**	
08.30 – 10.00	**Session I: Presentations** WHO list of Critically Important Antimicrobials for Human Medicine • Rationale for a Human CIA list • Methodology used to establish the list in 2005 • First revision 2007 • Second revision 2009	Peter Collignon
	Essential Medicines and Rational Use of Antimicrobials	Krisantha Weerasuriya
	Use of Top 3 CIA (fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides) in food-producing animals and public health consequences	H. Morgan Scott
	Infection control initiatives in Saudi Arabia and the Gulf Region	Hanan Balkhy
	Dissemination of CTX-M resistance in West Africa	Antoine Andremont
10.00 – 10.30	Coffee break	

11.00 – 12.30	**Session II: Working Groups** **WG 1:** Revision of the CIA list (Considering: (1) -Availability of new drugs (if any) and (2) antimicrobial resistance threats in the food chain **WG 2:** Use of the CIA list in managing antimicrobial resistance from a food safety perspective	
12.30 – 13.30	Lunch	
13.30 – 14.30	**Session III: WG Reports to Plenary** • Report from WG1 • Report from WG2	
14.30 – 15.30	**Session II (cont): Working Groups (cd)** **WG 1:** Revision of the CIA list (Considering: (1) -Availability of new drugs (if any) and (2) antimicrobial resistance threats in the food chain **WG 2:** Use of the CIA list in managing antimicrobial resistance from a food safety perspective	
15.30 – 16.00	Coffee break	
16.00 – 18.00	**Session III (cont): WG Reports to Plenary (cd)** • Final report from WG1 • Final report from WG2 Finalization and adoption of the CIA report Conclusions-Next steps	

Time	Friday 17June 2010	
09.00 – 10.30	**Working Groups** **Group 1:** Focus Group Discussion: Exploring possibilities to better share food safety data and information **Group 2:** Comments on the list of substances for evaluation at the 75th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)- Public Health and AMR issues	 Danilo Lo Fo Wong Sandrine Blanchemanche Awa Aidara-Kane
10.30 – 11.00	Coffee break	
11.00 – 12.30	Working Groups **Group 1:** Comments on the list of substances for evaluation at the 75th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)- Public Health and AMR issues **Group 2:** Focus Group Discussion: Exploring possibilities to better share food safety data and information	 Awa Aidara-Kane Danilo Lo Fo Wong Sandrine Blanchemanche
12.30 – 13.30	End of the Meeting	

ISBN 978 92 4 150401 0

WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

http://www.who.int/foodborne_disease/resistance/agisar/en/