REPORT
of the Regional Expert Workshop on
Harmonization and Standardization of
Antimicrobial Resistance Monitoring in the Asia-Pacific Region

Bangkok, 14-15 May 2013
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REPORT of
The Regional Expert Workshop on
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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
REGIONAL OFFICE FOR ASIA AND THE PACIFIC
Bangkok, 2013
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BACKGROUND

Antimicrobial resistance (AMR) is a growing global threat across drug classes and around the world. Although much of the evolving antimicrobial resistance can be attributed to (mis-)use of antimicrobials in humans, research by international scientific bodies supports the conclusion that the overuse of drugs in food animal production is a threat for continued availability of effective treatment of human and animal diseases.

Little systematic research and analysis on the use of antimicrobials (AMU) and AMR in micro-organisms associated with food animals is available for the Asia-Pacific region while individual studies on AMR in food borne pathogens such as Salmonella spp. and Campylobacter spp. suggest fairly widespread AMR to commonly used antimicrobials.

Against this background, APHCA delegates, at the 36th Session held in Negombo, Sri Lanka, recognised that action in each member country was needed to underpin regional and global AMR risk reduction measures. Delegates however also noted that AMR can only be tackled through a collective effort requiring a degree of harmonization and standardization of approach.

To foster a process of harmonization and standardization for the management of AMR, FAO is convening an Expert Workshop, bringing together national and international experts to exchange information and deliberate on ways forward.

The workshop has the following objectives:

- Exchange information about various protocols for AMU and AMR monitoring / surveillance used in countries of the Asia Pacific region (participants to provide brief report on protocol(s) / approach(es) applied in their country);
- Review approaches for monitoring of AMU in livestock that allows identification (and quantification) of risk factors for the development and occurrence of AMR;
- Review approaches to antimicrobial susceptibility testing (antimicrobial agents, test ranges, interpretive criteria, etc);
- Familiarize participants with methods for AMR risk assessment and risk management;
- Based on the OIE guidelines for AMR surveillance develop proposal for standardized AMR monitoring protocols;
- Identify country-specific support requirements to implement / move towards implementation of the above proposed protocols.
MODULE OUTLINES

THE GLOBAL PROBLEM OF AMR AND CRITICAL ANTIMICROBIALS FOR USE IN HUMANS (J. WAGENAAR)

Objective: To provide the participants with an overview of the discovery and development of antimicrobials over time and the development and trends of AMR parallel to the use of antimicrobials. The problems in humans and animals due to resistant microorganisms will be discussed as well as the relation between human and animal domain. Persistence and containment of resistance from a practical perspective will be covered.

Content: Relation usage-resistance; co-resistance; transfer of resistance (genes or microorganisms) between animals and humans; burden of resistance in animals and humans; persistence of resistance in the presence and absence of antimicrobials; geographical containment of resistance.

Key Points to be covered: Use of antimicrobials will induce resistance and human and animal domains are hardly separated from resistance point of view.

BASIC MICROBIOLOGY TO SET THE STAGE FOR AMR MONITORING AND RISK ASSESSMENT (S. SIMJEE)

Objective: To provide participants with an overview of key food-borne and commensal bacteria of importance to human health. Additionally the module will cover antibiotics, their mode of action and the mechanisms of antibiotic resistance. Genetics of resistance gene transfer will also be covered. This should help set the scene for understanding various aspects of risk assessment.

Content: Basic microbiology so no reference material will be required.

Key points covered:

- Fundamental microbiology
- Antimicrobial mechanism of action
- Antimicrobial mechanism of resistance
- Genetics of resistance

OIE ACTIVITIES ON AMR AND RECOMMENDATIONS OF THE GLOBAL CONFERENCE ON THE RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS FOR ANIMALS (H.T. MYINT)

Objective: To provide participants with an overview of OIE activities on AMR, inform them on the recommendations of the OIE Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals and follow up actions.

Content: OIE standards on terrestrial and aquatic animals, OIE list of Antimicrobial Agents of Veterinary Importance, Questionnaire an results on monitoring of the quantities of antimicrobial agents used in animals in OIE Member Countries, recommendations of the OIE Global Conference, follow up actions.

Key Points to be covered:

- Updates on OIE codes and standards and the OIE list of Antimicrobial Agents of Veterinary Importance
- Questionnaire and results
- Recommendations of the OIE Global Conference and follow up actions
AMU AND AMR MONITORING FOR AMR RISK ASSESSMENT AND RISK MANAGEMENT (T. Shryock)

Objective: To provide participants with an overview of risk assessment processes, data inputs and application for risk management intervention selection in order to facilitate implementation.

Content: The OIE Terrestrial Code Risk Analysis document, the Vose et al., 2003 paper and the Codex GL77 will be referenced, as will national regulatory risk assessment guidelines from the US and Australia.

Key points to be covered:
- Prerequisites for risk assessment
- OIE vs. Codex risk analysis approaches
- Practical considerations for implementation
- Where to begin?
- Next steps

APPROACHES TO AMU AND AMR MONITORING / SURVEILLANCE AND THEIR LIMITATIONS (D. Peiffer)

Objective: To provide participants with an introduction to methods for monitoring / surveillance of AMU and AMR

Content: Complexity of livestock production and food systems; linking risk assessment and monitoring/surveillance; bias and error in surveillance; surveillance/monitoring approaches

Key Points to be covered:
- Production/food system characteristics
- Drivers of AMU and AMR
- Risk and surveillance programme design
- Sources of bias
- Surveillance and monitoring approaches

ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST) WITH LIMITED RESOURCES (S. Simjee)

Objective: To provide an understanding of the key methods currently approved for AST. Help participants understand how best to perform AST with limited resources. The session will wrap up with methods currently available to interpret AST data and the need for harmonization for data comparison between regions.

Content: The CLSI M31, M37 and X08-R documents and the Franklin et al (2001) OIE paper will be referenced throughout the presentation.

Key points covered:
- AST Methods
- AST data interpretation
- The need for harmonization

RESPONSIBLE USE / CLINICAL PRACTICE GUIDELINES (T. Shryock)

Objective: To provide participants with an overview of Responsible Use Guidelines from WHO, OIE and Codex that describe stakeholder responsibilities and to provide Clinical Practice guidelines consistent with the World
Veterinary Association and regional / country veterinary medical organizations. The guidelines provide a roadmap to appropriate antimicrobial product use and can be used to change behaviors of those who administer antimicrobial products to animals.

**Content:** The WHO, OIE and Codex Responsible Use guidelines will be referenced, as will WVA and other veterinary practice guidelines, with supplemental documents also provided.

**Key Points to be covered:**
- Common themes among the documents for stakeholder responsibilities
- Clinical practice guidelines – consensus principles outlined
- Practical considerations for implementation
- Next steps
The global problem of AMR and critical antimicrobials for use in humans

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Outline
- Antimicrobial resistance: the problem
- Impact of veterinary use
  - MRSA
  - ESBLs
- What can we do to control increasing resistance
- The future and the way forward

Development of antimicrobials

Resistance
Consequence of use:
- Resistance to penicillin 1947
- Resistance to methicillin 1960 (3 months after introduction)
Presence of resistance

- Resistance genes are naturally present
  - Selection and transfer
  - Mobile elements (e.g. plasmids, transposons) or chromosomal
- 4 mechanisms of resistance (Dr. Simjee)
- Co-resistance!! (chloramphenicol resistance still present)

Selection and spread of resistance

- Exposure to antimicrobial
  - Selection
  - Spread
- Susceptible population
  - Resistant clones
  - Outbreak

Antimicrobials:
the more you use, the faster you lose
regardless if the use is in animals or in humans

Humans are just another type of animal….

Bacteria may transfer between animals to humans

- Pathogens:
  - Salmonella
  - Listeria
- Commensals (gut-flora = reservoir of resistance genes and transfer of resistance genes)
  - E. coli

Human, animal and environmental microbial compartments are not separated

Antimicrobial resistant microorganisms (and genes!) can transfer between compartments
Problem for public health

- Public Health threat: the emergence and spread of antibiotic resistance
- Use and misuse of antibiotics by individuals: threat to others
- Antibiotic resistance: increased health-care costs, failed treatments, and deaths.

Problem for animal health

- Resistance in animal pathogens?
  - Treatment of E. coli in poultry?
  - Treatment of respiratory pathogens?

Antimicrobial resistance: some considerations

- Widespread use of antimicrobials in livestock production …not only for therapeutic purposes
- Same classes of antimicrobials in humans and animals
- Few new antimicrobials in the pipeline
- Globalization (food trade, travel): need for international action
- Spread of resistant organisms (and genes!) through environment and food

Use of antibiotics in animals

- Therapeutic use: to treat sick animals
- Prophylactic use: to prevent infection in animals
- Meta-phylactic use: to treat preventively when spread is likely
- Growth promoters:
  - To improve feed utilization, production (economics!): antimicrobials used in subtherapeutic concentrations
  - Control of chronic diseases in intensively-reared animals
- More than 50% of all antimicrobials are used non-therapeutically in animal husbandry

2 examples

- MRSA (Methicillin Resistant Staphylococcus aureus)
- ESBL (Extended Spectrum Beta Lactamase producing bacteria)

LA-MRSA

- Dominated by ST398 (EU, US); ST9 (Asia)
- Recently introduced (‘invented’ in NL) 2005
- No problem for animal health but exposed humans may become carrier
- Health risks for humans and increased costs for health care
- In the Netherlands: strict infection control in hospitals (virtually no MRSA)
- Farmers experienced problems by themselves!!

Science (329), 27 August 2010
Prevalence MRSA veal farms: 88%
People living at veal farms on average 16%
Farmers: 33%
Family members: 8%

Prevalence MRSA on pig farms: >70%
People living on pig farms on average 14%
Farmers: 49%
Family members: 3%

ESBL Problem
- Enzymes in Gram-negative bacteria (E. coli, Klebsiella)
- ESBLs are resistant to all beta-lactams (penicillines and cephalosporines) and usually to many other classes of antimicrobials
- Increasing prevalence of ESBLs in human infections (general population and health care facilities)
- Rapid spread of resistance (genes on plasmids)
- The diversity of genes is huge!!

ESBL results from the Netherlands
- Almost all broilers are carrier of ESBLs in the gut.
  Most poultry meat is contaminated (>90%)
- About 40% of the pig farms is positive
  - Pork ± 15% contamination
- 50% of batches of veal calves are positive at slaughter
- 20% of clinical isolates from humans are genetically indistinguishable from poultry isolates

Changes needed
- How to change the farmer/veterinarian?
- How to change the husbandry system?
- What are the drivers behind these changes?
  - Economics
  - Media attention (with political consequences)
  - Farmers experience problems themselves

Future threats, predictions….
- Predicting outbreaks and new introductions of infectious diseases and antimicrobial resistance is difficult
Global distribution of relative risk of an EID event

Carbapenemases e.g. NDM-1: New Delhi Metallo-beta-lactamase 1

Way forward

- "More than 50% of all antimicrobials are used non-therapeutically in animal husbandry"
- Need for better control over use of antibiotics in husbandry (reduction!!): changes in the production system
- Keep animal and human antimicrobials separated (critically important antimicrobials for human medicine)
- Joined forces between WHO-FAO-OIE
- Active surveillance of evolution of microbes and resistance trends
- It is a global problem and all countries have their responsibility
- Development of new agents

Critically important antimicrobials for human medicine

- Improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine, is an important step towards preserving the benefits of antimicrobials for people. The World Health Organization (WHO) has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine.
- Collaboration between WHO, OIE and FAO!

For the near future…

- There is an urgency for action.
- Awareness at farmer/veterinarian and policy level.
- How to get it prioritized?
- Provide decision makers with data on usage and resistance

Don’t say:

- it all comes from abroad…..
  - Local policy is effective!!
- A big proportion of the problem comes from humans, they have to do something…..
  - that is true but it will not reduce our responsibility in animal production sector
Introduction to Microbiology, Antibiotics and Antibiotic Resistance

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APHCA AMR Expert Workshop
Bangkok, Sukosol Hotel, 14 to 15 May 2013

From Food Animal to MIC Data

Identification of Bacterial Cells by:
- Gram stain
- Biochemical reactions
- Serotyping
- Molecular banding
- Other

Gram stain

1844 Danish bacteriologist, Hans Christian Gram, devised method to stain and visualize bacteria
G+ and G- Bacteria

Cell Wall Architecture
Staining differences are explained by cell wall differences

Gram-negative cell wall
Gram-positive cell wall

Typing Methods: Biotyping
Speciation using biochemical testing

Cost:
- Commonly used API strips ~ £180 for a pack of 25
- Additional costs of around £12-£25 for reagents
- Additionally labour intensive (5 mins per strip)

DNA Sequencing confirmation
PCR of 16S rRNA subunit followed by DNA sequencing

Cost:
- Market cost around £95 for one isolate for region between 1 and 750bp

MALDI-TOF Biotyper System – Cost: market cost around £8 per isolate

Which Bacteria?
- Salmonella
- E. coli
- Campylobacter
- Enterococcus

Animal pathogenic bacteria that are targeted by the antibiotic are not the issue

E. coli O157:H7
- E. coli usually commensal; indicator organism
- Enterohemorrhagic (EHEC) serotype O157:H7 toxin causes hemorrhagic colitis and hemolytic uremic syndrome
- Not treated with antibiotics because that will kill the bacteria and release more toxin

Nontyphoidal Salmonella enterica
- Gram-negative pathogen; high morbidity, and some mortality
- Treatment options include fluoroquinolones, 3rd generation cephalosporins, etc.
- Multi-drug resistance e.g. ACSSuT and others
Campylobacter jejuni
• Gram-negative pathogen; high morbidity but low mortality
• Treatment options include: Fluoroquinolones (empiric), macrolides (diagnosed), etc.
• Not multi-drug resistant

Enterococcus
• Gram-positive bacterium, usually commensal; indicator organism for resistance genes
• Does not cause a true foodborne disease
• Nosocomial infections: UTI, intra-abdominal, pelvic, and soft tissue infections, bacteremia, endocarditis
• Treatment options: vancomycin, streptogramins, ampicillin-gentamicin, oxazolidinones, etc.

Sample Collection
If food animal samples then need to consider collection point
Most prevalent Salmonella serotypes in poultry by sampling status, 1997-2010
(Paula Cray, USDA, 2011)

Sample Origins
If the bacterial isolates will undergo susceptibility testing with the goal of using the data for risk assessment then the samples must originate from appropriate sources to provide data for the relevant steps of the risk assessment
• Release
  Samples should come from the farm
• Exposure
  Samples should come from slaughter houses or retail meat
• Consequence
  Samples should come from humans, ideally pre-treatment samples

Bacterial Storage
Bacterial Freezing Kit allow for a simple and convenient method for preserving bacteria directly from culture. Each vial contains sterile 3 mm glass beads and 250 µl 30% glycerol. Simply add 250 µl of culture broth with actively growing cells, mix, label and freeze. These tubes can be used for any temperature storage, though ultralow and cryogenic temperatures are most effective for long-term viability of bacteria.
Commercial cost : £125/100 ready made tube, cheaper to make in-house

Antibiotics
Major Classes of Antibiotics (cross-resistance)
• β-lactams (Penicillins and cephalosporins)
  amoxicillin, ceftriaxone; ceftiofur
• Macrolides and Lincosamides
  erythromycin; tylosin, tilmicosin, lincomycin
• Glycopeptides
  vancomycin, teicoplanin; avoparcin
• Aminoglycosides
  gentamicin; neomycin, apramycin
• Fluoroquinolones
  ciprofloxacin; enrofloxacin
• Tetracyclines
  doxycycline, tetracycline; oxytetracycline
• Sulfonamides
  sulfamethoxazole; sulfonamide + trimethoprim
• Streptogramins
  quinupristin/dalfopristin; virginiamycin
• Polypeptides
  bacitracin
• Orthosomycin
  avilamycin, evernimicin
• Polyether Ionophores
  monensin, narasin

Antibiotic Targets

## 4 Mechanisms of Action

### 4 Mechanisms of Resistance

- **Antibiotic inactivation**
  - Beta-lactams, Aminoglycosides, Chloramphenicol, Streptogramins

- **Alteration of target enzyme**
  - Sulfonamides, Fluoroquinolones

- **Alteration of target binding site**
  - Streptomycin, Erythromycin

- **Reduced cellular uptake; active efflux**
  - Tetracyclines, Macrolides, Fluoroquinolones, Phenics, B-lactams

## New Strain Development

New traits *e.g.* antibiotic resistance or virulence are acquired by:

- **Chromosomal mutation:**
  - Results in vertical transfer from parent to daughter cell

- **Mobile DNA:**
  - Plasmids, Transposons or Integrons
  - Results in both vertical and horizontal transfer
  - Horizontal transfer = transfer between bacteria of same species, same genus or different genus

## Gene Transfer

1. Transformation
2. Conjugation
3. Transduction

## Antibiotic Resistance Cycle (co-selection)

- Antibiotic kills susceptible bacteria – resistant survive
- Resistant bacterial population grows by cell division
- Antibiotic resistant bacteria in environment or host
- Resistance gene acquisition (on a plasmid)
- Resistant bacteria selection by exposure to antibiotic
- Susceptible bacteria are present with resistant bacteria...until

## Why Targeted Spectrum First Line?

Targeted spectrum act predominantly on one category

- **Gram negative**
- **Gram positive**

Broad spectrum act on both

## Questions?
OIE ACTIVITIES ON AMR AND RECOMMENDATIONS OF THE ‘GLOBAL CONFERENCE ON THE RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS FOR ANIMALS’

H.T. Myint

Contents
- OIE activities on prudent and responsible use of antimicrobial agents
- OIE list of Antimicrobial Agents of Veterinary Importance
- Questionnaire and results on monitoring of the quantities of antimicrobial agents used in animals in OIE Member Countries
- Recommendations of the OIE Global Conference
- Ongoing and future global collaboration

OIE Global Mandate: “to improve animal health veterinary public health and animal welfare world-wide”

Actions of the OIE
- Reinforcement of good governance of Veterinary Services for better control in registration, import, distribution and on-farm use of antimicrobials
- Develop and update standards for the containment of antimicrobial resistance & the responsible and prudent use of antimicrobial agents
- Encourage international coordination and solidarity programmes
- Support of capacity building
- Condemning the marketing and use of fake products

Responsible and Prudent Use of Antimicrobial Agents
- In accordance with its mandate, OIE considers the use of antimicrobial agents in food producing animals as a key issue for human health, animal health and animal welfare
- Since a decade, the OIE has been working actively on this issue

OIE Standard and Guidelines
- Section – 6: Veterinary Public Health
  - Chapter 6.6. Introduction to the recommendations for controlling antimicrobial resistance
  - Chapter 6.7. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes
  - Chapter 6.8. Monitoring of the quantities and usage patterns of antimicrobial agents used in food producing animals
  - Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine
  - Chapter 6.10. Risk assessment for antimicrobial resistance arising from the use of antimicrobial agents in animals

http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/
Chapter 6.1. Introduction to the recommendations for controlling antimicrobial resistance arising from the use of antimicrobial agents in aquatic animals (under development)

Chapter 6.2. Introduction to the recommendations

Chapter 6.3. Principles for responsible and prudent use of antimicrobial agents in veterinary medicine

Chapter 6.4. Monitoring of the quantities and usage patterns of antimicrobial agents in aquatic animals

Chapter 6.5. Development and harmonisation of national antimicrobial resistance surveillance & monitoring programmes for aquatic animals

Chapter 6.6. Risk assessment for antimicrobial resistance arising from the use of antimicrobial agents in aquatic animals

Chapter 6.7. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes

Chapter 6.8. Monitoring of the quantities and usage patterns of antimicrobials agents in food producing animal

Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine

Chapter 6.10. Risk assessment for antimicrobial resistance arising from the use of antimicrobial agents in animals

Chapter 6.x. Risk assessment for antimicrobial resistance arising from the use of antimicrobial agents in food producing animal

Part 3: General Guidelines:

3.1. Laboratory methodologies for bacterial antimicrobial susceptibility testing

http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/

Communication/Training

• Publications
• International and regional conferences
• Regional training for OIE National Focal Points on veterinary products

OIE Expertise

• Network of 236 OIE Reference Laboratories and 41 OIE Collaborating Centres

• Amongst this network:
  – Collaborating Centre for Veterinary Medicinal Products (France)
  – Collaborating Centre for Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia (Japan)
  – Collaborating Centre for Veterinary Drug Regulatory Programmes (USA)
  – Reference Laboratory on Antimicrobial Resistance (UK)

OIE Standard and Guidelines

Chapter 6.7. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes

• Criteria for development of national antimicrobial resistance surveillance and monitoring programmes
• Harmonisation of existing programmes in food producing animals and in products for human consumption
• Surveillance and monitoring programmes of the prevalence of resistance in bacteria in animals, food and environment is a critical part of animal health and food safety strategy
• Monitoring of bacteria from products of animal origin intended for human consumption collected at different steps of the food chain are also considered.

Chapter 6.8. Monitoring of the quantities and usage patterns of antimicrobials agents in food producing animal

• Monitoring the quantities and usage patterns of Antimicrobial Agents in food producing animals is essential for antimicrobial resistance risk analyses and for planning purposes
• Development and standardization of monitoring systems considering the sources of antimicrobial data, the types of use and reporting formats
• Essential elements when conducting risk assessments, as described in Chapter 6.10

Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine

• Responsible and prudent use is principally determined by the outcome of marketing authorization and by the distribution, prescription and administration of veterinary medicinal products containing antimicrobial agents. Recommendations are provided for each of the parties involved:
  – regulatory authority
  – veterinary pharmaceutical industry
  – wholesale and retail distributors
  – veterinarians
  – food-animal producers

Chapter 6.10. Risk assessment for antimicrobial resistance arising from the use of antimicrobial agents in animals

• Analysis of risks to human health, and
• Analysis of risks to animal health:
  – Definition of the risk
  – Hazard identification
  – Release assessment
  – Exposure assessment
  – Consequence assessment
  – Risk estimation
  – Risk management options

Section – 6: Veterinary Public Health

http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/
OIE List of Antimicrobial Agents of Veterinary Importance

- FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance in 2003 & 2004 recommended the OIE to develop the List
- The OIE sent a questionnaire to Member countries, responses were analyzed by experts, the List developed in 2006
- The International Committee unanimously adopted the List at its May 2007 General Session (Resolution XXVIII)

OIE List of Antimicrobial Agents of Veterinary Importance

- The OIE ad hoc Group on Antimicrobial Resistance met in July 2012 to review and update the List, taking into account the top three critically important antimicrobials of the WHO list for human medicine
- The revised list was endorsed by the Scientific Commission and will be submitted for adoption by the General Assembly in May 2013

Recommendations:
- Any use of antimicrobial agents in animals should be in accordance with OIE standards on responsible and prudent use laid down in Chapter 6.9 of the Code
- Antimicrobial agents in the OIE List should be classified according to the three categories (VCIA, VHIA and VIA)

OIE List of Antimicrobial Agents of Veterinary Importance

- Based on the response rate to the questionnaire and treatment of serious animal diseases, and availability of alternative antimicrobial agents, the following categories were established:
  - Veterinary Critically Important Antimicrobial Agents (VCIA)
  - Veterinary Highly Important Antimicrobial Agents (VHIA)
  - Veterinary Important Antimicrobial Agents (VIA)

2012 Revision of the List to be presented at 2013 General Assembly

For a number of Antimicrobial Agents there are no or few alternatives for the treatment of diseases in target species. In this context, particular attention paid on VCIA and VHIA.

Among the VCIA, some are also considered of critical importance for human and animal health (third and fourth generation Cephalosporins, and Fluoroquinolones):
- Not to be used as preventive treatment in feed or water or in absence of clinical signs
- Not to be used as first line, unless justified and bacteriological test
- Extra label/off label limited and reserved for instances no alternatives are available.

OIE Global Conference

on the Responsible and Prudent use of Antimicrobial Agents for Animals

Objectives
- Present an overview of the current global situation regarding antimicrobial use in animals and antimicrobial resistance
- Inform on initiatives taken by the OIE and other international organisations to promote prudent and responsible use of antimicrobial agents in animals at national, regional and international level
- Promote good governance practices and encourage international cooperation;
- Foster and strengthen cooperation with Veterinary Statutory Bodies, the veterinary profession and veterinary education establishments
- Present scientific findings on the alternatives that could be used in animal production replacing antimicrobial agents

Feedback from Global Conference: Questionnaire

Questionnaire divided into two parts:
1. General context (three main questions - legislation covering Veterinary Medicinal Products (VMP) - use of growth promoters in Member Countries - a system for collecting quantitative data on antimicrobial agents used in animals)
2. Implementation of the OIE standard (Chapter 6.8. of the Terrestrial Code) – 2 sub-parts:
   - One part for those countries that do not have an official system for collecting quantitative data on antimicrobial agents used in animals (seven main questions)
   - One part for those countries that have an official system for collecting quantitative data on antimicrobial agents used in animals (nine main questions)

Feedback from Global Conference: Questionnaire

Replies and analysis
- Sent to all the OIE Delegates and copied to the OIE National Focal Points for Veterinary Products in June 2012 (final deadline September 2012)
- 152 questionnaires received from 178 OIE Member Countries = 85% replied
- OIE National Focal Points for Veterinary Products were mainly in charge of filling in the Questionnaire

Proportion of OIE Member Countries banning the use of antimicrobial agents as growth promoters
The three antimicrobial agent groups the most often quoted by OIE MC are:

1. Polypeptides (e.g. bacitracine)
2. Bambermycins (e.g. flavophospholipol)
3. Macrolides (e.g. Tylosin)

Recommendations of the OIE Global Conference

To the OIE Member Countries

3. To develop and set up an official harmonised national system for collecting data on the monitoring of antimicrobial resistance in relevant animal pathogens and quantities of antimicrobial agents used in food producing animals at the national level based on the OIE standards

11. To contribute and to participate in global or regional cooperation aiming at developing measures for responsible and prudent use of antimicrobial agents in animals

Need for common actions!

- A stronger collaboration between WHO, FAO and OIE through the Tripartite agreement
- Sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interfaces
- Three 'flagship' topics:
  - Zoonotic influenza
  - Rabies
  - Antimicrobial resistance (AMR)

Proportion of OIE Member Countries with an official system for collecting quantitative data

To the OIE Member Countries

12. To promote good agriculture and aquaculture practices including the use of vaccines where applicable and interact with all relevant interested parties while ensuring compliance with OIE and Codex Alimentarius standards to minimise the development and spread of antimicrobial resistance

Conclusion: Antimicrobial Use in Animals

Problems related to AMR are linked to antimicrobial use in any environment, including human and non-human usages. Antimicrobial resistance is not a recent phenomenon, but it is critical to take action now to keep antimicrobial agents effective and useful to combat disease.

- Animal health and welfare must be sustained
- Food security and food safety must be ensured
- Practices at risk such as the use of antimicrobial agents for animal growth promotion should be carefully evaluated
- No universal optimal solution for the delivery of antimicrobial agents at farm level worldwide, the well qualified veterinarian is the key actor
- International solidarity is crucial in a globalised world
AMU AND AMR MONITORING FOR AMR RISK ASSESSMENT AND RISK MANAGEMENT

T.R. Shryock

Risk Assessment & Risk Management
AMU and AMR Inputs

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May, 2013
FAO-APHCA AMR Expert Workshop, Bangkok, Thailand

Risk Assessment Workshop Outline

• Risk Analysis Overview
  – Codex & OIE approaches to Risk Analysis
  – Applications
• Risk Analysis Guidelines
• Hazard Characterization / Risk Profile
• Your Journey Begins...

Summary of Actions and Recommendations
International and National Level

• Responsible Use
  – Appropriate veterinary antibiotic use practices described; education, disease prevention
• Resistance Monitoring
• Antibiotic sales Monitoring
• Regulatory Controls
  – Risk assessment-based regulatory decisions on microbial food safety guide decisions on product use:
    • Approval with appropriate label indications and use, prescription
• Research
  – New products

Global "authority" Reports/Recommendations since 1997

• WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture)
• Europe (CVMP, EFSA, Health Ministers, etc.)
• Australia (JETACAR)
• U.S. (CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
• Canada (Adv. Com. Report, CCAR)
• OIE
• Codex
• Other reports from APUA, IFT, etc.

What Should Risk-Based Evaluations Do?

• Provide detailed description of risk-generating system (causal pathway)
  – Requires multiple experts to be involved
  – Each step of the pathway is identified
  – Data gaps and research needs are noted
• Estimate of the probability and magnitude of consequence
  – This estimate can be used to support decisions
• Provide Risk Managers with intervention options to choose from based on their likelihood of efficiently reducing risk
  – Risk Assessors should ask Risk Managers what do they want? Value? What resources are available? [Risk Communication]
  – Need to provide a means to evaluate the effectiveness of the intervention option!
What do you Want to Manage?
(Application of Risk Assessment)

- Reduce food borne bacterial disease
  - Reduce microbial contamination on food
  - Reduce microbial load in animals on farm
- Reduce AMR food borne bacterial disease or commensals
  - Reduce the subset of AMR microbial food contamination
  - Reduce the subset of AMR bacteria on farm
- Provide antibiotic product regulation?
  - Ensure Responsible Use of antibiotics by Regulation
- Reduce AMR animal pathogens?

Risk Management - Guided by Risk Assessment

- How large will the risks and benefits to human (or animal) health caused by animal antimicrobial use become in the future in the absence of intervention i.e. maintain status quo?
  - For example, restrictions on some uses, better food hygiene
  - Focus on decisions and their future consequences, not on blame/distribution of past health effects
  - The perspective is not (situation → action), but rather (action → predicted consequence) → recommendation

Risk assessment starts by connecting the causal chain

The 3-step RA Process

1. Risk evaluation - the process of comparing the risk estimated in the risk assessment with the appropriate level of protection.
2. Option evaluation - the process of identifying, evaluating the efficacy and feasibility of, and selecting measures to reduce the risk associated with an importation in order to bring it into line with the Members appropriate level of protection. The efficacy is the degree to which an option reduces the likelihood and/or magnitude of adverse health and economic consequences. Evaluating the efficacy of the options selected is an iterative process that involves their incorporation into the risk assessment and then comparing the resulting level of risk with that considered acceptable. The evaluation for feasibility normally focuses on technical, operational and economic factors affecting the implementation of the risk management options.
3. Implementation - the process of following through with the risk management decision and ensuring that the risk management measures are in place.
4. Monitoring and review - the ongoing process by which the risk management measures are continuously audited to ensure that they are achieving the results intended

Risk Management - Guided by Risk Assessment

- An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance in food animals during treatment
  - Pelagic
- A person must ingest meat from a treated animal that is contaminated with those same antibiotic-resistant foodborne bacteria
  - Exposure
- The person that ingests these bacteria must become sick with a bacterial infection that cannot be appropriately treated with antibiotics as a result of those animal-derived antibiotic-resistant bacteria
  - Consequence

Remove any one element and risk is ZERO
**Your Journey Begins…**

- **Hazard**: Human illness, caused by an antimicrobial-resistant bacteria, attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest.
- **Hazardous agent**: Antimicrobial-resistant food-borne bacteria of human health concern that are in or on a food-producing animal as a consequence of the proposed use of the antimicrobial new animal drug.
- **Risk**: The probability that human food-borne illness is caused by an antimicrobial resistant bacteria, is attributable to an animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

**Definitions**

- **Hazard Identification**: The Ad hoc Group recommended the following: an independent risk assessment based on scientific data; an iterative risk analysis process; a qualitative risk assessment systematically undertaken before considering a quantitative approach; the establishment of a risk assessment policy; and the availability of technical assistance for developing countries.

**Risk profile (GL77)**

- The Ad hoc Group of experts on antimicrobial resistance, appointed by OIE, has developed an objective, transparent and defensible risk analysis process, providing a valid basis for risk management decisions in respect to antimicrobial resistance.
- The components of risk analysis and of different possible approaches in risk assessment (qualitative, semi-quantitative, and quantitative) are defined.
- The Ad hoc Group recommended the following: an independent risk assessment based on scientific data; an iterative risk analysis process; a qualitative risk assessment systematically undertaken before considering a quantitative approach; the establishment of a risk assessment policy; and the availability of technical assistance for developing countries.

**Continuum of Codex Risk Management Options**

- All interventions guided by National Risk Assessments.

**Regulatory Risk Assessment**

- Hazard Characterization
- Risk Characterization
- Risk Analysis
- Risk Evaluation
- Risk Management

**Definitions**

- **Risk Assessment**
  - Hazard Identification
  - Risk Characterization
  - Risk Evaluation

- **Risk Communication**
  - Risk Estimate
  - Risk Management
  - Risk Communication

**The Components of Risk Analysis**: a comparison of the systems used by Codex Alimentarius and OIE

- **Codex Alimentarius**
  - Risk Assessment
    - Hazard Identification
    - Risk Characterization
    - Risk Evaluation
    - Risk Management
  - Risk Communication

- **OIE**
  - Hazard Identification
  - Risk Assessment
    - Risk Release Assessment
    - Exposure Assessment
    - Consequence Assessment
  - Risk Estimate
  - Risk Management
  - Risk Communication

**Your Journey Begins…**

- Start by making a list of identified Food safety issues / or Risk Profile (GL77, Appendix 1 or a Hazard Characterization per OIE)
  - Identify key food borne bacteria of concern
  - Identify food animals, foods and human disease of concern
  - Identify key antibiotics to be evaluated
- THEN, choose one combination and begin to work on it
  - For example, fluoroquinolone resistant campylobacter from chickens
  - Assemble multi-disciplinary team
  - Consult available work already done on the combination
  - Prepare Risk Profile or Hazard Characterization
  - Move to next combinations on the list
- The Hazard Characterizations will show the need for Risk Assessments in priority order
Key Components

- **Key Point #1**
  - “Risk Analysis Expertise Needed”
    - Medical, food & veterinary microbiology
    - Veterinary medicine
    - Human infectious disease
    - Food processing (e.g., HACCP)
    - Epidemiology
    - Risk Analysis
    - Pharmacology
    - Literature search specialist
      - Ongoing searches
      - Reprint repository
    
    Other experts contribute as needed

- **Key Point #2**
  - “Pre-screening” saves time and resources
    - The value of Hazard Characterization
      - A list of animal-use antibiotic classes not used in human medicine is a valuable tool.
      - Be careful on cross-resistance
      - Such antibiotics usually only require a Hazard Characterization to address risk concerns
      - More time and effort can be spent generating and evaluating antibiotic classes that are cross-resistant with those used in human medicine

Other Risk Assessment Preparations

- National agencies need to be involved
  - Veterinary medicine regulatory agency
  - Risk-based product evaluation guidelines must be in place
  - Participation in national resistance monitoring programs
  - Desirable to have sales or use data on antimicrobials
  - Responsible Antibiotic Use guidelines for veterinarians
  - Food safety agency
  - On-farm disease prevention efforts
  - Contamination data for food
  - Participation in national resistance monitoring programs
  - Human disease agency
  - Surveys of food borne disease prevalence
  - Participation in national resistance monitoring programs
  - Independent experts need to be recruited
    - Stakeholders along food chain bring unique inputs to consider
    - Expertise not available within an agency
    - Can lend credibility to the process and outcome
### To Continue the Journey…
- A regulatory risk assessment guideline will be needed to continue.
  - Consult guidelines from other countries and Vose paper
  - Propose a Draft guideline for adoption
- Develop a list of agencies, experts and data sources needed
- Prepare a timeline of activities and responsibilities

### What do you Want to Manage? (Application of Risk Assessment)
- Reduce food borne bacterial disease
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  - Reduce microbial load in animals on farm
- Reduce AMR food borne bacterial disease or commensals
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  - Ensure Responsible Use of antibiotics by Regulation
- Reduce AMR animal pathogens?

### Critical Learning To Consider
1. Focus on causal pathway!
   - Farm → food / other → treatment failure.
   - Convert possibility to probability
   - Each bug-drug combination may be different
2. Assess impact of Risk Management options
   - Include a new section on benefits or value to animal health, welfare from proposed use of antibiotic
3. Multiple Risk Management Options should be considered

### Demonstrate the connections in the causal pathway even if you cannot quantify the exact risk
- Start with data on human illness with resistant foodborne / other bacteria
  - Salmonella, Campylobacter or other
  - NOT Enterococcus
  - Are resistant infections a problem and,
  - Are they more difficult to treat than non-resistant infections?

### Region-Specific Data Needs

Some data may be very difficult to find
- The incidence of campylobacteriosis
- Local surveillance data
- Meat consumption patterns
- HACCP and other contamination control measures that are used in processing

What agencies or organizations have relevant data? What is the quality?

### Key Learning 4
Despite the abundance of available information, important data gaps still exist and research in this area should continue
- How are the antibiotics used in the field
- Antibiotic selection outcomes
- Pathogen load
- Dose response
- Human health consequences
Approaches to AMU and AMR Monitoring and their Limitations

Dirk Pfeiffer
Professor of Veterinary Epidemiology
Honorary Professor at London School of Hygiene & Tropical Medicine

Outline
• general methodological principles
• systems perspective
• antimicrobial sales/usage
• antimicrobial resistance
• policy development
• conclusions

Monitoring versus Surveillance
• monitoring
  • systematic, continuous or repeated, measurement, collection, collation, analysis and interpretation of animal health related data not associated with pre-defined plan of action
  • surveillance
  • systematic, continuous or repeated, measurement, collection, collation, analysis, interpretation and timely dissemination of animal health related data, essential for describing health hazard occurrence and for planning, implementation, and evaluation of risk mitigation measures
Populations and Sampling

Criteria for Design of Integrated Surveillance Systems (based on AGISAR recommendations)

1. Study population
   - Humans, retail meats, food producing animals

2. Sampling strategy
   a. Representativeness
   b. Sampling bias
   c. Frequency of testing
   d. Sample size
   e. Sample source

3. Culture methodology
   a. Target organisms
   b. In vitro antimicrobial susceptibility testing methods
   c. Antimicrobials to be used in susceptibility testing

4. Data management and reporting
   a. Database design for appropriate data extraction
   b. Type of data to be reported
   c. Analysis and interpretation of data
   d. Information sharing
   e. Confidentiality policies should be established to protect proprietary data

Drug Value Chain

Structure of Poultry Production Systems in South-East Asia

Constraints to Cost-Effective AM Usage Monitoring in Low to Middle Income Countries

Monitoring Programme Design Questions

- product(s) to monitor
- data source
- data collection approach
  - complete data
  - sampling
- data analysis
  - detect change in quantity over time or in space
### Development of AM Usage Monitoring in Low to Middle Income Countries
- **targeted monitoring**
  - informed by risk assessment
  - temporal change in livestock population numbers
  - mortality reporting
  - census at meaningful intervals
- **identify high risk groups for targeted surveys**
  - livestock flow intensity
  - fluctuation in live animal prices?
- **disease-free compartments**
- **specific livestock production sectors**

### AMR Surveillance Systems
- **pathogen specific**
  - appropriate indicator organisms
    - Campy, Salmonella, E-coli, Enterococcus
- **syndromic**
  - samples based on animals not responding to treatment
  - likely to be biased if lack of reporting incentive
- **voluntary or compulsory sample submission**
- **data source**
  - farm, slaughter house, food products

### Diagnostic Methods
- **definition of ‘resistance’**
- **antimicrobial susceptibility testing**
- **genotypic or phenotypic**
  - molecular diagnostics
    - strain typing
      - e.g. pulsed-field gel electrophoresis (PFGE), whole-genome sequencing (WGS), multi-locus sequence typing (MLST)
    - genome sequencing
- **voluntary or compulsory sample submission**
- **data source**
  - farm, slaughter house, food products

### Constraints to AMR Surveillance in Low to Middle Income Countries
- **passive surveillance inadequate**
  - need for representative surveys
  - surveys are problematic
  - large sample sizes needed for representative data
  - often laboratory-based -> bias
  - expensive, time-consuming, labour-intensive

### Ideas for AMR Surveillance in Low to Middle Income Countries
- **focus on detection and/or containment?**
  - sentinel surveillance networks
    - herds/population
    - target specific livestock production sectors
    - abattoirs/livestock markets
    - regional
    - emphasis on quality rather than quantity
    - data collection and diagnostics
- **abattoirs**
  - livestock markets
  - disease-free compartments
  - specific livestock production sectors
Actors involved in Risk Management

Stakeholders and Impact of Risk Management
- impact is dependent on stakeholders continuing with current behaviour or accepting value making changes
- need to assess stakeholders’ willingness to change
- behaviour change will occur if stakeholders accept that risk is their problem too and therefore want its management

Challenges for Surveillance Policy Development in Low to Medium Income Countries
- engagement of all relevant stakeholders
  - understand drivers of behaviour
  - behaviour change
    - incentives to change
      - animal health management
    - tackle illegal trade and use
  - avoid policy which is unlikely to be effective

Context
- Societal, cultural and ecological influences
  - Goal(s)
    - e.g., public health, economic security, social stability, animal and environmental health
- Institutional context
  - Animal and human health service
  - Patterns, provision and access
  - Regulation and governance
- Antimicrobial usage
- Antimicrobial resistance
- Animals
- Humans
- Environment

Conclusions
- monitoring / surveillance strategy
  - needs to be informed by transdisciplinary risk assessment
  - identify and ideally involve key stakeholders
  - AM trade value chain mapping
  - agree with stakeholders on monitoring / surveillance purpose

Conclusions cont.
- monitoring / surveillance strategies
  - AM usage
    - sales monitoring
    - targeted data collection
    - predictive modelling
    - livestock density
  - AMR
    - national/regional sentinel surveillance
    - focus on specific livestock sectors
  - monitoring / surveillance policy development
    - adapted to needs of local stakeholders
ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST) WITH LIMITED RESOURCES

S. Simjee

Antibiotic Susceptibility Testing and Data Interpretation

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APHCA AMR Expert Workshop
Bangkok, Sukosol Hotel, 14 to 15 May 2013

Agenda

1. Antibiotic Susceptibility Testing Methodology
2. Quality Control and Interpretive Criteria - Does it Matter?
3. Interpretation of Antibiotic Susceptibility Data - Are We Harmonised?
4. Q&A

What Are You Measuring?

Minimal Inhibitory Concentration (MIC)
The lowest concentration of an antimicrobial agent that prevents visible growth (to the naked eye) of a microorganism in an agar or broth dilution susceptibility test.

AST Methods

British Society of Antimicrobial Chemotherapy (BSAC)
European Committee on Antimicrobial Susceptibility Testing (EuCAST)
Clinical and Laboratory Standards Institute (CLSI)

The basic for each method

- Isolate bacterium in pure culture
- Inoculate broth
- Standardize turbidity 0.5 McFarland
Agar Dilution Susceptibility Test

An *in vitro* antimicrobial susceptibility test method conducted using serial concentrations of an antimicrobial agent incorporated into an agar growth medium in separate Petri dishes that are inoculated with a bacterial suspension to determine the minimal inhibitory concentration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>0.50</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>1.00</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>2.00</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>4.00</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>8.00</td>
<td>2</td>
</tr>
<tr>
<td>G</td>
<td>16.00</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>32.00</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE: When this procedure is carried out in test tubes, it is referred to as broth macrodilution; when performed in microdilution plates, it is called broth microdilution.

Broth Dilution Susceptibility Test

An *in vitro* antimicrobial susceptibility test conducted using serial concentrations of an antimicrobial agent incorporated in liquid nutrient media that are inoculated with a bacterial suspension to determine the minimal inhibitory concentration of an antimicrobial agent.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.03</td>
<td>≤0.03</td>
</tr>
<tr>
<td>B</td>
<td>0.06</td>
<td>≤0.03</td>
</tr>
<tr>
<td>C</td>
<td>0.12</td>
<td>≤0.03</td>
</tr>
<tr>
<td>D</td>
<td>0.25</td>
<td>≤0.03</td>
</tr>
<tr>
<td>E</td>
<td>0.50</td>
<td>≤0.03</td>
</tr>
<tr>
<td>F</td>
<td>1.00</td>
<td>≤0.03</td>
</tr>
<tr>
<td>G</td>
<td>2.00</td>
<td>≤0.03</td>
</tr>
<tr>
<td>H</td>
<td>4.00</td>
<td>≤0.03</td>
</tr>
</tbody>
</table>

Controls
Approved AST methods

• A number of organisations have approved AST methods e.g. BSAC, EUCAST, CLSI
• Each one has slight differences in the methodology e.g. media used or incubation times. Each of these factors have some influence on the results and thus the interpretation of the data
• Use of a standard method ensures reproducibility of the AST and thus comparison of data between laboratories

• EUCAST have interpretive criteria BUT these are based on bacteria of human origin and against human use antibiotics
• CLSI is the only organisation that has veterinary specific interpretive criteria

Why use QC strains?

• QC = Quality Control strains, these can be considered ‘positive controls’
• QC are bacterial isolates that have undergone rigorous testing to ensure that under a standard test system they will always give the same MIC range with a given antibiotic
• If a QC is out of range it invalidates the AST and indicates there are problems in the method e.g. pH, ion concentrations, temperature etc

• As long as our QC strains are in range we have a valid test system
• It does NOT tell us if test bacteria are susceptible or resistant

What are interpretive criteria?

• These are commonly known as breakpoints; S, I, R (Susceptible, Intermediate, Resistant)
• Susceptible
  This category implies an infection due to the isolate may be appropriately treated with the dosage regimen of an antimicrobial agent recommended for that type of infection and infecting species, unless otherwise indicated.
• Intermediate
  This category implies an infection due to the isolate may be appropriately treated in body sites where the drug are physiologically concentrated or when a high dosage of drug can be used; also indicates a ‘buffer zone’ that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretation.
• Resistant
  Resistant isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy has not been reliable in treatment studies.
Need for Harmonisation

At the outset it is important to emphasise that all of the reviewed surveillance systems have merit, especially when considering resistance trends within the countries in which the surveillance has been instigated.

The major challenge when analysing data across surveillance systems is a lack of harmonisation in sampling, susceptibility testing methods and in such basic terms as defining resistance.

All these factors can confound data interpretation even when analysing data vertically within a country but in horizontal analysis, across countries, it can become almost impossible.

Clinical vs. Epidemiologic

- **Clinical Resistance**
  - Isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely (e.g., β-lactamases), and clinical efficacy has not been reliable in treatment studies.

- **Epidemiological (Resistance)**
  - Isolate is defined as non-wild type (NWT) by the presence of an acquired or mutational resistance mechanism to the antibiotic. Isolates may or may not respond clinically to antimicrobial treatment.

Let's Compare Data

Within a country

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>NWT (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>C</td>
<td>0.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Definition of Resistance

National surveillance schemes do not all define resistance in the same way, there is considerable variability in what is defined as “resistant.”

This means that it is not possible to simply compare resistant rates from different surveillance schemes as they are not measuring the same parameter.

Indeed even within national surveillance schemes methods of analysis have changed over time such that % resistance values need to be viewed with caution.

Table: NWT distribution (% for all salmonella strain = 228) tested for antibiotic susceptibility in 2004.
Ciprofloxacin resistance in E. coli
DANMAP (Denmark) uses >0.03 µg/ml
MARAN (Netherlands) and SVARM (Sweden) use >0.06 µg/ml
VAV (Spain) uses >2 µg/ml

ABSTRACT
The European Food Safety Authority and the European Centre for Disease Prevention and Control have analysed the information on antimicrobial resistance among zoonotic and indicator bacteria in 2009 submitted by 25 European Union Member States. This information covers antimicrobial resistance in Salmonella and Campylobacter isolates from humans, food and animals, and in indicator Escherichia coli and enterococci isolates from animals and food.

Page 17:
“The results must therefore be interpreted with care and no direct comparison between countries should be made. Where countries have used the same method over the time period covered by the report, then an evaluation of trends is likely to be valid, though may lack sensitivity dependent on the specific breakpoint used.”
Responsible Antibiotic Use

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May 14-15, 2013
FAO-APHCA AMR Expert Workshop,
Bangkok, Thailand

Food Economics and Consumer Choice

An overview of the challenge ahead:

Key Data:

50% of the world's population will enter the food system by 2050.

70% of the food that we eat comes from efficiency improving technology.

AVMA Veterinarians Oath

"Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge."

Effective 2010

The Problem

• Veterinary vs. Medical need for antimicrobials
• Selective pressure of antibiotic use in animals
• Zoonotic bacteria may be exposed to drug during antimicrobial use for food animal infections
  – Animal antibiotic use is not the source of all human antibiotic resistance!

Global "authority" Reports/Recommendations since 1997

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• OIE
• Codex -various
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TECHNOLOGY’S ROLE IN THE 21ST CENTURY

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  - Risk assessment-based regulatory decisions on microbial food safety guide decisions on product use:
    - Approval with appropriate label indications and use, prescription
- Research
  - New products

Objectives of Prudent Use (based on OIE)

- Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals:
- maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimizing both their efficacy and safety in animals;
- comply with the ethical obligation and economic need to keep animals in good health;
- prevent, or reduce, as far as possible, the transfer of microorganisms with their resistance determinants within animal populations;
- maintain the efficacy of antimicrobial agents used in food-producing animals;
- prevent or reduce the transfer of resistant microorganisms or resistance determinants from animals to humans;
- maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials;
- prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);
- protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs, and the ability to transfer antimicrobial drug-resistant microorganisms to humans.

Stakeholder Responsibilities

- Regulatory Authorities
- Veterinary Pharmaceutical Industry
- Wholesale and Retail Distributors
- Veterinarians
- Food Animal Producers

Codex CAC/RCP 61-2005 Code of Practice for Responsible Use

- Responsibilities of stakeholders
  - Regulatory
  - Manufacturers
  - Veterinarians
  - Producers
- Expect implementation at national level
  - In general, OIE and WHO guidelines are in alignment
- OIE Terrestrial Code
- WHO Responsible Use Guidelines

Approved Antibiotic Label Indications

- Efficacy
  - Disease Treatment
  - Disease Control
  - Disease Prevention
  - Production Use
- Therapeutic
  - Treatment
  - Disease control
  - Disease prevention
- Production (not in EU, some other locations)
  - Nutritional, Physiological and Immunological effect on Average Daily Gain and Feed Efficiency

DEFINITION OF TERMS

Population Medicine

Number of Animals with:
- Mortality
- Morbidity

Baseline

PREV. CONTROL
TREATMENT

Studies of Admin:
- Oral (water, feed)
- Injection, infusion

Timing of administration relative to the progression of disease within a group

Based on Guidance 209

Ensuring Animal Health

- Prevention strategies emphasized
  - Minimize environmental contamination; vaccinate; biosecurity, nutrition, housing, management at high levels
- Minimize therapeutic use
  - Treat only at-risk or ill animals
- Utilize only licensed products by label direction; exercise clinical judgment for off-label usages
- Utilize culture and sensitivity
- Use narrow spectrum antibiotics when possible
- Vet-client-patient relationship encouraged
- Record keeping
- Periodically review usage practices
<table>
<thead>
<tr>
<th>Extralabel Use (AVMA) (does not apply to feeds)</th>
<th>Why Veterinarian Oversight?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Veterinarians are viewed as having the necessary experience and accountability to prescribe antibiotics — just like physicians — Therapeutic indications!</td>
<td>• Disease presentation, diagnostics, client relationship and other considerations require veterinary expertise to integrate into a medication decision</td>
</tr>
<tr>
<td>• May need to consider non-vets or vet technicians with certifications to “cover” remote areas</td>
<td>• Consistent with Responsible Use Principles</td>
</tr>
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<table>
<thead>
<tr>
<th>Biosecurity Poster USDA</th>
<th>Quality Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Quality (potency, formulation, etc.)</td>
<td>• Quality (potency, formulation, etc.)</td>
</tr>
<tr>
<td>• Cost</td>
<td>• Cost</td>
</tr>
<tr>
<td>• Distribution (storage conditions, market channels)</td>
<td>• Distribution (storage conditions, market channels)</td>
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<tr>
<td>• Technical service support</td>
<td>• Technical service support</td>
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<tr>
<td>• Counterfeit or other product quality issues</td>
<td>• Counterfeit or other product quality issues</td>
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<table>
<thead>
<tr>
<th>Retailer Antibiotic use Policy</th>
<th>Practical Actions to Take</th>
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</thead>
<tbody>
<tr>
<td>• Communication and Education</td>
<td>• Communication and Education</td>
</tr>
<tr>
<td>— Inform veterinarians and producers of:</td>
<td>— Inform veterinarians and producers of:</td>
</tr>
<tr>
<td>• Actions they can take to minimize disease (biosecurity)</td>
<td>• The need to follow clinical practice guidelines</td>
</tr>
<tr>
<td>• The need to follow clinical practice guidelines</td>
<td>— Seek support from veterinary medical organizations, schools of veterinary medicine, food production companies and others</td>
</tr>
<tr>
<td>• Improve diagnostic capabilities and capacity</td>
<td>• Improve diagnostic capabilities and capacity</td>
</tr>
<tr>
<td>— Laboratory or quick-test applications to guide antibiotic use decisions</td>
<td>— Laboratory or quick-test applications to guide antibiotic use decisions</td>
</tr>
<tr>
<td>— Use of CLSI clinical breakpoints when possible</td>
<td>— Use of CLSI clinical breakpoints when possible</td>
</tr>
</tbody>
</table>
DEVELOPING NATIONAL AMU & AMR MONITORING / SURVEILLANCE PLANS

M.J. Otte

Developing National AMU & AMR Monitoring / Surveillance Plans

Joachim Otte (FAO)
AMU & AMR Expert Workshop
Bangkok, 14-15 May 2013

Threats of rapid livestock sector growth

- Environment
  - Natural resource erosion
  - Pollution
  - GHG emission associated with livestock production
- Health
  - Infectious diseases affecting animals (PRRS, FMD)
  - Emerging zoonotic diseases (e.g. HPAI)
  - Proliferation of antimicrobial resistance (AMR)
- Social
  - Marginalization of small-scale producers
  - Exploitation of 'cheap' labour

Consequences of AMR in the USA

- Longer hospitalization (11 days)
- Increased treatment cost (US$20,000)
- Higher case fatality rates (2.2 fold)
- General therapy shift to more expensive drugs (even for non-AMR-resistant cases)

'SPPLI Policy Process'

- Political economy
- Network of like-minded stakeholders
- Research
- Transparency

Suggested Approach

1. Analysis: what are the strengths and weaknesses of 'your' current system of AMU & AMR monitoring?
2. Setting Targets: What do you see as priority issues needing to be addressed in the short term (12 to 24 months)?
3. Action Plan: What actions need to be taken to address the priority issues?

Some Questions

- Does 'your' AMR monitoring system have a clearly defined purpose?
- What risk(s) do 'you' want to manage?
- What links exist between results of AMR monitoring and actions?
- Does the system provide the information needed to guide actions?
Some more Questions

- What can / will you do to improve the system?
- How can you mutually support each other?
- What can FAO (OIE) do to support you?
RECOMMENDATIONS

DEVELOPING NATIONAL AMU AND AMR MONITORING ACTION PLANS

The key objective of in each country is to develop detailed and costed country-specific ‘action plans’ to enhance national AMU and AMR monitoring and management capacity over a 12 and 24 months horizon. The following steps are suggested.

Step 1 – Analysis of current situation: In light of the information presented, review the strengths and weaknesses of the current national system for AMU and AMR monitoring and management, covering the aspects of:

1. Licensing of antimicrobials for use in food animals
2. Monitoring of sales of antimicrobials for use in food animals
3. Monitoring of use of antimicrobials in food animals
4. Sample collection from food animals / animal products for AMR testing
5. Testing protocols for micro-organisms isolated from food animals
6. Collation and analysis of AMR test results
7. Information on AMR infections of humans with farm animal related micro-organisms
8. Use of information for AMR management

Step 2 – Setting targets: Where would you like national AMU and AMR monitoring and management capacity to be with regards to the above in 12 and in 24 months? It would probably be useful to restrict the target to key food-borne bacteria of concern, key food animals, foods and human diseases of concern and key antimicrobials.

Step 3 – Identifying necessary and sufficient actions: Identify key actions that need to take place to move from the current situation to the 12 and 24 month targets, who needs to take these actions and their financial, political and social implications (stakeholder analysis and involvement).

<table>
<thead>
<tr>
<th>Item</th>
<th>Current situation</th>
<th>Target 12 / 24 months</th>
<th>Actions</th>
<th>Who</th>
<th>Cost</th>
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<tbody>
<tr>
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</table>
WORKING GROUP ON VETERINARY AMR RISK MANAGEMENT (VAMRRM)

Objective

The objective of the working group is to advocate for increased national and regional policy development and action in APHCA member countries on the issue of AMR in bacteria of food animal origin (including pathogens of food animals, zoonotic bacteria and commensals).

A core group of invited experts will assist selected APHCA country representatives to draft and implement actions per the Terms of Reference.

Terms of Reference

- Develop educational and information materials on AMR and risk management approaches to facilitate discussions on policy and funding
  - Identify key decision-makers in each country
  - Identify key stakeholders in each country
  - Prepare communication / outreach plan to engage in dialogue
- Develop context-specific guidelines for the responsible and prudent use of antimicrobials in food animal production tailored to the situation prevailing in FAO and APHCA member countries
- Propose harmonised science-based guidelines for AMR monitoring programme development:
  - The appropriate collection methodology of samples for the isolation of farm animal-related bacteria to be assessed for AMR
  - Use standardized laboratory methods for the assessment of AMR
  - Collation, analysis and reporting of AMR laboratory results on a regular basis
- Propose science-based guidelines for AM sales/use data programme development
  - Harmonized reporting among countries as much as possible, depending on data sources, availability, etc.
- Develop national or regional regulatory agency AMR risk assessment for antimicrobial products that guide risk management decisions
  - Will take into consideration the AMR monitoring and AM sales/use data
- Establish an information / data base on alternatives to antimicrobial use in food animal production
  - Disease prevention practices; biosecurity, consumer hygiene practices, etc.
  - Alternative disease interventions locally available
- Share the results of the work conducted via symposia, web posting or other means
- Seek financial support to enhance national AMR management capabilities and capacities

International Expert Members

- Myint, H.T. – International Standards on AMR risk management and prudent use of antimicrobials
- Pfeiffer, D.U. – Surveillance & Epidemiology
- Simjee, S. – Microbiology & AMR Surveillance
- Shryock, T.R. – Regulatory Affairs (e.g. Risk Assessment, etc)
- Wagenaar, J.A. – Evolutionary Biology of AMR

National Expert Members

- To be nominated by each country
SYSTEMATIC REVIEW OF ANTIMICROBIAL RESISTANCE IN THE ASIA PACIFIC REGION

Background
Awareness about the threat of AMR development and spread is low among public authorities and professionals involved with animal production and few countries in the region have systems in place to monitor AMU and AMR, carry out necessary risk assessments and put in place evidence-based policies for AMR management. The aim of this literature review is to enhance current knowledge on the extent and patterns of AMR in different countries in the Asia-Pacific region as basis for devising strategies for AMR management.

Outputs
1. A review of published and unpublished literature on antimicrobial resistance in bacterial microorganisms isolated from livestock and livestock products in the Asia-Pacific region;
2. An interim report on specifying the search / inclusion criteria to be used as well as classification criteria to apply for synthesizing study;
3. An electronic archive (CD) of compiled literature;
4. A final report on methodology and findings.

Suggested Approach
1. Define study inclusion criteria, search algorithm and databases
2. Determine classification criteria to use for synthesizing study results
3. Identify, compile and review the literature, both published and unpublished, on the subject
4. Extract and assemble relevant information
5. Analyse and critically discuss findings
6. Write and submit a report in MS Word format
### TIMETABLE

#### Tuesday 14 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30 – 09:00</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>09:00 – 09:30</td>
<td>Opening remarks</td>
<td>DG DLD APHCA Secretary</td>
</tr>
<tr>
<td>09:30 – 10:15</td>
<td>The global problem of AMR and critical antimicrobials for use in humans</td>
<td>Prof. J. Wagenaar</td>
</tr>
<tr>
<td>10:15 – 10:45</td>
<td><em>Group Photo &amp; Coffee / tea break</em></td>
<td></td>
</tr>
<tr>
<td>10:45 – 11:30</td>
<td>Basic microbiology to set the stage for AMR monitoring and risk assessment</td>
<td>Dr S. Simjee</td>
</tr>
<tr>
<td>11:30 – 12:15</td>
<td>OIE activities on AMR and recommendations of the ‘Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals’</td>
<td>Dr H.T. Myint</td>
</tr>
<tr>
<td>12:15 – 13:45</td>
<td>Lunch break</td>
<td></td>
</tr>
<tr>
<td>13:45 – 14:15</td>
<td>AMU and AMR monitoring for AMR risk assessment</td>
<td>Dr T. Shryock</td>
</tr>
<tr>
<td>14:15 – 14:45</td>
<td>Approaches to AMU monitoring and their limitations</td>
<td>Prof. D. Pfeiffer</td>
</tr>
<tr>
<td>14:45 – 15:15</td>
<td>Coffee / tea break</td>
<td></td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>Antimicrobial susceptibility testing (AST) with limited resources</td>
<td>Dr S. Simjee</td>
</tr>
<tr>
<td>15:45 – 16:15</td>
<td>Responsible use / clinical practice guidelines</td>
<td>Dr T. Shryock</td>
</tr>
<tr>
<td>16:15 – 16:45</td>
<td>Template for the development of national AMU / AMR monitoring plans</td>
<td>Dr J. Otte</td>
</tr>
<tr>
<td>17:30 – 19:00</td>
<td>Hosted dinner courtesy of DLD</td>
<td></td>
</tr>
</tbody>
</table>

#### Wednesday 15 May

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00 – 09:15</td>
<td>Recap of day 1 and presentation of day 2 work plan</td>
<td>Tbd</td>
</tr>
<tr>
<td>09:15 – 12:00</td>
<td>Country delegates to develop structured ‘Action Plan’ for stepwise improvement of national AMR management system</td>
<td>Delegates assisted by workshop leaders</td>
</tr>
<tr>
<td>12:00 – 13:30</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13:30 – 15:30</td>
<td>Presentation and discussion of country ‘Action Plan’ proposals Identification of common themes with possibility of regional collaboration</td>
<td>Delegates and workshop leaders</td>
</tr>
<tr>
<td>15:30 – 16:00</td>
<td>Coffee / tea break</td>
<td></td>
</tr>
<tr>
<td>16:00 – 16:30</td>
<td>Wrap-up / next steps / feedback / closure</td>
<td></td>
</tr>
</tbody>
</table>
LIST OF PARTICIPANTS

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