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Areas of interest of focal points on veterinary products:

Antimicrobials Introduction

Workshop for OIE national Focal Points for Veterinary Products
23 – 26 November 2010, Johannesburg, South Africa

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Introduction

- **Antimicrobial agents represent one of the main therapeutic tools both in human and veterinary medicine to control and treat bacterial infectious diseases.**
- **However, the use and misuse of antimicrobials in both human and veterinary medicine has resulted in the emergence of strains of bacteria that no longer respond to antimicrobial therapy.**
- **This is a problem for animal health, but also for public health when transmitted to humans.**
- **As very few new antimicrobials are coming on the market, addressing the issue of antimicrobial resistance is a priority in the fields of public health today**

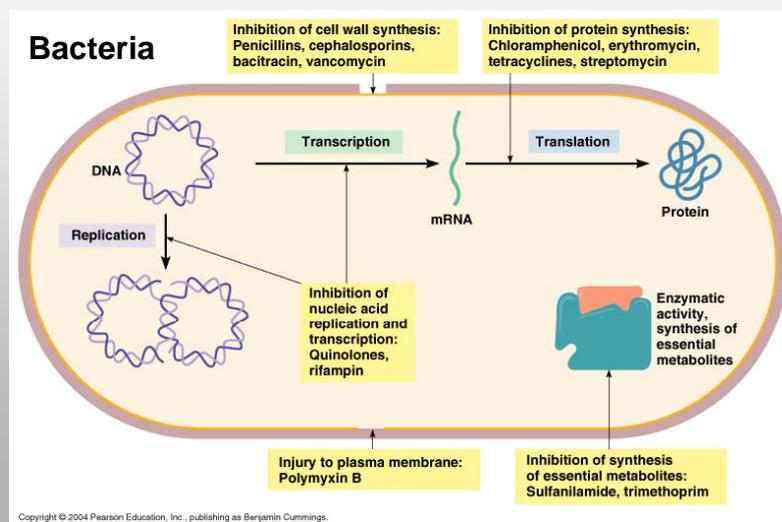
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Understanding Antimicrobial resistance

- Antimicrobial - Mode of action
- Antimicrobial resistance - mechanism
- Antimicrobial resistance - consequences
- Selection of antimicrobial resistance bacteria
- Factors promoting the emergence of antimicrobial resistance
- Main public health concerns
- Strategy to fight against antimicrobial resistance

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Modes of Antimicrobial Action

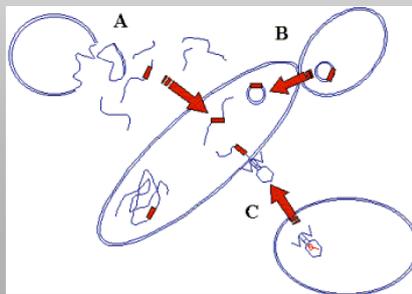


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Antimicrobial resistance

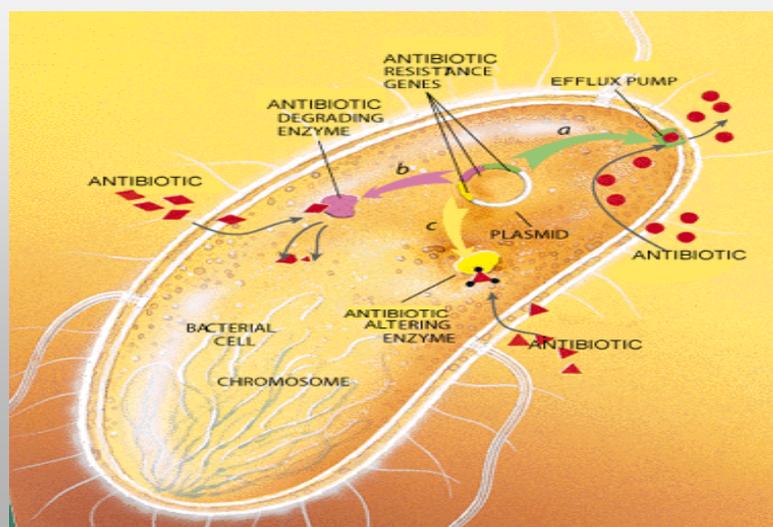
- Bacteria can be naturally resistant to antimicrobials
- Antimicrobial resistance was present before the use of antimicrobials
- Bacteria can acquire resistance genes through different mechanisms :

Resistance genes can be on the chromosome or on plasmids an result from spontaneous mutation aor can be acquird by : A = Transformation; B = Conjugation; C = Transduction



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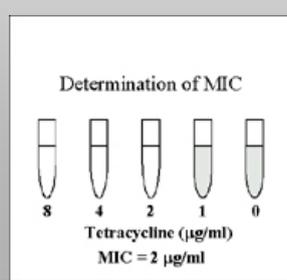
Antimicrobial resistance Biochemical mechanisms



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Antimicrobial Resistance consequence

- Relative or complete lack of effect of antimicrobial against a bacteria leading to lack of efficacy

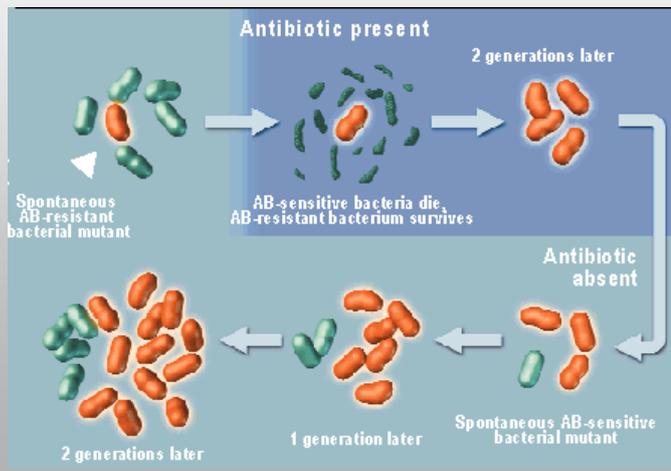


Antimicrobial resistance = increase in MIC
(MIC = Minimum inhibitory Concentration)

Selection of Antimicrobial resistant strains

Antimicrobial Treatment

Selection pressure



Factors promoting emergence of resistance



- Unnecessary use, inappropriate use: wrong drug, dose or duration of treatment;
- Intensive use in hospital settings and in farms;
- Poor quality drugs, unregulated sales, self-medication.
- Poor sanitation and overcrowding;
- Inadequate control of infection
- International travel and trade, population movements.
- ...

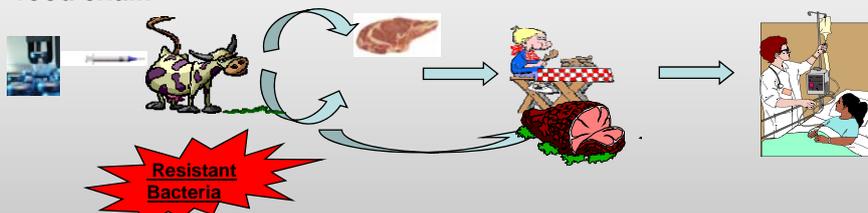
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Main public health concerns



Main route:

- Transmission of antimicrobial resistant bacteria through the food chain



Main issues:

- **Salmonella**
 - Fluoroquinolone-resistance
 - 3rd – 4th gen. Cephalosporin resistance
- **Campylobacter**
 - Fluoroquinolone-resistance
 - Macrolide-resistance
- **ESBL: Extended spectrum Beta lactamase**
- **MRSA: Methicillin resistant Staphylococcus aureus (contact transmission)**

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Strategies to fight against Antimicrobial Resistance



- Prevent infection
- Diagnose and treat infection effectively
- Use antimicrobials wisely
- Prevent transmission

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**OIE work on Antimicrobial
Resistance
Main steps**

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■ OIE work on antimicrobial resistance

- Consistently to its missions, OIE considered in 1997 the use of antimicrobial substances in rearing as a key issue for public health, animal health and animal welfare

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■ OIE work on antimicrobial resistance

- **1997: request from the Regional Commission for Europe**
- **1998: debate at the international session**
- **1999: recommendations from the OIE Regional Commission for Europe, OIE Standards Commission, OIE International Committee to set up an**

“International Ad hoc Group”

To address: human and animal health risks related to antimicrobial resistance, and the contribution of antimicrobials usage in veterinary medicine.

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■ OIE work on antimicrobial resistance

- 1999: First OIE European Scientific conference
 - « the use of antimicrobials in animals ensuring the protection of public health »
- 2001 : « Second OIE international conference on antimicrobial resistance »

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■ Work of the OIE Ad hoc group

- Terrestrial animal health codeSection - 3.9 : antimicrobial resistance
 - Appendix 3.9.1 : Guidelines for the harmonisation of antimicrobial resistance surveillance and monitoring programmes
 - Appendix 3.9.2 Guidelines for the monitoring of the quantities of antimicrobials used in animal husbandry
 - Appendix 3.9.3 : Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine (Revised 2005)
 - Appendix 3.9.4: Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals
- **Manual of Diagnostic Tests and vaccines for Terrestrial Animals**
 - Laboratory methodologies for bacterial antimicrobial susceptibility testing

2003

2003

2003

2004

2003

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OIE antimicrobial resistance related activities



Joint FAO/WHO/OIE activities



2003

- FAO/WHO/OIE experts consultation (Geneva) on non human antimicrobial usage and antimicrobial resistance

2004

- FAO/WHO/OIE experts consultation (Oslo) on non human antimicrobial usage and antimicrobial resistance

2006

- FAO/WHO/OIE Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance (Seoul)

2007

- FAO/WHO/OIE expert consultation on CIA and VCIA (Roma)



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First joint FAO/OIE/WHO meeting on non human antimicrobial usage and antimicrobial resistance



• Geneva - 2003

<http://www.who.int/salmsurv/links/en/GSS1JointFAOOIEWHOWorkshopAMRdec%2003.pdf>

Page 26 recommendation 5:

- *Antimicrobial classes that are **“critically important” for human medicine need to be defined and identified by an expert medical group appointed by WHO. These proposals should be shared with risk managers and other interested parties, including FAO and OIE. This classification should be reviewed on a regular basis...***



Second joint FAO/OIE/WHO meeting on non human antimicrobial usage and antimicrobial resistance



Oslo - 2004

<http://www.oie.int/download/WHO-CDS-CPE-ZFK-2004.8.pdf>

Final conclusion p12 and 13

- 3. Risk management options for antimicrobial resistance should be developed by **a Codex/OIE task force...**
- 5. The concept of **“critically important” classes of antimicrobials for humans** should be pursued by WHO. The Workshop concluded that **antimicrobials that are critically important in veterinary medicine should be identified**, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE.



Critical Important antimicrobials - WHO



WHO working group on Critically Important Antimicrobials Agents for Human medicine for risk management strategies of non human use held in Canberra in 2005.

The list included : Aminoglycosides, Ansamycins, Carbapenem and other penems, Cephalosporin 3rd and 4th generation, Lipopeptides, Glycopeptides, Macrolides, Oxazolidinones, Penicillins, Quinolones, Streptogramins, Drugs used to treat tuberculosis and other mycobacterial diseases.

http://www.who.int/foodborne_disease/resistance/amr_feb2005.pdf

Second WHO Expert Meeting on Critically Important Antimicrobials for Human Medicine: Categorization for the Development of Risk Management Strategies to contain Antimicrobial Resistance due to Non-Human Antimicrobial Use held in Copenhagen in 2007

Designation of quinolones and 3rd/4th generation cephalosporins for Salmonella and other enterobacteriaceae and Quinolones and macrolides for campylobacter to be considered in priority.

http://www.who.int/foodborne_disease/resistance/antimicrobials_human.pdf

List of veterinary critically important antimicrobial agents



- In 2005, the OIE Ad hoc group defined and designated Veterinary critically important antimicrobials (VCIA)
- The concept was adopted in general session
- The ad hoc group prepared a questionnaire to collect proposals of VCIA, sent to the 167 member countries (MC)
- Ad group report, including the list based on OIE MC responses was presented at the general session in may 2006

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List of veterinary critically important antimicrobial agents



- In May 2006, OIE International committee adopted Resolution n XXXIII asking to refine the list
 - The OIE Ad hoc group on Antimicrobial resistance met in September 2006 and proposed a new list
- In May 2007 OIE International committee adopted the List of Antimicrobials of Veterinary Importance (Resolution n XXVII)

The list can be found at:

http://www.oie.int/download/Antimicrobials/OIE_list_antimicrobials.pdf

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Joint FAO/OIE /WHO Expert Consultation on Critically Important Antimicrobials



- Rome - 2007

- http://www.who.int/foodborne_disease/resources/Report%20joint%20CIA%20Meeting.pdf

- The expert group proposed to **retain criteria when establishing the priorities** and proposed three possible approaches.
 - Page 15
 - **3.5 Using the criteria – three possible approaches**
 - **Three different approaches that might be used to combine these criteria into a final prioritization process** at the individual country level or at international level. The use of any approach should result in an output that prioritizes for risk assessment the combination of antimicrobial agent, the species of animal and the foodborne bacterium.
 - The WHO and OIE lists of critically important antimicrobials should be considered when establishing Priorities.



2. Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance



- Seoul - 2007 2008 2009

- <http://codextfamr.kfda.go.kr/eng/index.html>



- This task force was established during the 29th session of the Codex Alimentarius Commission, as a Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial resistance. The objectives, as defined in the terms of reference, is to provide **guidance on how to assess the risks to human health** associated with the presence in food and feed of resistance organism or resistance genes.

Last meeting October 2010

Collaboration between international organisations



- MEETING OF THE OIE/FAO/WHO CONSULTATIVE AD HOC GROUP ON COLLABORATIVE ACTIVITIES ON ANTIMICROBIAL RESISTANCE

Paris, 30 September – 1 October 2009

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Potential future collaboration (OIE/WHO/FAO)



- 1. Guidelines, standards and harmonisation
 - Information and avoiding duplication of efforts
- 2. Legislation, inspection/control
 - Information and avoiding duplication of efforts
- 3. Data collection and surveillance on the use antimicrobials and of antimicrobial resistance
 - *Proposal to have the development and implementation of the pilot studies project, initiated by WHO, as a future joint activity..*
- 4. Capacity building with reference to education and training
 - Main focus points for future collaboration.
- 5. Communication and stakeholder interaction
 - promotion for a holistic approach to the containment of antimicrobial resistance
 - development of common wording of key messages, and communication and advocacy tools.

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OIE GUIDELINES

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Work of the OIE Ad hoc group

- **Terrestrial animal health codeSection - 3.9 : antimicrobial resistance**
 - Appendix 3.9.1 : Guidelines for the harmonisation of antimicrobial resistance surveillance and monitoring programmes
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 - Laboratory methodologies for bacterial antimicrobial susceptibility testing

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

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Objectives of the Responsible and Prudent Use GL

- Rational use of antimicrobials with the purpose of optimising both 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 emergence and transfer of resistant bacteria within animal populations
- Maintain the efficacy of antimicrobial agents used in livestock

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Objectives of the Responsible and Prudent Use GL

- Prevent or reduce the transfer of resistant bacteria from animals to humans
- Prevent the contamination of animal derived food with antimicrobial residues that exceed the established maximum residues level (MRL)
- Maintain the efficacy of antimicrobial agents used in human medicine and prolong their usefulness
- Protect consumer health by ensuring the safety of food of animal origin

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Objectives of the Responsible and Prudent Use GL (contd)

- Communication, consensus, training: between the relevant professionals, acting for the prudent use

Need for every country to start a programme aiming at “the responsible and prudent use of antimicrobials”...

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

• Responsibilities of the regulatory authorities

- Marketing authorisation
- Submission of data for the granting of the marketing authorisation
- Market approval registration procedures
- Quality control of antimicrobial agents
- Assessment of therapeutic efficacy
- Assessment of the potential of antimicrobials to select for resistance

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

• Responsibilities of the regulatory authorities

- Establishment of acceptable daily intake, maximum residue level and withdrawal periods for antimicrobial compounds
- Protection of the environment
- Establishment of a summary of product characteristics for each veterinary antimicrobial product (VAP)
- Post-marketing antimicrobial surveillance
- Supply and administration of the antimicrobial agents used in veterinary medicine
- Control of advertising
- Training of antimicrobial users
- Research

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

- **Responsibilities of the veterinary pharmaceutical industry**
 - Marketing authorisation of VAPs
 - Marketing and export of VAPs
 - Advertising
 - Training
 - Research

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

- **Responsibilities of wholesale and retail distributors**
 - Distribution only on prescription
 - Detailed records
 - Training

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

● **Responsibilities of veterinarians**

- Use of antimicrobial agents
- Choosing an antimicrobial agent
- Appropriate use of the antimicrobial chosen
- Recording
- Labelling
- Training

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

● **Responsibilities of food-animal producers**

- Good farming Practice
- Use of antimicrobial agents only on prescription
- Respect for the dosages
- Isolation of sick animals
- Respect for the storage conditions
- Respect of hygienic conditions
- Respect for the recommended withdrawal periods
- Suppression of surplus antimicrobials under safe conditions for the environment
- Preservation of all the laboratory records
- Preservation of adequate records of all medicines used
- Report to the responsible veterinarian of recurrent disease problems

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...how to implement and follow a programme of “Prudent use”

- **By collecting information and implementing surveillance systems:**
 - Origins and quantities of antimicrobials used
 - Antimicrobial use practices
 - Prevalence and trends of resistant bacteria in animal pathogens and in zoonotic species responsible of human infections
- **By developing a comprehensive methodology**

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Guidelines for the harmonisation of antimicrobial resistance surveillance and monitoring programmes

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national antimicrobial resistance surveillance and monitoring programmes

- Follow trends in antimicrobial resistance in bacteria
- Help detection of emergence of new antimicrobial resistance (new antibiotic – new mechanism)
- Provide a basis for policy recommendations for animal and public health
- Provide information for prudent use recommendations and better efficacy of prescription
- Provide data for conducting risk analysis

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national antimicrobial resistance surveillance and monitoring programmes

The guideline indicates :

- The sampling strategies
- The sample sources (in animals, in food and animal feed)
- Sample specimens to be collected
- Bacterial isolates to monitor: Animal bacterial pathogens, Zoonotic bacteria, Commensal bacteria
- The storage of bacterial strains
- The antimicrobials to be used in susceptibility testing
- The type of data to be recorded and stored
(data on antimicrobial susceptibility should be reported quantitatively)
- The recording, storage and interpretation of results

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

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monitoring the quantities of antimicrobial used in animal husbandry

- **Quantitative information on usage patterns, including potency and type of use.**
- **These data can be used for:**
 - **Interpreting** surveillance data on resistance
 - Targeted **response** to problems of antimicrobial resistance
 - **Evaluating** the effectiveness of prudent use guidelines
 - **Risk analysis and planning**

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- **Development and standardisation of monitoring systems**

- **Sources of antimicrobial data**

- **Basic sources** (import and export data, manufacturing and manufacturing sales data ...)
- **Direct sources** (Data from animal drug registration, wholesalers...)
- **End-use sources** (veterinarians and food animal producers)

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- **Development and standardisation of monitoring systems**

- **Categories of data**

- **Requirements for data on antimicrobial use** (weight, use ...)
 - **Classes of antimicrobials**
 - **Species and production systems** (keep a register of all animal use of antimicrobials)
- **Other important information**
 - **Breakdown of farm livestock into species and production categories**

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**Guidelines on Laboratory
methodologies for bacterial
antimicrobial susceptibility testing
(AST)**

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Laboratory methodologies for AST testing

**Recommendations for validated methods
and proficiency testing**

**Need for every country to start a
program aiming at “monitoring AMR
and consumptions of antibiotics”**

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**Guidelines for analysing the risks to
animal and public health from
antimicrobial resistant micro-
organisms of animal origin**

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**RISK ASSESSMENT FOR ANTIMICROBIAL RESISTANCE
ARISING FROM THE USE OF ANTIMICROBIALS IN ANIMALS**

- **Divided in 3 parts :**
 - Guidelines for analysing the risks to animal and public health from antimicrobial resistant micro-organisms of animal origin
 - Analysis of risks to human health
 - Analysis of risks to animal health

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- **Guidelines for analysing the risks to animal and public health from antimicrobial resistant micro-organisms of animal origin**
 - **Objective :**
provide Member Countries with a transparent, objective and scientifically defensible method of assessing and managing the human and animal health risks associated with the development of resistance arising from the use of antimicrobials in animals.
 - Within the principles of risk analysis described in Section of this [Terrestrial Code](#).

Risk analysis challenges

- **These information and surveillance systems must be strictly managed through a sound risk analysis methodology aiming at:**
 - Identification of potential hazards related to antibiotic resistance in pathogenic bacteria (animal, human)
 - Risk analysis, quantitative when possible
 - Science based decision making process

OIE Recommendations for Risk Analysis

- Risk analysis should be **objective** and defensible,
- Process should be **transparent** and consistent
- Risk management /assessment functions should be separated to ensure **independence** of decision-making process and evaluation of the risk

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OIE Recommendations (ctnd)

- Risk management should be conducted using a **policy framework**
- Risk assessment should be based on **sound science**
- **Communication** between managers, assessors and stakeholders is essential
- **Help developing countries** develop/access skills required for risk assessment – Effort of harmonisation

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CONCLUSION

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Recommandation

- ◆ **Adopted by the International Committee of the OIE during its 77th General Session 24 – 29 May 2009**

THE COMMITTEE RECOMMENDS THAT OIE MEMBERS

- ◆ Nominate a national focal point for OIE on matters related to veterinary products ...
- ◆ Promote the responsible and prudent use of veterinary medicinal products, in particular of antimicrobials used in veterinary medicine, and the monitoring of the potential existence or development of antimicrobial resistance.

AND THAT THE OIE

- ◆ **Continue to develop and update standards, guidelines and recommendations on diagnostic tests, vaccines and veterinary drugs, including antimicrobials.**

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World organisation for animal health

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