



## Global Perspectives of Antimicrobial Resistance

**Scott A Brown, DVM, PhD, DACVCP**  
Pfizer Animal Health  
representing IFAH



### Who is IFAH?



**International Federation for Animal Health - IFAH**

The International Federation for Animal Health (IFAH) is the global representative body of companies engaged in research, development, manufacturing and commercialization of veterinary medicines, vaccines and other animal health products in both developed and developing countries across the five continents.


## Corporate members



## Member associations



## Member associations



<p><b>EUROPE</b></p> <ul style="list-style-type: none"> <li>• Europe</li> <li>• Belgium</li> <li>• Denmark</li> <li>• France</li> <li>• Germany</li> <li>• Ireland</li> <li>• Italy</li> <li>• Netherlands</li> <li>• Portugal</li> <li>• Spain</li> <li>• Sweden</li> <li>• Switzerland</li> </ul> <p>• United Kingdom</p>	<p>IFAH-Europe Pharma.be VIF SIMV BfT APHA AISA FIDIN APIFARMA VETERINDUSTRIA LIF SGCI Chemie Pharma Schweiz NOAH</p>	<p><b>NORTH AMERICA</b></p> <ul style="list-style-type: none"> <li>• Canada</li> <li>• Mexico</li> </ul> <p>• United States</p> <p><b>CENTRAL &amp; SOUTH AMERICA</b></p> <ul style="list-style-type: none"> <li>• Argentina</li> <li>• Brazil</li> </ul> <p><b>ASIA/PACIFIC</b></p> <ul style="list-style-type: none"> <li>• Australia</li> <li>• Indonesia</li> <li>• Israel</li> <li>• Japan</li> <li>• Korea</li> <li>• New Zealand</li> <li>• South-East Asia</li> <li>• Thailand</li> </ul>
<p><b>AFRICA</b></p> <ul style="list-style-type: none"> <li>• South Africa</li> </ul>	<p>SAAHA</p>	<p><b>CAHI</b> INFARVET -CANIFARMA AHI</p> <p>CAPROVE SINDAN</p> <p>The Alliance ASOHI MAI JVPA KAHPA AGCARM AAHA Thai AHPA</p>

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## Why does IFAH exist?



**The mission of IFAH is**

- to foster a greater understanding of animal health matters and
- to promote a predictable, science-based regulatory environment that facilitates the supply of innovative and quality animal medicines, vaccines and other animal health products into a competitive market place.


These products contribute to the health and welfare of animals and importantly provide a safe food supply for people.

**General objectives and goals**

- To achieve a balanced regulatory and trade framework that fosters innovation while recognising the social and political environment;
- To encourage constructive dialogue with governments, public policy makers, legislators, regulators, the veterinary profession, the food chain, consumers and other stakeholders;
- To ensure that the contribution of the animal health industry to health and quality of animal and human life through the advancement of sound science is understood by society at large.

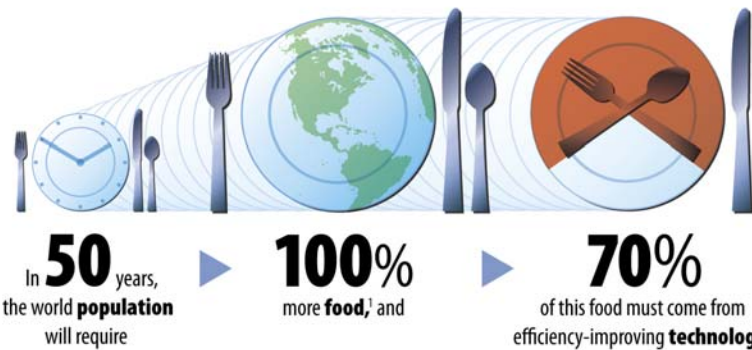
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## Food Economics and Consumer Choice



**An overview of the challenge ahead**

**Key Data**



In **50** years, the world **population** will require **100%** more **food**,<sup>1</sup> and **70%** of this food must come from efficiency-improving **technology**<sup>2</sup>


1 Green, R. et al. January 2005. "Farming and the Fate of Wild Nature." Science 307.5709: 550-555; and Tilman, D. et al. August 2002. "Agricultural sustainability and intensive production practices." Nature 415.6868: 671-677.

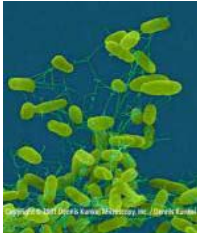
2 "World Agriculture: toward 2015/2030." 2002. United Nations Food and Agriculture Organization, Rome. Accessed 12/8/08. <ftp://ftp.fao.org/docrep/fao/004/y3557e/y3557e.pdf>.

**TECHNOLOGY'S ROLE IN THE 21<sup>ST</sup> CENTURY**


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## Antibiotic Resistance in Zoonotic Bacteria



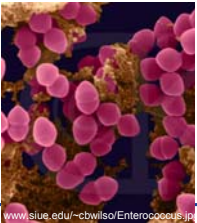


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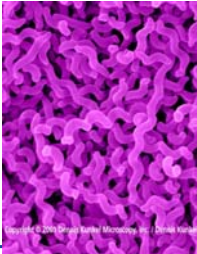


www.ericsecho.org/images/ecoli.jpg

- *Salmonella*
- *E. coli*
- *Campylobacter*
- *Enterococcus*



www.siu.edu/~cbwilsa/Enterococcus.jp



www.ericsecho.org/images/ecococcus.jpg

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

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It's a complex issue, often incorrectly simplified, thus misleading to the public



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**The challenge**



- Strong agreement among experts for balancing “one” global health; the question is:

How can we preserve the efficacy of currently available antimicrobials for use in people and animals?



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## Veterinary Drug Discovery



- 10+ years and \$100 million investment
  - Quality, safety (human and animal) and effectiveness
- Global animal health anti-infectives market
  - Approximately \$3 billion dollars in 2008
- Industry consolidation means less internal antibiotic expertise available, similar to human pharma
  - Most current "new vet antibiotics" discovered in 1980s
  - Most came from Human Discovery programs
  - Now seeking external opportunities
- Internal business competition of antibiotic opportunities vs. non-antibiotic candidates
  - Return on investment for shareholders
  - Probability of technical and regulatory success
  - External stakeholder issues



## Large US and European Pharmaceutical Companies Conducting Antibacterial Research

1980 (N=36)		1998 (N=20)	
Abbott	Miles	Abbott	Novartis
Astra	Parke Davis	Astra	Parke Davis
Ayerst	Pfizer	Bayer	Pfizer
Bayer	Pharmacia	Bristol-Myers Squibb	Pharmacia & Upjohn
Beecham	Proctor & Gamble	Glaxo Wellcome	Rhone-Poulenc Rorer
Bristol-Myers	Rhone-Poulenc	Hoechst Marion Roussel	Roche
Burroughs	Rorer	Johnson & Johnson	Sanofi
Ciba-Geigy	Roche	Lilly	Schering
Dow	Roussel	Merck	SmithKline Beecham
DuPont	Sandoz		Wyeth-Ayerst
Glaxo	Sanofi		Zeneca
Hoechst	Schering		
ICI	SmithKline		
Lederle	Squibb		
Lilly	Upjohn		
Marion	Warner-Lambert		
Merck	Wellcome		
Merrell	Wyeth		

2010 (N=3 to 7)*	
AstraZeneca (Glaxo SmithKline)	Novartis (Pfizer -Wyeth)
(Johnson & Johnson)	Sanofi-Aventis
(Merck-Schering Plough)	

\* ( ) = diminished effort

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Slide courtesy KA Bush, Indiana University

## Major Classes of Antimicrobials (shared human use classes)



<b><math>\beta</math>-lactams</b>	Penicillin, amoxicillin; ceftiofur
<b>Macrolides &amp; lincosamides</b>	Tylosin; tilmicosin; tulathromycin, lincomycin
<b>Aminoglycosides</b>	Gentamicin; neomycin
<b>Fluoroquinolones</b>	Enrofloxacin, danofloxacin
<b>Tetracyclines</b>	Tetracycline; oxytetracycline, chortetracycline
<b>Sulfonamides</b>	Various
<b>Streptogramins</b>	Virginiamycin
<b>Polypeptides</b>	Bacitracin
<b>Phenicols</b>	Florfenicol
<b>Pleuromutilin</b>	Tiamulin

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## Why people & animals share antibiotic classes



- Pathogens are similar in people and animals
- R&D-driven for humans; animals secondary (yet important) beneficiaries

Potential risks cited for "sharing"	Potential risks cited for not "sharing"
Resistance development, with human health implications	Animal mortality
Residues in meat/milk from improper use	Disease outbreaks, with animal and human health risks
	Illegal and off-label use

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## Global Reports on Animal Antibiotic Use since 1997



- WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture, AGISAR)
- OIE Terrestrial Code
- Codex –various (TFAMR)
- Europe (CVMP, EFSA, ECDC; EU commission)
- Australia (JETACAR)
- U.S. (NRC, CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
- Canada (Adv. Com. Report, CCAR)
- Other reports from APUA, IFT, Pew



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## WHO CIA List criteria



### 2.2 The WHO list of critically important antimicrobials

The WHO list of critically important antimicrobials was based on the following criteria for categorization as developed by two Expert Meetings (WHO, 2005; WHO, 2007):

- **Criterion 1** Sole therapy or one of few alternatives to treat serious human disease.
- **Criterion 2** Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources.

The definitions of the different categories were as follows:

*Critically important* antimicrobials are those that meet criteria 1 and 2

*Highly important* antimicrobials are those that meet criteria 1 or 2

*Important antimicrobials* are those that meet neither criteria 1 nor 2

FAO/WHO/OIE. 2008. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials. Report of a meeting held in FAO, Rome, Italy, 26–30 November 2007. FAO, Rome Italy, and WHO, Geneva, Switzerland.<sup>16</sup>

## Joint Consultation, Rome, 2008



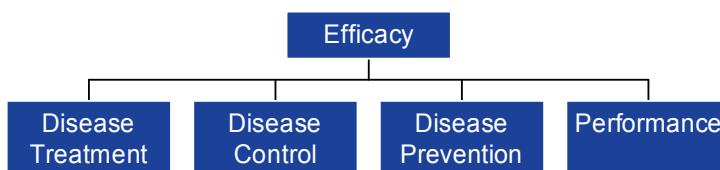
**Table 4.** Comparison of the human clinically important antimicrobials and veterinary clinically important antimicrobials lists

Critically important antimicrobials used in human medicine	Veterinary critically important antimicrobials
Aminoglycosides	Aminoglycosides
Cephalosporins (3rd and 4th generation)	Cephalosporins
Macrolides	Macrolides
Penicillins (natural, aminopenicillins and antipseudomonal)	Penicillins
Quinolones	Quinolones
Tetracyclines (only tigecycline)	Tetracyclines
Ansamycins	
Carbapenems	
Glycopeptides	
Oxazolidinones	
Streptogramins	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	
	Phenolics
	Sulfonamides



FAO/WHO/OIE. 2008. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials. Report of a meeting held in FAO, Rome, Italy, 26–30 November 2007. FAO, Rome <sup>17</sup> Italy, and WHO, Geneva, Switzerland.

## Antibiotic Uses



- **Disease treatment**
  - Therapeutic
- **Disease control**
  - Therapeutic
- **Disease prevention**
  - Therapeutic
- **Performance or “Growth promotion”**

## Key Messages



- Risk analysis is product and indication specific
  - all antibiotics are not created equal
- Monitoring / surveillance of resistance trends are important
  - respond to relevant data, not perceptions
- Responsible use by veterinarians is a primary risk mitigator
  - animals get sick and need medicines, just like people

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## Risk Analysis



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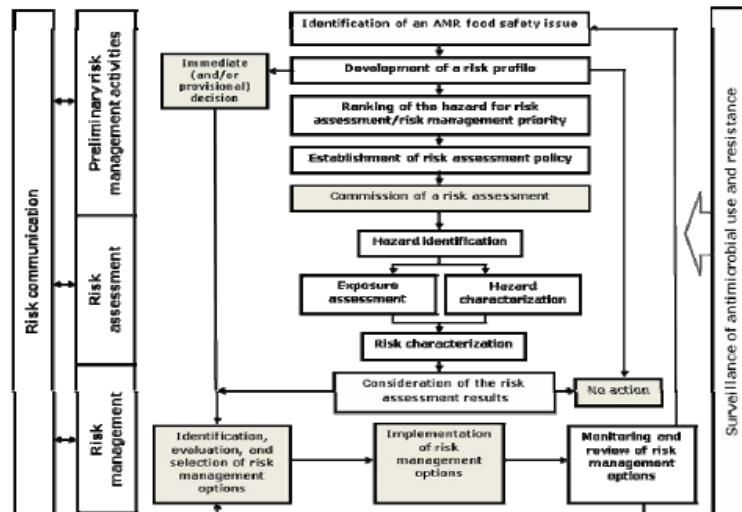
## Risk Assessment Recommendations



- WHO Responsible Use Guidelines (# 18 and 19)
- OIE Terrestrial Code (Chapter 6.11)
- Codex GL61 on Responsible Use
- Codex Task Force on Antimicrobial Resistance
- US Public Health Action Plan (#49-51)
- US Regulatory risk assessment G152

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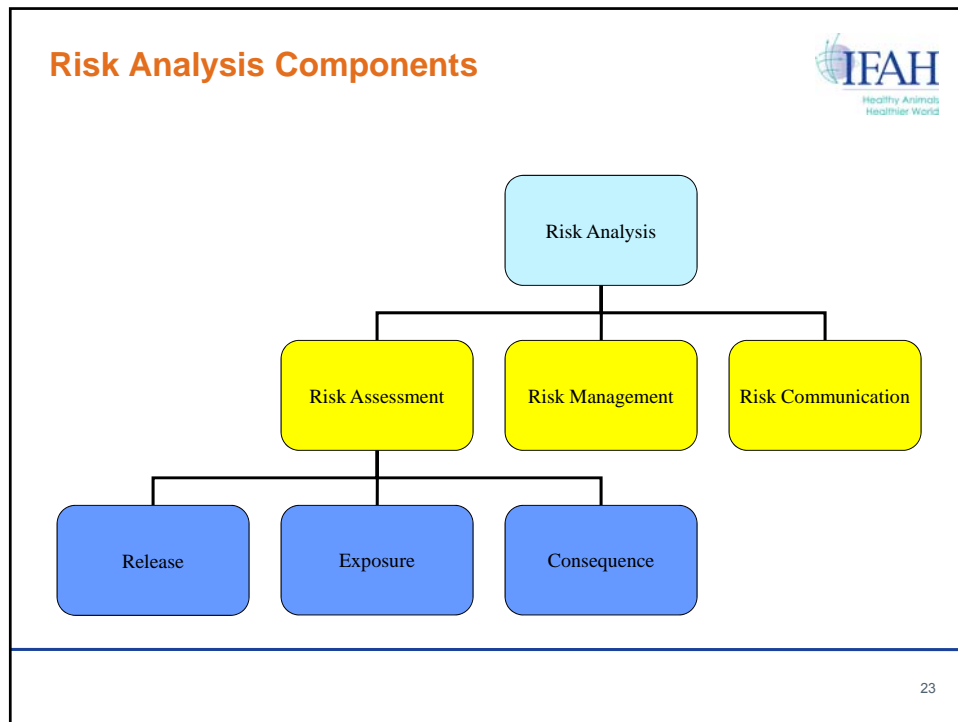
## Codex Alimentarius Microbiological Risk Analysis Flow Chart




Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR risk analysis; the box on "the relevance of antimicrobial use and resistance" is not a component of conventional risk analysis, however, it is useful at various stages of the foodborne AMR risk analysis process.

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AI33\_42e, p.34



## Comparison of Qualitative and Quantitative Risk Assessments



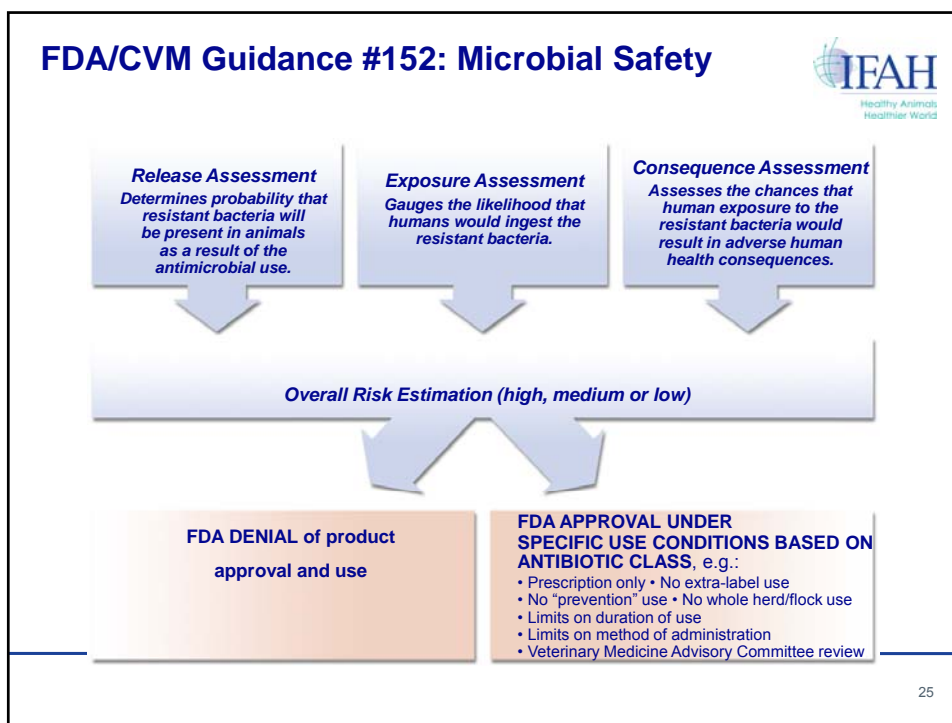
### Qualitative Risk Assessments

- Easier to understand
- Require less quantitative data
- Provide categorical assessments (based on predefined terms and criteria)

### Quantitative Risk Assessment

- More complex, often extensive math operations
- Require more and quantitative data
- Provide numerical outcomes that can be compared with known risks

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## How do companies use Guidance #152?

- **Early default assessment of new products/indications**
  - Does the concept fit with Guidance #152?
  - What hurdles would be expected?
  - Guides the "pursue or drop" development decisions
- **Provides the template for studies, data collection, and dossier outline**
  - Companies seek FDA concurrence on research approaches to answer questions
  - Companies provide data and interpretations of research; FDA reviews & questions

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## Virginiamycin (Vancomycin resistant - Quinupristin-dalfopristin resistant *E. faecium*)



- CVM
  - The first scenario assumes that 10% of the risk of acquiring resistant streptogramin-resistant *E. faecium* in the hospital is due to a food pathway.
  - Average risk to a random hospitalized member of the US population ranges from 6 to 120 chances in 100 million in one year. For a random member of the general US population, the risk estimates range from 0.7 to 14 chances in 100 million in one year.
- Cox et al.
  - Model shows a ban on VM would reduce average treatment failures by 1.8 cases over 5 years and mortalities by 0.29 cases

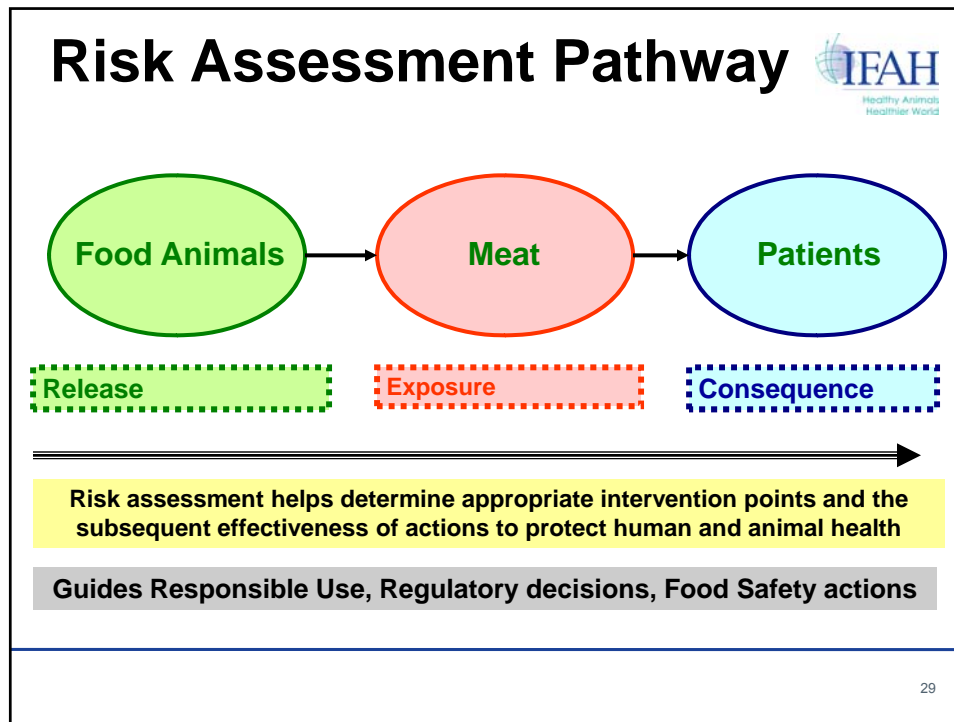
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## Risk Management Components



- Risk Evaluation
  - Comparison of the risk assessment outcome to acceptable level of risk
- Option Evaluation
  - Process of identifying, evaluating the efficiency and feasibility of, and selection of measures to reduce the risk
- Implementation
  - Following through with the risk management decision and ensuring that the risk management measures are in place
- Monitoring and Review
  - Auditing process to ensure that results expected are being achieved without unexpected adverse impacts

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## Summary

- Risk assessment process is critical to making science-based decisions on animal antibiotic use
  - Risk estimate helps to prioritize risk-reducing efforts
    - Current feed antibiotic risks are very low!
  - Risk assessment can help to identify appropriate interventions and probable outcomes
  - Data gaps can be identified for further research
    - AMR surveillance, on-farm antibiotic use data, human food borne disease estimates and treatment outcome data

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## Precautionary Principle



- Defined in European legislation:
  - The precautionary principle may be invoked where urgent measures are needed in the face of a possible danger to human, animal or plant health, or to protect the environment where scientific data do not permit a complete evaluation of the risk. It may not be used as a pretext for protectionist measures. This principle is applied mainly where there is a danger to public health. For example, it may be used to stop distribution or order withdrawal from the market of products likely to constitute a health hazard.
- A decision to take measures without waiting until all the necessary scientific knowledge is available

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## Guidelines for use of the precautionary principle



- The precautionary principle should be informed by three specific principles:
  - implementation of the principle should be based on the fullest possible scientific evaluation. As far as possible this evaluation should determine the degree of scientific uncertainty at each stage;
  - any decision to act or not to act pursuant to the precautionary principle must be preceded by a risk evaluation and an evaluation of the potential consequences of inaction;
  - once the results of the scientific evaluation and/or the risk evaluation are available, all the interested parties must be given the opportunity to study of the various options available, while ensuring the greatest possible transparency.
- Besides these specific principles, the general principles of good risk management remain applicable when the precautionary principle is invoked. These are the following five principles:
  - proportionality between the measures taken and the chosen level of protection;
  - non-discrimination in application of the measures;
  - consistency of the measures with similar measures already taken in similar situations or using similar approaches;
  - examination of the benefits and costs of action or lack of action;
  - review of the measures in the light of scientific developments.
  - the burden of proof

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## Bans on antibiotic growth promoters in feed



Korea: July 2011 (discontinued AB's in feeds)



European Union, 2006



Switzerland, 1999



Denmark, 1998



Sweden, 1986

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## Government Actions (withdrawal or limiting of approval)

- US – Baytril water soluble approval revoked by FDA in 2005
- EU - Label restrictions on use as first-line therapy (2011)
  - fluoroquinolones and cephalosporins
- Netherlands (current) – (proposed)
  - To ban all livestock use of beta-lactams, fluoroquinolones, macrolides, lincosaminides in livestock
  - To limit all new antimicrobials to human use
  - To eliminate all in-feed use of antimicrobials
- US – PAMTA (proposed)
  - Eliminates AGP, prevention and control claims for premix and water soluble products with critical antimicrobial animal drugs – unless Health and Human Services Secretary determines safety
  - Defines “critical antimicrobial animal drug” as one that is: “(1) intended for use in food-producing animals; and (2) is composed wholly or partly of—(A) any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide; or (B) any other drug or derivative of a drug that is used in humans or intended for use in humans to treat or prevent disease or infection caused by microorganisms.”
- US – Extra-label Drug Use restrictions/prohibitions (proposed)
- US – Elimination of growth promotion indications for medically important ABs (proposed)

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### Additional (Possible) Approaches to Risk Mitigation (1)



- Veterinary involvement for all antimicrobial uses
- Animal-side diagnostic tests – ID pathogen and resistance gene expression to tailor treatment more effectively
- Pre-harvest and at-harvest pathogen-reduction programs
  - Food safety vaccines
  - HACCP
  - At-harvest antimicrobial intervention
- Improvements in susceptibility surveillance programs that make them truly “prevalence” tools
- Understand “probabilistic” vs “possibilistic” aspects of antibiotic resistance

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### Additional (Possible) Approaches to Risk Mitigation (2)



- Management changes
  - All in, all out, all clean in between
  - Improve transport-related biosecurity
  - Reduce commingling and subsequent dispersal of animals
- Education
- Incentivize R&D investment
- Longer exclusivity times for those companies that invest significantly in “boots on the ground” technical assistance in judicious use education and monitoring.

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## Susceptibility Monitoring and Surveillance



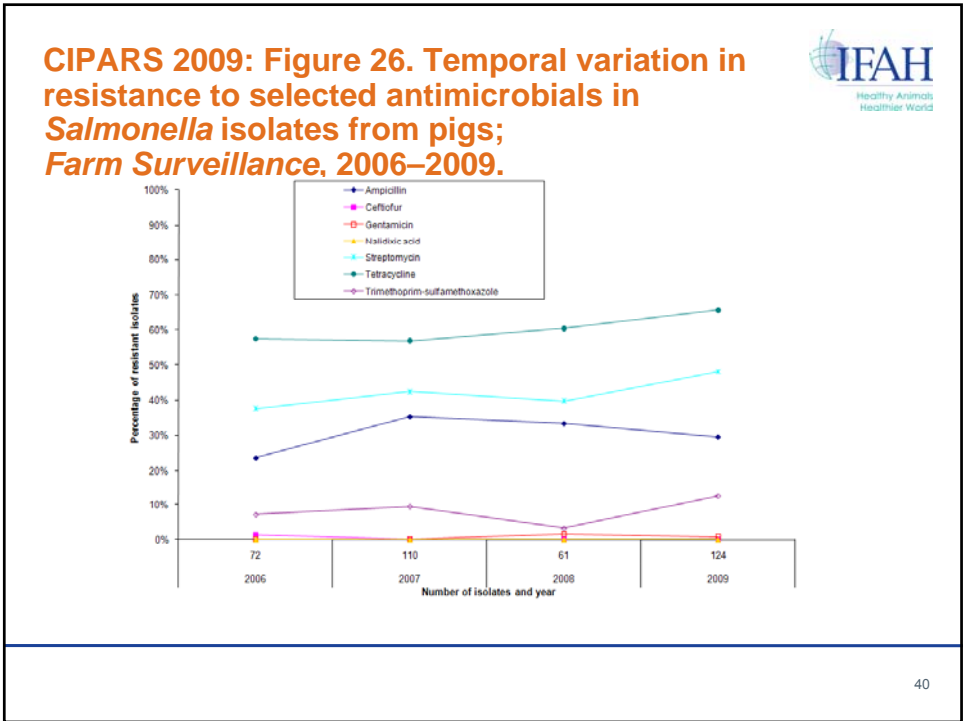
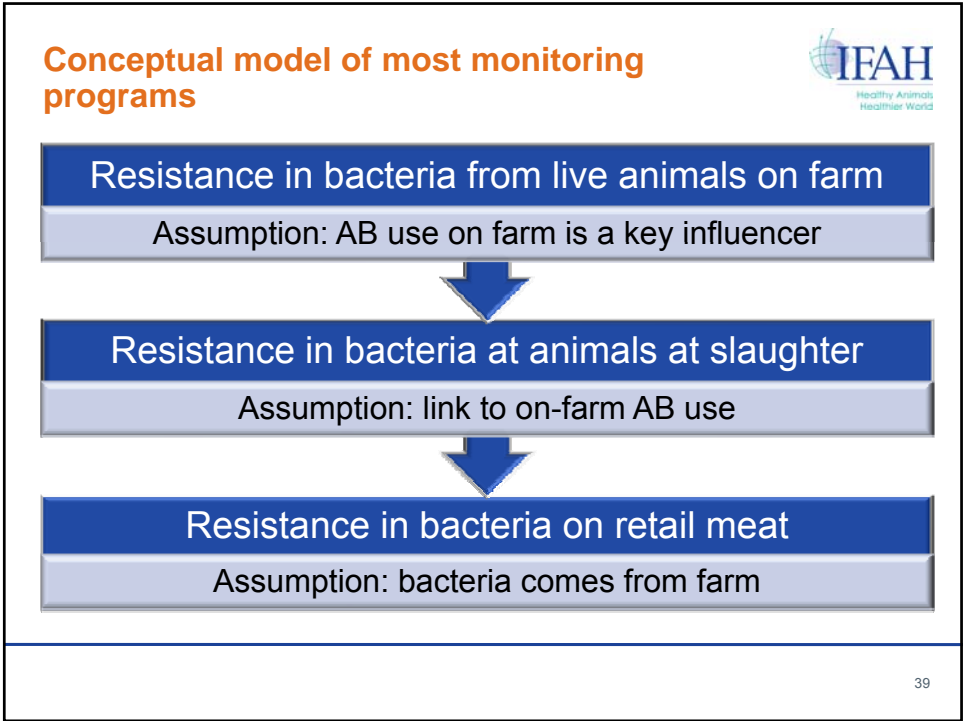
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## Examples of national antibiotic susceptibility monitoring programs

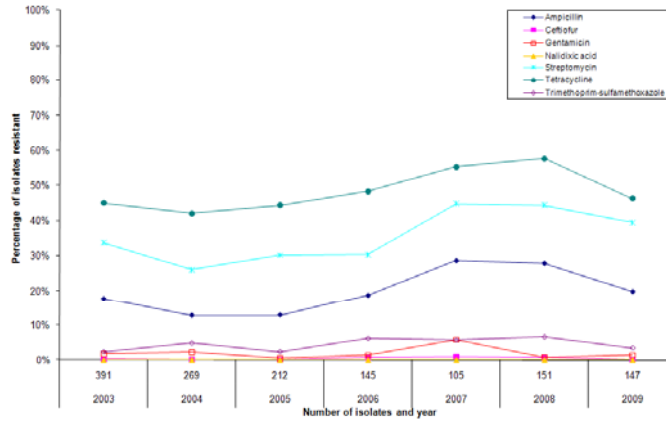


- Canada: Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- Denmark: DANMAP
- Netherlands: Monitoring of Antimicrobial Resistance and Antimicrobial Usage in Animals in the Netherlands (MARAN)
- US: National Antimicrobial Resistance Monitoring System (NARMS)

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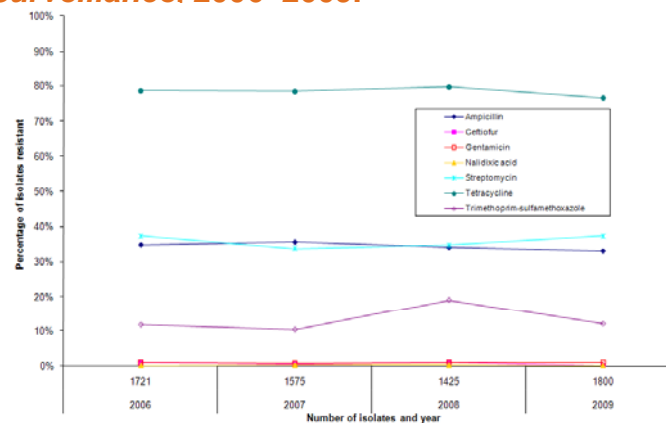


**CIPARS 2009: Figure 28. Temporal variation in resistance to selected antimicrobials in *Salmonella* isolates from pigs; *Abattoir Surveillance, 2003–2009.***

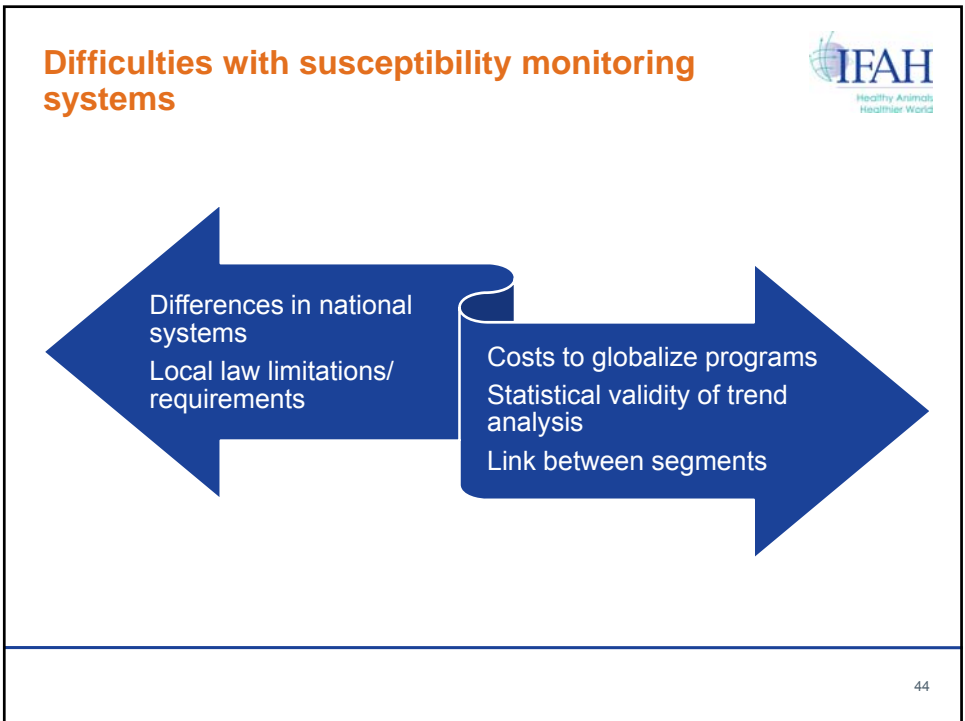
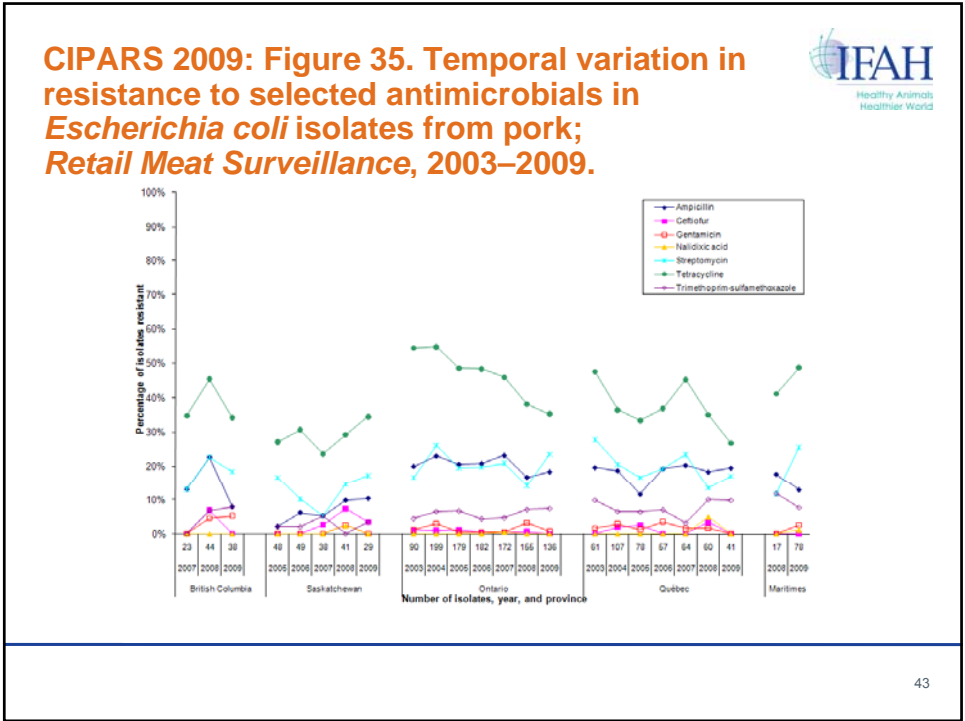


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**CIPARS 2009: Figure 31. Temporal variation in resistance to selected antimicrobials in *Escherichia coli* isolates from pigs; *Farm Surveillance, 2006–2009.***



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## Responsible use by veterinarians



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## Responsible Use Guidelines



- WVA
- Codex
- OIE
- WHO
- EPRUMA
- AVMA
- Many others...

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## Judicious use and responsible stewardship



- Unique challenges: Population medicine
  - Barn, farm or geographic location
- What we are doing to meet these challenges
  - Preventive medicine
  - Biosecurity
  - Disease surveillance
  - Best management practices



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## Appropriate Antibiotic Use in Animals



### LOCALLY

- Prevention first
  - Patient health/husbandry/sanitation/nutrition/vaccination
- Consult veterinarian for proper animal health intervention
- Proper diagnosis to select appropriate antimicrobial
- Use approved antimicrobials for treatment, minimizing extra-label use
- Treat as long as necessary to effect a cure
- Maintain accurate records of treatment and outcome

### GLOBALLY

- Better producer education programs
- Better vet services and distribution systems in developing countries for vaccine/medicine use

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## WHO Responsible Use - 2000



### ***Prophylactic use of antimicrobials***

33. Use of antimicrobials for prevention of disease can only be justified where it can be shown that a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a substitute for good animal health management.
34. Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped. Efforts to prevent disease should continuously be in place aimed at reducing the need for the prophylactic use of antimicrobials.

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## WHO Responsible Use - 2000



### **D. Antimicrobial growth promoters**

18. Use of antimicrobial growth promoters that belong to classes of antimicrobial agents used (or submitted for approval) in humans and animals **should be terminated or rapidly phased out in the absence of risk-based evaluations**. The termination or phasing-out should be accomplished preferably by voluntary programmes of food animal producers, but by legislation if necessary.
19. Risk-based evaluations of all antimicrobial growth promoters should be continued. Characterization of the risk may include consideration of the present and potential future importance of the drug to human medicine, its selection of resistance, the potential exposure to humans from resistant bacteria from food animals, as well as other appropriate scientific factors.

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## OIE Responsible Use Therapeutic Uses



### 12. Supply and administration of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the *antimicrobial agents* used in *animals* are:

- a) prescribed by a *veterinarian* or other authorised person;
- b) supplied only through licensed/authorised distribution systems;
- c) administered to *animals* by a *veterinarian* or under the supervision of a *veterinarian* or by other authorised persons.

The relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

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## Veterinarian Oversight includes...



- Establish veterinarian-client-patient-relationship
- Establish herd/flock health care program to minimize disease prevalence
- Obtain accurate disease diagnosis and/or utilize clinical judgment
- Determine need for treatment and appropriate product
- Administer product per label directions or extra-label use algorithm when necessary
- Maintain adequate records of treatment and clinical outcome to guide subsequent use



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## Why Veterinary Oversight?



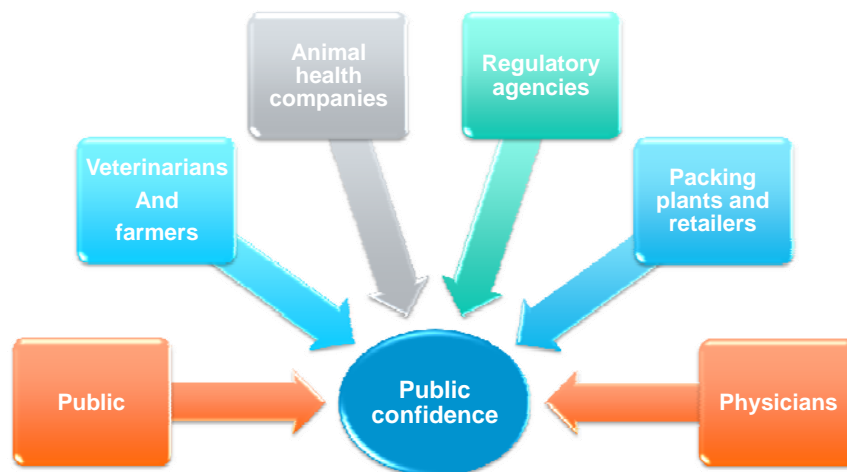
- Veterinarians are viewed as having the necessary experience and accountability to prescribe antibiotics as physicians
- Disease presentation, diagnostics, client relationship and other considerations require veterinary expertise to integrate into a medication decision
- Consistent with Responsible Use Principles

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## Working together going forward



*Building public trust will require work across stakeholders*



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## Summary of Actions and Recommendations International and National Level



- **Responsible Use**
  - Appropriate veterinary antibiotic use practices described; education, disease prevention
- **Resistance Monitoring**
- **Antimicrobial Usage 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

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## Going forward as an industry

- Reinforce by action that medicines are not used indiscriminately
- Producers must have protocols ensuring appropriate use, such as
  - Veterinarian *routinely validating* all uses
  - Independent audits to verify appropriate use
- Non-therapeutic uses
  - No rationale seems to comfort to consumers and many in public health
- Improve our communication skills on safeguards



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## Key Messages



- Risk analysis is product and indication specific
  - all antibiotics are not created equal
- Monitoring / surveillance of resistance trends are important
  - respond to relevant data, not perceptions
- Responsible use by veterinarians is a primary risk mitigator
  - animals get sick and need medicines, just like people

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## Closing thoughts...



- Contrary to popular belief, veterinarians don't have that many options for treating diseases.
- Responsibly developing new antibiotics is important to both human and animal health and the regulatory pathway needs to remain transparent and science based, as it is today.
- Ethical companies are investing in alternatives to antimicrobials to control and prevent infectious diseases in animals, but...
- Antibiotics (and new ones) will always be needed for animal and human health

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