Global vision on prudent use of antimicrobial agents in food animals
Unequal competition!

Spread of AMR

AMR management (control & prevention)
AMR control keys

- Research intervention
- AMU & AMR surveillance
- Rational use & Regulation
- Clean animal husbandry
- Infection prevention
- Public education
**Prudent:** wise and careful in action or judgment, avoiding risks

**Judicious:** having or showing reason and good judgement, making decisions

**Responsible:** having an obligation to do something, or having control over or care for someone, as part of one's job or role

**NOT** a direction of antibiotic use
Prudent use:
Usage of antimicrobials, which maximizes therapeutic effect and minimizes the development of antimicrobial resistance (WHO, 2000)

Responsible use:
The use of animal medicines carries with it responsibilities (Veterinarians’ and Farmers’) (RUMA, 2005).

Judicious use:
Antibiotics should be used to maximize the benefits of the therapeutic antibiotic use while minimize the development of resistance

Keep balance
<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Veterinary Medical association, 2007</td>
<td>Judicious use of Antimicrobials in Poultry</td>
</tr>
<tr>
<td>Federation of veterinarians of Europe, 1999</td>
<td>Antibiotic Resistance &amp; Prudent use of Antibiotics in Veterinary Medicine</td>
</tr>
<tr>
<td>OIE, 2011</td>
<td>Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine</td>
</tr>
<tr>
<td>WHO, 2000</td>
<td>WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food</td>
</tr>
<tr>
<td>Australian Veterinary Association, 2005</td>
<td>Guidelines for Prescribing, Authorizing and Dispensing Veterinary Medicines</td>
</tr>
<tr>
<td>AVPA, 2001</td>
<td>Code of practice for the use of antibiotics in the poultry industry</td>
</tr>
<tr>
<td>JETACAR, 1999</td>
<td>The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans</td>
</tr>
<tr>
<td>EPRUMA, 2008</td>
<td>European Platform for the Responsible Use of Medicines in Animals</td>
</tr>
</tbody>
</table>
## Most highly regarded guideline to prudent or judicious use

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA/FDA, 2012</td>
<td>Guidance for Industry # 209 The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals</td>
</tr>
<tr>
<td>World Veterinary Association, 2011</td>
<td>Draft position paper on responsible use of antimicrobials: The Global Basic Principles</td>
</tr>
<tr>
<td>EU, 2015</td>
<td>Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine 2015/C 299</td>
</tr>
<tr>
<td>Alliance for the Prudent Use of Antibiotics</td>
<td>Antibiotics Use in Food Animals</td>
</tr>
<tr>
<td>Canadian Food Inspection Agency</td>
<td>Prudent Use of Veterinary Drugs in Livestock Feeds</td>
</tr>
<tr>
<td>Canadian Veterinary Medicine Association</td>
<td>Guidelines on the Prudent Use of Antimicrobial Drugs in Animals</td>
</tr>
<tr>
<td>WHO, 2017</td>
<td>Guidelines on use of medically important antimicrobials in food-producing animals</td>
</tr>
</tbody>
</table>
Suggestions for guideline for judicious use of Antimicrobials in Food Animals

- Not so restrictively as to replace professional judgement of practitioners or to compromise animal health or welfare.
- Species-specific clinical practice guidelines on the responsible use of veterinary antimicrobial drugs
- Make recommendations on different AMU but vet will determine the final choice.
- Developed with multidisciplinary support by scientific data & knowledge; disease & AMR situation
- Subject to peer review
- Compatible with existing regulation
- Human concern
- Revised regularly
### Global basic principles of prudent use of antibiotics

1. Antibiotics are health management tools that are licensed to be used to enhance good husbandry practices for the purpose of disease prevention, disease treatment and production enhancement.

2. Codes of good practices, Quality assurance programmes, Herd Health Surveillance Program, and education programmes should promote the responsible and prudent use of antibiotics.

3. Antibiotics shall be used under the supervision of a veterinarian.

4. Therapeutic antibiotics should be used when it is known or suspected that an infectious agent is present which will be susceptible to therapy. It is the responsibility of the veterinarian to choose the antibiotic product, based on his/her informed professional judgement balancing the risks and benefits for humans and animals.

5. When antibiotics need to be used for therapy, bacteriological diagnosis with sensitivity testing should, whenever possible, be part of the informed professional clinical judgement.

6. Label instructions should be carefully followed and due attention paid to species and disease indications and contra-indications, dosage regimen, withdrawal periods, and storage instructions. Off-label use of antibiotics should be exceptional and always be under the professional responsibility of a veterinarian.

7. Antibiotics used for therapy should be used for as long as needed, over as short a dosage period as possible, and at the appropriate dosage regimen.

8. Records should be kept of all antibiotic administrations.

9. Co-ordinated susceptibility surveillance should be conducted and the results be provided to the prescriber, supervising veterinarians and other relevant parties.

10. Efficacious, scientifically proven alternatives to antibiotics are needed as an important part of good husbandry practices.
WHO Guidelines on use of medically important antimicrobials in food-producing animals

Critically Important Antimicrobials for Human Medicine
5th Revision 2016
Ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use

Medically important antimicrobials used in human medicine

Prioritize by Prioritization Criterion 1, 2, 3

- Critically Important
- Highly Important
- Important

- Highest Priority
- High Priority
### WHO Guidelines on use of medically important antimicrobials in food-producing animals

<table>
<thead>
<tr>
<th>C1</th>
<th>Criterion 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C2</th>
<th>Criterion 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from nonhuman sources, or (2) bacteria that may acquire resistance genes from nonhuman sources.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P1</th>
<th>Prioritization criterion 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>High absolute number of people, or high proportion of use in patients with serious infections in health care settings affected by bacterial diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P2</th>
<th>Prioritization criterion 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frequency of use of the antimicrobial class for any indication in human medicine, or else high proportion of use in patients with serious infections in health care settings, since use may favour selection of resistance in both settings.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P3</th>
<th>Prioritization criterion 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources.</td>
<td></td>
</tr>
</tbody>
</table>
Summary of classification and prioritization of antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>CRITICALLY IMPORTANT ANTIMICROBIALS</th>
<th>C1</th>
<th>C2</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGHEST PRIORITY</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cephalosporins (3rd, 4th and 5th generation)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Glycopeptides</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Macrolides and ketolides</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Polymyxins</td>
<td>●</td>
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<tr>
<td>Quinolones</td>
<td>●</td>
<td>●</td>
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<tr>
<td>HIGH PRIORITY</td>
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<tr>
<td>Aminoglycosides</td>
<td>●</td>
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<tr>
<td>Ansamycins</td>
<td>●</td>
<td>●</td>
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<td>●</td>
<td>●</td>
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<tr>
<td>Carbapenems and other penems</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Glycylcyclines</td>
<td>●</td>
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<tr>
<td>Lipopeptides</td>
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<tr>
<td>Monobactams</td>
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<td>●</td>
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<tr>
<td>Oxazolidinones</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tr>
<tr>
<td>Penicillins (natural, aminopenicillins, and antipseudomonal)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Phosphonic acid derivatives</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Drugs used solely to treat tuberculosis or other mycobacterial diseases</td>
<td>●</td>
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</tr>
</tbody>
</table>
### WHO Guidelines on use of medically important antimicrobials in food-producing animals

#### Summary of classification and prioritization of antimicrobials (cont.)

<table>
<thead>
<tr>
<th>Highly Important Antimicrobials</th>
<th>C1</th>
<th>C2</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amidopenicillins</td>
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<tr>
<td>Amphenicols</td>
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<tr>
<td>Cephalosporins (1st and 2nd generation) and cephamycins</td>
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<tr>
<td>Lincosamides</td>
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<tr>
<td>Penicillins (anti-staphylococcal)</td>
<td></td>
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<tr>
<td>Pseudomonic acids</td>
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<tr>
<td>Riminofenazines</td>
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<tr>
<td>Steroid antibacterials</td>
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<tr>
<td>Streptogramins</td>
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<tr>
<td>Sulfonamides, dihydrofolate reductase inhibitors and combinations</td>
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</tr>
<tr>
<td>Sulfones</td>
<td></td>
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<tr>
<td>Tetracyclines</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important Antimicrobials</th>
<th>C1</th>
<th>C2</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminocyclitolos</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic polypeptides</td>
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<tr>
<td>Nitrofurantoin</td>
<td></td>
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<tr>
<td>Nitroimidazoles</td>
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<tr>
<td>Pleuromutilins</td>
<td></td>
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</tbody>
</table>

*NA* indicates not applicable.
### WHO Guidelines on use of medically important antimicrobials in food-producing animals

**Recommendation 1: Overall antimicrobial use**

We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.

*Strong recommendation, low quality evidence*

**Recommendation 2: Growth promotion use**

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.

*Strong recommendation, low quality evidence*

**Recommendation 3: Prevention use (in the absence of disease)**

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

*Strong recommendation, low quality evidence*

**Recommendation(s) 4: Control and treatment use (in the presence of disease)**

**Recommendation 4a**

We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals.

*Conditional recommendation, very low quality evidence*

**Recommendation 4b**

We suggest that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.

*Conditional recommendation, very low quality evidence*
WHO Guidelines on use of medically important antimicrobials in food-producing animals

Best practice statement 1

Any new class of antimicrobials or new antimicrobial combination developed for use in humans will be considered critically important for human medicine unless categorized otherwise by WHO.

Best practice statement 2

Medically important antimicrobials that are not currently used in food production should not be used in the future in food production including in food-producing animals or plants.
Prudent Use Guidelines in Japan

Veterinarians and livestock farmers.

Main Points:

1. Prevention of infection
   - The standards of Rearing Hygiene Management
   - The guidelines on good hygienic practice

2. Definite diagnosis
   Identify the cause of infection and determine tx measures based on veterinarian’s definite diagnosis

3. Effective use of antimicrobials
   - Choose effective antimicrobial drugs with sensitivity test
   - Fluoroquinolones, 3rd generation cephalosporins, etc. should be used only if the first choice drug is not effective

4. Information sharing
   Share information about AMR bacteria among the relevant parties
Guidelines on prudent use of antimicrobials in food–producing animals

COMMISSION NOTICE

Guidelines for the prudent use of antimicrobials in veterinary medicine

(2015/C 299/04)
Guidelines on prudent use of antimicrobials in food-producing animals

- avoiding the prophylactic use of antimicrobials in new-born piglets (and after weaning), as a part of a herd health strategy;
- implementing an ‘all-in all-out’ system of production, thoroughly cleaning and disinfecting production units when animals move into, within and out of the herd;
- considering a vaccination strategy where available;
- establishing appropriate feeding strategies based on the pigs' age, especially at weaning;
- avoiding mixing within the herd, or quarantining stock for an appropriate period prior to mixing;
Antimicrobials should not be used routinely on the arrival of day-old chicks at the farm.

The use of antimicrobials for non-infectious diseases with limited secondary infections should be avoided.

The use of 3\textsuperscript{rd} and 4\textsuperscript{th} generation of cephalosporins in poultry (including eggs) should be prohibited.

Fluoroquinolones should be reserved for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antimicrobials and, whenever possible, should only be used where susceptibility testing has first been carried out.

Antimicrobials shall not be used as a specific method to control \textit{Salmonella}. 
Ensuring alignment between human and veterinary sectors to minimise risks arising from use of antibiotics

Adopts a ‘One Health’ approach but recognises the specific nature of the human and veterinary sectors

Different priorities drive the activities
- For human, medicines promote the availability of antimicrobials to treat multidrug resistant organisms
- For veterinary, medicine ensure the continued availability of veterinary antimicrobials whilst limiting the risk to man from the use of antimicrobials in animals
### Responsible Use of Antibiotics

**Category**  | **Risk to Public Health** | **Antimicrobials Included** | **Advice on use** |
--- | --- | --- | --- |
1 | Low/limited risk to public health | Narrow spectrum Penicillins, Macrolides, Tetracyclines | General principles of responsible use to be applied |
2 | Higher risk to public health | Fluoroquinolones, systemic 3\(^{rd}\) /4\(^{th}\) generation Cephalosporins, (Aminoglycosides, broad-spectrum Penicillins), Colistin | Restricted to use where there are no alternatives or response to alternatives expected to be poor |

**Fluoroquinolones, 3\(^{rd}\) and 4\(^{th}\) generation cephalosporins and colistin** are recognised as the most important of the CIAs, as designated by EMA.
Guidelines of Judicious Use in the US

Guidance for Industry #152

Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Guidance for Industry #213

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Guidance for Industry #209

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

- Does not have the force of law.
- Provides the agency’s position on regulatory matters.
- Voluntary is relative.
- #152 provides guidance on evaluating the potential effects of antimicrobial new animal drugs on non-target bacteria as part of the new animal drug application process.
Two key principles:

1. Limit use of medically important antimicrobial drugs to those uses considered necessary for assuring animal health (i.e., therapeutic purposes)
2. Increase veterinary involvement/consultation

- Use for growth promotion and nutritional efficiency of antibiotics in classes used in human medicine are **injudicious** or was bot called **unsafe**.
- Uses of the others in the same classes of antibiotics are under **veterinary oversight**.
- Discontinuing claims or migrating production claims to disease prevention is voluntary work.

- Initiating step
- Goal to preserve availability of effective ABO for both human and animals.
Guidelines of Judicious Use in the US

Guidance for Industry #213

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

- Provides more detailed guidance on implementation of key principles in Guidance 209
- Growth Promotion and Nutritional Efficiency labels was removed by Dec. 2016.
- Remaining therapeutic uses under VFD or prescription for affected products (Medically Important).
- Most growth promotion uses will end within 3 years.
- Most feed grade antibiotics will no longer be available over-the-counter but will require a veterinary “order”.
- Administered in feed/water is Rx.
- Stakeholder concerns that removing production uses might negatively impact animal health.
- Potential new therapeutic uses
  Therapeutic = treatment, control, prevention
- All OTC to Rx or VFD.

Global Issues

Drugmakers Agree to U.S. Ban on Livestock Antibiotics
by Carey L. Bron (Washington) | Thursday, March 27, 2014
Inter Press Service

WASHINGTON, Mar 27 (IPS) - Pharmaceutical companies have overwhelmingly agreed to new U.S. government guidelines aimed at decreasing the use of antibiotics in the raising of livestock, new data shows.
Judicious Use Principle

Veterinarian-Client-Patient relationship (VCPR).

- Assume the responsibility for making clinical judgements and the need for medical tx.
- Have sufficient knowledge of the flock & recently seen the flock.
- Be readily for consultation and follow-up evaluation & emergency.

(AVMA, 2005)
Classification of antimicrobials based on importance and use in both human and poultry

**Class I:** Important in human medicine; to be held in reserve for treatment in poultry

**Class II:** Human medicine use where alternatives exist; exposure in poultry is moderate; **erythromycin, penicillin, gentamicin, sulfonamides, cefiofur, tetracycline class**

**Class III:** No or minimal use in human medicine or low exposure in poultry; **bacitracin, streptomycin, tylosin, lincomycin, spectinomycin, neomycin**
Antimicrobials should be used in animals only after careful review.

- Use narrow-spectrum antimicrobials whenever appropriate.
- Use microbial culture and antimicrobial susceptibility results to aid in the selection of antimicrobials when clinically relevant.
- Regimens for antimicrobial treatment, control, or prevention of disease should be based upon current scientific and clinical principles, such as microbiological and pharmacological tenets.
- To minimize selective pressure, therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed for the desired clinical response.
- Limit therapeutic antimicrobial treatment to ill or at-risk animals, treating the fewest animals indicated.
Research Unit in Microbial Food Safety & Antimicrobial Resistance

Center for Antimicrobial Resistance Monitoring in Foodborne Pathogens (in cooperation with WHO)

GFN: SE Asia & Western Pacific

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Faculty of Veterinary Science,
Chulalongkorn University

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