The Contribution of Antimicrobial use in Food Animal Production to the Emergence of Antimicrobial Resistance in Humans

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Promoting Science

Enabling Action
INTRODUCTION

- Widespread use of antimicrobials in livestock production ....not only for therapeutic purposes
- Same classes of antimicrobials are used both in humans and animals..
- Few new antibiotics are being developed to replace those becoming ineffective through resistance
- Food is generally considered to be the most important vector for spread of resistance between animals and humans
- Globalization of food trade, need for international action
Risk Analysis

Risk Assessment
* Science based

Risk Management
* Policy based

Risk Communication
* Interactive exchange of information and opinions concerning risks
"There is a pathway from good science to publication to evidence, and to programs that work. In this way research becomes an inherent part of problem-solving and policy implementation"

Julio Frenk
Former Mexican Minister of Health
Dean, Harvard School of Public Health
Attributable Fractions
Salmonella Source Account

- Registered human cases
  - Sero-, phage- & DNA types

- Prevalence in food animal reservoirs
  - Sero-, phage- & DNA types

- Comparison of types
  - Certain types almost exclusively isolated from single sources
  - Other types ascribed to source proportionally to indicative types

- Beef (0.3-0.5%)
- Table eggs (20-25%)
- Unknown (24-28%)
- Travels (14-18%)
- Broilers (2-4%)
- Turkeys and ducks (5-8%)
- Imported pork (4-6%)
- Imported poultry (10-14%)
- Pork (6-8%)
Improvements

- Food control systems to re-allocate funds from senseless control to sensible data gathering
- Combination of active surveillance and new typing systems to enable source attribution
- Reducing risk through efficient interventions
Outline

- History of WHO's work on AMR from animal use
- How does AMR use in animals impact human health?
- What WHO is doing to address the issue
- Future perspectives on foodborne AMR
Recommendations (1997):

- Monitoring of antimicrobial resistance in food animals and food of animal origin
- Risk Assessment
- Risk management at the primary food production level: Prudent use of antimicrobials
WHO Global Principles for the Containment of AMR in food-animals

- Geneva, June 2000
- To minimise the public health impact of the use of antimicrobial agents in food animals
- Large consultation incl. stakeholders
WHO Global Principles....
(Usage and monitoring)

- Use of antimicrobial growth promoters ..... should be terminated or rapidly phased-out in the absence of risk-based evaluations

- Data generated from the surveillance of antimicrobial resistance and antimicrobial usage should play a key role in national policies for the containment of AMR

- Programmes to monitor antimicrobial resistance in animal pathogens, zoonotic agents and indicator bacteria should be implemented on bacteria from animals, food of animal origin and humans.
WHO-panel on impacts of growth promoter termination in Denmark (2003)

- Independent interdisciplinary review panel;

- Assessed impacts on human health, AH and welfare, animal production and economic consequences.
Joint FAO/WHO/OIE consultative process on Non-human use of antimicrobials and antimicrobial resistance (Requested by Codex)

- 1rst Workshop on Risk Assessment, Geneva, December, 2003
- 2nd workshop on risk management options, Oslo, March 2004
- WHO Expert Consultation on critically important antimicrobials for Human, Canberra, February 2005
- Consultation on use of antimicrobials in aquaculture and resistance, Seoul, June 2006
How does AMR use in animals impact human health?

1. Most foodborne diseases are zoonoses (Campylobacteriosis, Salmonellosis, VTEC, …)

2. Use of antimicrobials in animals select for zoonotic bacteria that can transfer resistance (bacteria, genes) to human pathogens

3. FBD with resistant bacteria associated with increase adverse human health consequences
Figure SU1. The reported incidences of the zoonoses in humans, 2006

- Campylobacteriosis: 175,561 cases
- Salmonellosis: 160,649 cases
- Yersiniosis: 8,979 cases
- VTEC: 4,916 cases
- Listeriosis: 1,583 cases
- Brucellosis: 1,033 cases
- Echinococcosis: 458 cases
- Trichinellosis: 231 cases
- Lyssavirus: 0 cases

Incidence per 100,000 population
How does AMR use in animals impact human health?

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More than 50% of all antimicrobials are used non-therapeutically in animal husbandry

Use of antimicrobials in food animals can lead to Antimicrobial Resistance (AMR) in human pathogen.

- E.g. Antibiotics added to drinking water to decrease diseases of crowding and as growth promoters (not in EU)
  - Any use of antibiotics can lead to Antimicrobial Resistance

Antibiotics…"the more you use them, the faster you lose them"
Classes of antibiotics used for humans and animals

- Aminoglycosides
- 3rd and 4th gen. Cephalosporins
- Fluoroquinolones
- Glycopeptides
- Penicillins
- Macrolides
- Tetracyclines
- Carbapenems
- Linezolid*
Antimicrobial use estimation – we need real data!

Drug use for humans and animals

France, 2005

Denmark, 2007
Quinolone-resistant Salmonella Typhimurium DT104 (UK)

November 93 – Enrofloxacin licensed for animal use

Percent of isolates

<table>
<thead>
<tr>
<th>Year</th>
<th>Chickens</th>
<th>Cattle</th>
<th>Pigs</th>
<th>Humans</th>
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<tbody>
<tr>
<td>92</td>
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Fluoroquinolone resistance in human Campylobacter (USA)

- Approved for use in humans
- Approved for use in poultry
- FDA withdrew approval

Year

- 86
- 90
- 95
- 97
- 2000
- 2005

Percent resistant

0% Sentinel survey

CDC began surveillance

CDC
MRSA

- Until 2003 only considered a human problem

- After 2003 – emergence of isolates among production animals, originally pigs, but now also cattle and poultry, that spread and cause infections in humans
The proportion of NT-MRSA ≅ CC398 has increased from 0% in 2003 to 33% of all new reported cases of MRSA in the 2007
Effect of Ceftiofur voluntary withdrawal of in ovo use
2003–2008 in Québec, Canada

E. coli - retail chicken
S. Heidelberg – chicken
S. Heidelberg - human

Food as a Source of AMR

- Antimicrobial resistant bacteria: *direct hazard*
  - Humans can be infected after food ingestion or handling
  - Examples
    - Zoonotic bacteria e.g. *Salmonella*, *Campylobacter*
    - Non-zoonotic bacteria e.g. *Shigella*, *Vibrio*

- Antimicrobial resistance genes: *indirect hazard*
  - Transfer of resistance genes to pathogen from commensal
  - Mobile genetic elements harboring resistance determinants can readily be transferred horizontally between bacteria from animals and humans
    - Can also take place in natural environments
    - Examples: *E. coli* and *Enterococcus* spp.
Summary of importance of the animal reservoir

- Larger selective pressure
- Most important reservoir for antimicrobial resistant Salmonella and Campylobacter.
- An increasingly important reservoir for MRSA
- Important, but not quantified reservoir for E. coli
- Transferable genes
How does AMR use in animals impact human health?

- 1-Most foodborne diseases are zoonoses (Campylobacteriosis, Salmonellosis, VTEC, ...)
- 2-Use of antimicrobials in animals select for zoonotic bacteria that can transfer resistance (bacteria, genes) to human pathogens
- 3-FBD with resistant bacteria associated with increase in adverse human health consequences
Health consequences of AMR

- Increased number of infections
- Increased frequency of treatment failures
- Increased severity of infections
  - Prolonged duration of illness
  - Increased frequency of bloodstream infections
  - Increased hospitalization
  - Increased mortality
- Increased costs to society
WHO's approach to minimise antimicrobial resistance in humans due to use of antimicrobials in food animals

1) The Concept of Critically Important Antimicrobials
(= CIA, developed in collaboration btw OIE, FAO and WHO)

2) The Integrated Approach
(Advisory Group on Integrated Surveillance of Antimicrobial Resistance)
WHO CIA list:
Categorization of antimicrobials
according to their importance in human medicine

**Q:** WHY should we do it?

**A1:** The same drugs are used in animals and humans and most antimicrobials are used in animal sector

**A2:** Enabling focus on antimicrobials as "last resort" for humans
WHO list of Critically Important Antimicrobials (CIA)

- **Criterion 1**: Antimicrobial agent used as *sole therapy* or one of few alternatives to treat serious human disease

- **Criterion 2**: Antimicrobial agent is used to treat diseases caused by
  1) organisms that may be **transmitted to man** via non-human sources, or
  2) diseases caused by organisms that may **acquire resistance genes** from non-human sources

...three categories.
WHO list of Critically Important Antimicrobials (CIA)

- **Critically Important**: those antimicrobials which meet both criteria 1 and 2

- **Highly Important**: those antimicrobials which meet either criterion 1 or 2

- **Important**: those antimicrobials which meet neither criterion 1 nor 2

  Criterion 1: Sole therapy
  Criterion 2: Non-human source
Critically Important Antimicrobials

<table>
<thead>
<tr>
<th>Aminoglycosides</th>
<th>Macrolides and ketolides</th>
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<tr>
<td>Ansamycins</td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td>Carbapenems and other penems</td>
<td>Penicillins (natural, aminopenicillins and antipseudomonal)</td>
</tr>
<tr>
<td>Cephalosporins (3\textsuperscript{rd} and 4\textsuperscript{th} generation)</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Streptogramins</td>
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<tr>
<td>Glycylcyclines</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>Drugs used solely to treat TB or other mycobacterial diseases</td>
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<tr>
<td><strong>Aminopenicillins</strong></td>
<td><strong>Pseudomonic acids</strong></td>
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<tr>
<td>Aminocyclitols</td>
<td>Penicillins (Anti-staphylococcal)</td>
</tr>
<tr>
<td>Aminoglycosides (Other)</td>
<td>Pleuromutilins</td>
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<tr>
<td>Amphenicols</td>
<td>Polymyxins</td>
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<tr>
<td>Cephalosporins (1\textsuperscript{st} and 2\textsuperscript{nd} generation)</td>
<td>Riminofenazines</td>
</tr>
<tr>
<td>Cephamycins</td>
<td>Sulfonamides, DHFR inhibitors and combinations</td>
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<tr>
<td>Fusidic acid</td>
<td>Sulfones</td>
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<td>Monobactams</td>
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</table>
Highest Priority Critically Important Antimicrobials

- **Quinolones** are widely used in food animal production and are known to select for quinolone-resistant *Salmonella* spp. in animals. At the same time, quinolones are one of few available therapies for serious Salmonella infections, particularly in adults.

- **3rd and 4th generation cephalosporins** are widely used in food animal production and are known to select for cephalosporin-resistant *Salmonella* spp. in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella infections, particularly in children.

- **Macrolides** are widely used in food animal production and are known to select for macrolide-resistant *Campylobacter* spp. in animals. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment.
WHO's approach to minimise antimicrobial resistance in humans due to use of antimicrobials in food animals

1) The Concept of Critically Important Antimicrobials (= CIA, developed in collaboration btw OIE, FAO and WHO)

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

- WHO-AGISAR (December 2008): to support WHO's efforts to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals.

**Subcommittees**

- Usage Monitoring
- Antimicrobial Resistance Surveillance
- Capacity Building
- Software Development

The AGISAR group
AGISAR Activities on AMR

- WHO list of Critically Important Antimicrobials
- Development of protocols and training packages
- Software development
- Country pilot studies
- Provision of scientific advice
- Teleconferences and Annual meetings
  - 1st meeting: Copenhagen, Denmark, 15-19 June 2009.
  - 2nd meeting: Guelph, Canada on 5-7 June, 2010.
Expected results

- WHO list of critically important antimicrobials updated every two years.

- Harmonized protocols for monitoring antimicrobial usage and resistance in animals, food and humans developed and disseminated.

- Software for data collection and analysis developed and disseminated.

- Support WHO capacity-building activities in Member countries through GFN (Global Foodborne Infections Network) training courses.

- Data generated through country pilot projects: Kenya, China, Columbia focused research projects: Senegal, Cameroon, China, Costa Rica, Brazil
Future perspectives on AMR

- A continuing problem...
- New challenges will arise, including food safety, trade issues
- Need harmonization of methods and reliable data on antimicrobial use and antimicrobial resistance (capacity building, pilot studies in developing countries)
- Codex AMR Task force to provide guidance
- Codex to set standards
- Need for holistic approaches
  - WHO-AGISAR
  - Proper prevention and control measures
- Basic and applied research
  - Mechanisms, trends and risk factors
  - New antimicrobials, alternatives to antimicrobials, vaccines
- Need for audacity in solutions – end unnecessary use!
For more information visit WHO/FOS AMR webpage

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