Antimicrobial resistance and food safety: a slumgullion stew of science, policy, and practice

NIFA-IFSN Webinar Series
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Slumgullion stew...

• "a meat stew..."¹

• Best described as: an ‘if it’s’ stew
  - “If it’s in the refrigerator it goes into the mix”²

¹ Merriam-Webster’s online dictionary
² Shared Tastes WordPress blog
Outline

• Contemporary ‘science’ of antimicrobial resistance
  – Overview of AMR at the interface of food production and public health
  – Introduction to several critical issues
    • ESBL and AmpC producing Enterobacteriaceae
    • Carbapenemase producing Enterobacteriaceae
    • Colistin resistance

• Issues impacting antimicrobial use policy: from farm to fork
  – The debate about agricultural uses of antibiotics and possible solutions

• Practice evidence: identifying and implementing best practices to reduce or mitigate AMR risks
  – Risk assessment and risk management
Mechanisms of Resistance

- **Random genetic mutations**
  - Strains propagate where fitness advantage exists for the mutation

- **Acquired resistance**
  - Horizontal gene transfer

- **Resistance genes code:**
  - **Efflux pumps** (rid the cell of the antimicrobial)
  - **Enzymes** that metabolize the antimicrobial
  - **Ribosomal protection**
  - **Physical-chemical features** that inhibit antimicrobial entry into the cell

Graphics: FDA
How does antimicrobial selection pressure help to propagate and transmit AMR?

One example from: Lipsitch and Samore (2002)
ECOLOGY OF ANTIMICROBIAL RESISTANCE

LAND BASED

AQUACULTURE
Cultured finfish (salmon, trout, arctic charr and cod)

NETCAGE

sea

drinking water

rivers and streams

drinking water

SOIL

WILDLIFE

Sewage

Vegetation, Seed Crops, Fruit

HUMAN

HOSPITALIZED
COMUNITY
- URBAN
- RURAL

EXTENDED CARE FACILITIES

HUMAN

Industrial & Household Chemicals

Rendering

Animal feeds

offal

ANIMAL

SHEEP
CATTLE
POULTRY
VEAL CALVES
OTHER FARmed LIVESTOCK

ANIMAL

commercial abattoirs

meat

handling preparation consumption

direct contact

COMPANION ANIMALS

R. Irwin: after Linton (1977)
What do we know about the risks from agricultural use of antimicrobials?

Surprisingly little...
One risk assessment framework

Figure 1: Hurd (Microbe, 2006)

- Macrolide given to animals
- RzD selected above background
- RzD escapes from farm

Viable organisms with RzD present in food for further processing
Viable organisms with RzD present in retail meat
Probability of mishandling and presentation to human

Patient gets ill
Patient treated with macrolide

Stop sign: Macrolide is ineffective

Release assessment: Describes the probability that factors related to the antimicrobial use in animals will result in the emergence of resistant bacteria or resistance determinates (RzD).

Exposure assessment: Describes the likelihood of human exposure to the RzD through particular exposure pathways.

Consequence assessment: Describes the relationship between specified exposures to the RzD (the hazardous agent) and the consequences of those exposures (CVM-defined hazard)

Risk

Stepwise risk assessment-based approach for estimating the impact on human health from macrolide resistance that develops on poultry farms.
CDC threat report

- September, 2013

- Three threat levels
  - Urgent
  - Serious
  - Concerning
Introduction - Urgent threat

- Of concern to U.S. food production
  - *Carbapenem-resistant Enterobacteriaceae (CREs)*

*Direct selection by carbapenems does not occur in US agriculture*
Notes from the Field...
Introduction – Serious threat

- Of concern to U.S. food production
  - *Drug-resistant *Campylobacter
  - *Drug-resistant non-typhoidal *Salmonella
  - *Extended spectrum β-lactamase producing *Enterobacteriaceae (ESBLs)
    - 3rd and 4th generation cephem resistance
  - *Methicillin-resistant *Staphylococcus aureus
  - Vancomycin-resistant *Enterococcus spp.

*Commonly found in U.S. animal agriculture
THE SPREAD OF ANTIBIOTIC RESISTANCE

An increasing proportion of bacteria display resistance to common antibiotics.

- Fluoroquinolones
- Cephalosporins (3rd gen)
- Aminoglycosides
- Carbapenems
- Polymyxins

Resistance in bacteria (% of samples, worldwide)


*Enterobacteriaceae, including Escherichia coli, Klebsella pneumoniae, Enterobacter and Salmonella

Source: CDDEP ResistanceMap, based in part on data obtained under license from IMS MIDAS

Nature: after CDDEP
Salmonella resistance to ceftiofur (NARMS 1997-2007)

Cattle slaughter and diagnostic laboratory isolate sources

Data source: www.ars.usda.gov
Extended spectrum beta-lactams

- **Beta-lactams**
  - Penicillin (1)
  - Ampicillin, amoxicillin
  - Cephalosporins (2)
    - 1\textsuperscript{st} generation (cefalotin,…)
    - 2\textsuperscript{nd} generation (cefoxitin,…)
    - 3\textsuperscript{rd} generation (ceftriaxone,…)
    - 4\textsuperscript{th} generation (cefepime,…)
  - Carbapenems
    - Imipenem, ertapenem, meropenem
Extended Spectrum Beta-lactamases (ESBLs)

- **Beta-lactamases**
  - **Penicillin**
  - **Ampicillin, amoxicillin**
    - \((TEM-1, SHV-1)\)
  - **Cephalosporins**
    - 1\(^{st}\) generation (cefalotin) \((TEM, SHV-1)\)
    - 2\(^{nd}\) generation (cefoxitin) \((CMY-2)\)
    - 3\(^{rd}\) generation (ceftriaxone) \((CMY-2, CTX-M, SHV-2)\)
    - 4\(^{th}\) generation (cefepime) \((CTX-M)\)
  - **Carbapenems**
    - Imepenem, ertapenem, meropenem \((KPC, NDM, OXA-48, IMP)\)
Extended Spectrum Beta-lactamases (ESBLs)

• The abbreviations or acronyms that make up the beta-lactamase ($bla_{\text{subscript}}$) name are generally logical, in some cases historically informative, and occasionally amusing.
  – The CTX-M family of genes (active on cefotaxime, first isolated at Munich) family has multiple subtypes designated starting at CTX-M-1,
  – The SHV family refers to the sulfhydryl reagent variable,
  – The TEM was named after the patient from whom the bacterial isolate was discovered (Temoneira), and
  – The CMY family indicates it is active on cephameycins.
ESBL/AmpC β-lactamase disk diffusion test

(CTX = cefotaxime, CAZ = ceftazidime, CLA = clavulanic acid, FOX = cefoxitin, FEP = cefepime)

**ESBL**

- **FEP**
- **CTX**
- **FOX**
- **CAZ**
- **CTX-CLA**
- **CAZ-CLA**

Synergy!

**AmpC**

- **FEP**
- **CTX**
- **FOX**
- **CAZ**
- **CTX-CLA**

No synergy!

Courtesy: Rene Hendriksen, DTU
ESBLs versus AmpC in food animal species and food products

- **Europe**
  - ESBLs, particularly CTX-M
  - Poultry in Netherlands
- **USA (and Canada)**
  - AmpC, particularly CMY-2
  - Cattle and poultry in USA and Canada
Carbapenems

- Carbapenems
  - Imipenem, ertapenem, meropenem
  - No agricultural direct selection
  - Lots of background noise
  - KPC and NDM have been found in food animals overseas

- CREs
  - KPC***
  - NDM***
  - VIM
  - OXA-48
  - IMP

Maryn McKenna, Nature, July 24, 2013
Colistin

• Very old drug (Polymixin E)
  – Polymixin class
  – Effective against coliforms
• Nephrotoxic so rarely used in humans until recently
• Highly variable use in agriculture around the world
• So far as we know…
  – Lots in China, S and SE Asia, S America and Europe
  – Very little to no use in US and Canada
Colistin use in Europe

Figure 3: Percentage of sales for food producing animals (including horses), in mg per population correction unit (mg/PCU), of polymyxins, by country, for 2010 (ESVAC, 2012). No sales reported in Finland, Iceland, Ireland or Norway.

Figure 4: Distribution of sales by pharmaceutical form for polymyxins, in tonnes of active ingredient, by country, for 2010 (ESVAC, 2012). No sales reported in Finland, Iceland, Ireland or Norway. Negligible amounts sold as bolus, oral pastes, intramammary and intrauterine preparations.
**FIRST GUARD™**
*(Colistimethate Sodium)*
*Sterile Powder*

1. **Date:** June 1996
2. **Name of Applicant:** ALPHARMA INC.
3. **Address:** One Executive Drive
   Fort Lee, NJ 07024
4. **Description of Proposed Action**
   4.1 **Request Approval**

   This environmental assessment is submitted to the new animal drug application (NADA) for the sterile powder First Guard™ (Colistimethate Sodium) for the treatment of colibacillosis in day-old chicks to prevent mortality in young chickens infected with *Escherichia coli* (early chick mortality).

   The ultimate purpose is to increase the availability of poultry for human consumption. Economic benefits are to reduce the cost of poultry production, thereby reducing the cost of poultry products to the consumer.
The plasmid carrying \textit{mcr-1} was mobilised to an \textit{E. coli} recipient at a frequency of $10^{-1}$ to $10^{-3}$ cells per recipient cell by conjugation, and maintained in \textit{K. pneumoniae} and \textit{Pseudomonas aeruginosa}.

Liu et al 2016 (online November 2015)
France as one example

- EU surveillance directive
  - 5.9% prevalence in turkey *E. coli*
- High levels of colistin use in animal agriculture

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**Table 1. Isolate information for colistin-resistant isolates selected for whole genome sequencing.** Sample ID, serotype, sample origin information (year of collection, sample type, and French department [Dept.]), phenotypic antimicrobial susceptibility data, Genbank accession number, and plasmid replicon harboring *mcr-1* for each isolate

| Sample ID     | Serotype    | Year | Sample Type                        | Dept. | A  | M  | A  | C  | H  | E  | I  | C  | S  | T  | G  | E  | A  | L  | N  | O  | S  | T  | Acc. | Replicon harboring \textit{mcr-1} |
|---------------|-------------|------|------------------------------------|-------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----------|----------------------------------|
| 12CEB4337SAL  | Paratyphi B | 2012 | ready-to-cook guinea fowl pie     | 56    | A  | M  | A  | C  | H  | E  | I  | C  | S  | T  | G  | E  | A  | L  | N  | O  | S  | T  | LKJK000000000 | IncX4                            |
| 12CEB2196SAL  | Paratyphi B | 2012 | chicken breast with skin          | 85    | A  | M  | A  | C  | H  | E  | I  | C  | S  | T  | G  | E  | A  | L  | N  | O  | S  | T  | LKJJ000000000 | IncX4                            |
| 2013LSAL04524 | I 4,[5],12:i- | 2013 | boot swabs from broiler farm      | 01    | A  | M  | A  | C  | H  | E  | I  | C  | S  | T  | G  | E  | A  | L  | N  | O  | S  | T  | LKJD000000000 | IncP                             |

Black blocks represent resistance; AMP, ampicillin; AMC, amoxicillin-clavulanic acid; CHL, chloramphenicol; CAZ, cefazidime; CEF, cefalotine; CIP, ciprofloxacin; CST, colistin (highlighted in gray); CTX, cefotaxime; GEN, gentamicin; KAN, kanamycin; NAL, nalidixic acid; OFX, ofloxacine; STR, streptomycin; SSS, sulfonamides; SXT, trimethoprim-sulfamethoxazole; TET, tetracycline N/A; no information available

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<table>
<thead>
<tr>
<th>Year</th>
<th>Animals</th>
<th>E. coli strains tested for MIC N</th>
<th>E. coli strains resistant to colistin N</th>
<th>Proportion of <em>mcr-1</em> positive (n) among colistin-resistant E. coli strains (N) n/N</th>
<th>Prevalence of <em>mcr-1</em> positive E. coli strains % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Turkeys</td>
<td>239</td>
<td>14</td>
<td>14/14</td>
<td>5.9 (2.9-8.8)</td>
</tr>
<tr>
<td></td>
<td>Broilers</td>
<td>227</td>
<td>4</td>
<td>4/4</td>
<td>1.8 (0.1-3.5)</td>
</tr>
<tr>
<td>2013</td>
<td>Pigs</td>
<td>196</td>
<td>1</td>
<td>1/1</td>
<td>0.5 (0.0-1.5)</td>
</tr>
<tr>
<td></td>
<td>Broiler</td>
<td>193</td>
<td>3</td>
<td>3/3</td>
<td>1.8 (0.3-3.3)</td>
</tr>
<tr>
<td>2012</td>
<td>Pigs</td>
<td>194</td>
<td>0</td>
<td>N.a.</td>
<td>N.a.</td>
</tr>
<tr>
<td></td>
<td>Broiler</td>
<td>201</td>
<td>0</td>
<td>N.a.</td>
<td>N.a.</td>
</tr>
<tr>
<td>2011</td>
<td>Pigs</td>
<td>200</td>
<td>1</td>
<td>1/1</td>
<td>0.5 (0.0-1.5)</td>
</tr>
<tr>
<td>2007</td>
<td>Turkeys</td>
<td>ND\textsuperscript{a}</td>
<td>ND\textsuperscript{a}</td>
<td>9/246</td>
<td>0 (0.0-1.2)</td>
</tr>
<tr>
<td>Total</td>
<td>All</td>
<td>1,450</td>
<td>23</td>
<td>N.a.\textsuperscript{b}</td>
<td>N.a.\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} As susceptibility to colistin was not tested in 2007, each isolate obtained in that year was tested for the presence of *mcr-1*.

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Perrin-Guyomard Eurosurveillance 2016
Critically Important Antimicrobials for Human Medicine

5th Revision 2016
Ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use

World Health Organization

8. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (P1, P2, and P3): quinolones, third- and fourth- and fifth-generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

Quinolones are known to select for quinolone-resistant Salmonella and E. coli in animals. At the same time, quinolones are one of few available therapies for serious Salmonella and E. coli infections. Given the high incidence of human disease due to Salmonella and E. coli, the absolute number of serious cases is substantial.

Cephalosporins (3rd and higher generation) are known to select for cephalosporin-resistant Salmonella and E. coli in animals. At the same time, third- and higher generation cephalosporins are one of few available therapies for serious Salmonella and E. coli infections in humans, particularly in children. Given the high incidence of human disease due to Salmonella and E. coli, the absolute number of serious cases is substantial.

Macrolides and ketolides are known to select for macrolide-resistant Campylobacter spp. in animals, especially Campylobacter jejuni in poultry. At the same time, macrolides are one of few available therapies for serious Campylobacter infections, particularly in children, for whom quinolones are not recommended for treatment. Given the high incidence of human disease due to Campylobacter spp., especially Campylobacter jejuni, the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptide-resistant Enterococcus spp. in food animals (e.g., when avoparcin was used as a growth promoter, vancomycin-resistant enterococci (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals, and the very serious consequences of treatment failures in such cases, glycopeptides are classified as being of the highest priority.

Polymyxins (e.g., colistin) are known to select for plasmid mediated polymyxin-resistant E. coli in food animals. At the same time, intravenous polymyxins are one of few available therapies for serious Enterobacteriaceae and Pseudomonas aeruginosa multi-resistant infections in people in healthcare settings in many countries, especially in seriously ill patients in critical care. Given the high incidence of human disease due to Enterobacteriaceae, the absolute number of serious cases where colistin is needed can be considered substantial.
Policy: perspectives and values
Shared perspectives

• Antimicrobials enhance the health and well-being of humans and animals

• There is overuse/misuse of antimicrobials in both human and animal settings

• Protecting the efficacy of antimicrobials for future generations is a good thing to do
One person’s perspective

• Human medicine takes precedence over veterinary medicine and animal agriculture
• Precautionary principle should prevail
• Increasing order of defensible use: growth promotion, prophylaxis, control, treatment
• Drugs deemed critically important to human medicine should not be used at all in animal agriculture
Systemic Intervention - Values

• “Purposeful action by an agent to create change \textit{(in relation to reflection upon boundaries)}”... (Midgley 2006)

(after Cabrera 2008, and modified by Midgley)
Another person’s perspective

• Antimicrobial therapy should be viewed as a last resort
  – A systemic ‘failure’ of sorts
• Prevention and control of disease in food animals improves both animal and human health
• Antimicrobials help improve food security in a world with growing needs
Systemic Intervention - Values

(after Cabrera 2008, and modified by Midgley)
The ‘economies’ of antibiotic use

• Monetary economics
  – Cost/benefit
  – ‘Behavioral control’

• Political economy
  – Regulations, patent law

• Moral economy
  – Attitudes, beliefs, moral and social norms, trust, intentions, behavioral constraints
**I have a moral duty to use antimicrobials as therapy**

Level of respondent agreement with the statement:
I have a moral duty to treat acutely ill feeder cattle with antimicrobials

<table>
<thead>
<tr>
<th>Respondent Type</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree/disagree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feedlot operator</td>
<td></td>
<td></td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Veterinarian</td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Responses do not differ at $P = 0.413$
I have a **moral duty** to use antimicrobials as non-therapy

Graphs by respondent type

Level of respondent agreement with the statement:
I have a moral duty to use subtherapeutic antimicrobials in 'at-risk' feeder cattle

Responses differ at P < 0.0001
The future: where do we go from here?
"To preserve the effectiveness [of antibiotics], we simply must use them as judiciously as possible"

Dr. Joshua Sharfstein, then US FDA deputy commissioner, in June of 2010 suggesting that antibiotics should only be used to protect the health of an animal and not to help it grow faster or more efficiently
“Preserving antimicrobial effectiveness in the future through ethical practices today”

McDonald’s Global Vision for Antimicrobial Stewardship in Food Animals*

“Preserving antimicrobial effectiveness in the future through ethical practices today”

As the body of scientific evidence grows, and scientific consensus emerges, we recognize the importance of continuing to evolve our position on antimicrobial use. In 2014, McDonald’s assembled a team of experts from around the world to study, debate and comment on antimicrobial use in food animals. These experts represented veterinarians, physicians, academicians, clinical pharmacologists, epidemiologists, ethicists, animal health and welfare experts and other food animal production experts, and developed recommendations for antimicrobial stewardship in food animals, building on McDonald’s 2003 global policy on antibiotic use in food animals.

We anticipate the body of knowledge on antimicrobial use in food animals and its impact on antimicrobial resistance in animal and human populations will continue to evolve. As a global enterprise conducting business in more than 100 countries, we also understand the complexities of different global industry structures, government bodies and regulations, and regulatory oversight where we conduct business, making it difficult to implement a single approach that has the same impact globally. It is our intent to work with governments, non-government organizations (NGOs), veterinary and university extension networks, industry leaders and retailers in roundtables to gain alignment and identify paths forward.
Antibiotics: World leaders sign groundbreaking UN declaration to tackle 'biggest global health threat'

If antibiotics lose their effectiveness then key medical procedures – including gut surgery, caesarean sections, joint replacements and chemotherapy – could become too dangerous to perform

Adam Withnall | @adamwithnall | Wednesday 21 September 2016 | 17 comments
Practice evidence: the role of informed policy
WHO (2000) Global Principles on Containment of AMR

• “The[se] strengthen and endorse earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, and the need to establish surveillance systems on antimicrobial consumption”.
Antibiotic usage data?
It depends who is counting

www.pewhealth.org

www.fooddialogues.com
The workshop process has resulted in suggestions for a way forward in this area, for Codex, as well as for FAO, WHO and OIE. Among the important conclusions were the following:

- The risks associated with non-human antimicrobial use and antimicrobial resistance should be part of the human safety assessment. The concept of “thresholds of resistance” should be pursued as a tool for risk management. A range of risk management actions should be triggered if these thresholds are exceeded.

- The concept of “critically important” classes of antimicrobials for humans should be developed by WHO with a view to enabling specific resistance-preventive actions for these antimicrobials in the context of non-human use. A similar list of “critically important” classes of antimicrobials for animals should be pursued by OIE.
Criticality – what it is, and why it’s important
History of the lists of criticality

- **U.S. regulatory actions**
  - FDA late 1990s with fluoroquinolones and glycopeptides banning extra-label uses
  - Again in 2012 with cephalosporins

- **Historical succession of mandates and recommendations** culminating in 2005-2017 lists from WHO and OIE

- **Updates and revisions**
  - Ongoing revisions with WHO and OIE (and FDA GFI #152 Appendix A?)
WHO List of Critically Important Antimicrobials

- When a new class of [human] drug comes on the market, it should be considered critically important from the outset unless strong evidence suggests otherwise.

- Existing drugs such as carbapenems, linezolid, tigecycline, and daptomycin, which are not currently used in food production, should likewise not be used in the future in animals, plants, or in aquaculture.
Practice evidence in U.S. food production

• Good news!
  – No CRE or colistin (mcr-1) resistance reported as of yet in US pigs or pork products
  – No direct selection pressure for CRE and no labeled direct selection pressures for mcr-1
  – ESBL are infrequently reported, 3GC resistance dominated instead by CMY-2
  – Extra-label uses of cephalosporins generally prohibited since 2012
Practice evidence in U.S. food production

• Bad news?
  – We are seeing increased 3GC and FQ resistance over past few years
    • Wider variety of genes (e.g., CTX-M-27,-1, -55, -32 and qnrB)
  – We now have documented plasmid-borne CRE in food animals in USA
  – Multi-drug resistance (MDR) means co-selection (as opposed to direct selection) can threaten expansion of genes through use of tetracyclines and other classes
The way forward?

- Less use is better; however, zero is not an option
  - Less use will slow the rise in antimicrobial resistance; however, it will not eliminate it
  - Zero use is unacceptable: animal health and well-being are important shared values in our society
  - Defining ‘judicious use’ (or, what is not…) and developing and promoting stewardship suited to modern production agriculture are key
Thank you and acknowledgements!

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