Antimicrobial Resistance and Food Animal Pathogens
What's hot and what's the risk?

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Types of heat

**Biological**
- Evolution and ecology of R
- Mechanisms of R
- How Ab usage affects R
- Impact of Ab use in animals
- LA-MRSA
- ESBL E. coli

**Medical**
- MRSA
- VRE
- New Delhi-Metallo-1 (NDM-1)
- MDR Pneumococcus
- Malaria and Tuberculosis
- MDR Salmonella

**Political**
- Use of Ab in food animal production

**Resistant infections with major human health impact**
Food animals and zoonotic disease

Direct and Occupational exposures

Environmental exposures

HUMAN RISK

ANIMAL RESERVOIRS

Commensals

Host specific animal pathogens

Multihost animal pathogens

Wildlife

Domestic Animals

Food Animal Populations

Foodborne exposures
Hazard vs. exposure vs. risk

What’s the hazard?

What’s the exposure?

What’s the risk?
“Warm to Hot” Hazards: Food animals

- Foodborne pathogens
  - *Salmonella*
  - *Campylobacter spp.*
  - *Listeria spp.*
  - *E. coli* - STEC
  - *Yersinia enterocolitica*
  - ...

- Commensals
  - *E. coli* - ESBL
  - *Enterococcus spp.*
  - *S. aureus* - MRSA
  - *C. difficile*
  - ....
Relative rates of laboratory-confirmed enteric infections in the USA (FoodNet 2010)

*Y. enterocolitica* not monitored after >50% reduction
Improved pork safety

Foodborne outbreaks linked to pork (CDC)

Toxoplasma in market hogs

Human Trichinella Cases in US

Salmonella on carcasses

Baseline prevalence 1994
Baseline prevalence 1997
The simple model

Other Sources

Other Factors

Transfer to Humans
Pathogens
Commensals
Genes

Selects Resistant bacteria

More treatment Failures
Higher medical costs
More fatalities

More Resistant Infections

Which uses?
AB use in Food Animals

Other benefits for animal and human health

How, which bacteria and how often?

How often and which bacteria?
Concepts of Interspecies Transmission

- **Complete host adaptation**
  - Human flora
  - Swine flora
  - No interspecies transmission

- **No host adaptation**
  - Human flora
  - Swine flora
  - Equal propensity to colonize both species

- **Marked host adaptation**
  - Human flora
  - Swine flora
  - Rare interspecies transmission

- **Some host adaptation**
  - Human flora
  - Swine flora
  - Common interspecies transmission
Attribution – joining the dots

- Difficult to establish links between cases of resistant infections and treatment failure to exposures originating from food animals
  - Non-zero risk
- Exposure pathways
- Molecular epidemiology
  - When are two bacteria ‘identical’?
  - Does finding ‘identical’ strains mean transmission?
  - Which direction?
Extended spectrum beta-lactamase resistance in E. coli

- **ESBL** *E. coli* an emerging problem in human clinical medicine
  - Intestinal commensals
  - Extraintestinal infections - septicemia
  - Urinary tract

- *E. coli* diverse within and across host species
  - MLST and other typing methods

- ESBL resistance involves many different genes
  - TEM, SHV, CTX-M, CMY, NDM...
ESBL in poultry meat and humans in NL
(Overdevest et al, 2011)

- ESBL genes in chicken meat and human rectal swab specimens were identical.
  - also in human blood culture isolates
- Typing showed a high degree of similarity of *E. coli* strains from meat and humans.
- ‘Abundant presence of ESBL genes in the food chain may have a profound effect on future treatment options for a wide range of infections caused by gram-negative bacteria’
Causal inference

Strain ABCD + Strain ABCD

= Unless

Strain ABCD

Or Strain ABCDE

Strain ABCD

Strain ABCDZ
Ab use in poultry is an important factor in emergence of ESBL-ExPEC?

Troubling observations?

- 30 of 33 unrelated ESBL-producing E. coli from healthy poultry lacked virulence genes associated with human-pathogenic strains (Bortolaia, 2011)
- ESBL strain of highly virulent (mainly human- and avian-restricted ExPEC lineage ST95) in urban rats points to important role in epidemiology of E. coli strains (Ewers et al., 2012)
- ESBL prevalence similar in organic and conventional poultry (Cohen et al, 2012)
ESBL producing and AmpC producing *E. coli* from livestock and companion animals: putative impact on public health (Ewers et al., 2012)

- MLST and plasmid ESBL/AmpC genes in *E. coli* present in humans and animals
  - Livestock and Companion animals
- MLST revealed the existence of ESBL-producing isolates throughout the *E. coli* population, with no obvious association with any ancestral group.
ESBL producing and AmpC producing E. coli from livestock and companion animals: putative impact on public health (Ewers et al., 2012)

- A similar distribution of major ESBL/AmpC types was apparent only in human isolates, regardless of their geographical origin.
- In animals, varied extensively between animal groups and across different geographical areas.
- The opinion that animal ESBL-producing *E. coli* is a major source of human infections is oversimplified, and neglects a highly complex scenario.
The role of antimicrobial use in emergence of Livestock Associated MRSA

- LA-MRSA ‘uniformly tetracycline resistant’
  - Emergence due to growth promotant usage
- MRSA emergence in horses
  - Tetracyclines not used
- Role of antimicrobial use in food animals
  - ‘Therapeutic’ vs. ‘non-therapeutic’ uses
  - Few growth promotants are beta lactams
  - Newer injectable products
    - Long acting cephalosporins
Other selective pressures? (Aarestrup 2010)

- MSSA in pigs also tetracycline resistant
  - No selective pressure for MRSA
- Zinc
  - 74% of ST398 MRSA in DK had high MIC to zinc
  - All 60 ST398 MSSA strains had low MIC to zinc
- Widespread use of zinc since AGP ban
  - Prevention of enteric disease in weaned pigs
  - Used on most DK swine herds
- Law of unintended consequences?
Global strain collection
- MRSA and MSSA
- Swine and veal isolates

Study showed that zinc resistance widespread among ST398 LA-MRSA

Use of zinc in feed might have contributed to the emergence of LA-MRSA
Growth promotants as the evil?
MRSA cases in Denmark (all types)

- MRSA ST398 in people in DK
- MRSA ST398 in pigs in NL
- MRSA ST398 in pigs in DK

Ban of AGP in nurseries
Ban of AGP in finishers
Summary

- Interspecies transmission of bacteria and resistance genes is complex
- Simple, single-factor cause and effect relationships are rare at best
- ‘Name, blame, and shame’ approach to food animal industries is not constructive
- Time and effort required to understand the risks associated with apparently novel agents