Human health impacts of antibiotic use in animal agriculture

Beliefs, opinions, and evidence

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Terminology

- **Antibiotic**
  - Compound produced by an organism which at low concentration kills or inhibits growth of another organism
  - Drug use to treat bacterial infections

- **Antibiotic resistance**
  - Ability of microbes to grow in the presence of an antibiotic that would normally kill them or limit their growth
  - Resistance of a microorganism to an antibiotic that was originally effective for treatment of infections caused by it
The Antibiotic Resistance Crisis

- Antibiotics are ‘miracle’ drugs
- Efficacy of antibiotics is declining
- Modern medicine is dependent on antibiotic use
  - A tribute to medical advancement
- Modern agriculture is dependent on antibiotic use
  - A condemnation of agricultural practices
‘Antibiotics are commonly used in animal husbandry, bee-keeping, fish farming and other forms of aquaculture, ethanol production, horticulture, antifouling paints, food preservation, and domestically’

‘It is vital that the nonmedical use of antibiotics is critically examined and that any nonessential use is halted’
Resistance to antimicrobials of human importance has been generated in animals...

... and is spread to humans with the potential to cause major harm and we..

...but the evidence that it has spread to humans and caused major harm is minimal or non-existent and..

Must take action to minimize it! No action is required!
Level of Emphasis

- All organisms/genes great and small
- Nebulous

- Specific pathogens and antibiotics
- Established public health impact
- Specific concerns
  - Drug-Bug
- Uncertain risks
- Interspecies transmission equivocal
Antibiotic resistance threats in the USA
(CDC, Am Fam Physician. 2014 Jun 15;89(12):938-941.)

Urgent
• Clostridium difficile
• Carbapenem-resistant Enterobacteriaceae
• Drug-resistant N. gonorrhea

Concerning
• Vancomycin-resistant S. aureus
• Erythromycin-resistant group A Streptococcus
• Clindamycin-resistant group B Streptococcus

Serious
• Multidrug-resistant Acinetobacter
• Drug-resistant Campylobacter
• Fluconazole-resistant Candida
• ESBL–producing Enterobacteriaceae
• Vancomycin-resistant Enterococcus
• MDR Pseudomonas aeruginosa
• Non-typhoidal Salmonella
• Salmonella serotype Typhi
• Drug-resistant Shigella
• MRSA
• MDR Streptococcus pneumoniae
• Drug-resistant tuberculosis
Antibiotic resistance threats in the USA

Foodborne

Urgent

• Clostridium difficile
• Carbapenem-resistant Enterobacteriaceae
• Concerning
• Vancomycin-resistant S. aureus
• Multidrug-resistant Acinetobacter
• Drug-resistant Campylobacter
• ESBL–producing Enterobacteriaceae
• Vancomycin-resistant Enterococcus
• Non-typhoidal Salmonella

Concerning

Serious

• Drug-resistant Campylobacter
• Non-typhoidal Salmonella
Antibiotic resistance threats in the USA

*Foodborne?*

**Urgent**
- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae

**Concerning**
- Vancomycin-resistant S. aureus

**Serious**
- Multidrug-resistant Acinetobacter
- **Drug-resistant Campylobacter**
- ESBL–producing Enterobacteriaceae
- Vancomycin-resistant Enterococcus
- **Non-typhoidal Salmonella**
- MRSA
Foodborne pathway: animal antibiotic use to medical treatment failure

Food animals Exposed to Antibiotics → Selection of Resistant Organism/gene → Organism/gene persists until market age

Food animals Exposed to Antibiotics

Human exposure to resistant organism/gene → Organism/gene Persists through Supply chain → Organism/gene Contaminates Product

Disease due to resistant pathogen needs medical care → Treatment with Antibiotic → Clinical Treatment Failure
Review papers (n=25) citing specific organism-antibiotic pairs re animal use

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotics</th>
<th>Count</th>
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<tr>
<td><strong>Enterococci</strong></td>
<td>Vancomycin</td>
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<tr>
<td></td>
<td>Quinupristin/dalfopristin</td>
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<tr>
<td><strong>Salmonella</strong></td>
<td>Multiple drug resistance</td>
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<tr>
<td></td>
<td>Fluoroquinolones</td>
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<tr>
<td></td>
<td>Ceftriaxone</td>
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<td><strong>Campylobacter</strong></td>
<td>Fluoroquinolones</td>
<td>12</td>
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<td></td>
<td>Macrolides, Tetracyclines</td>
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<td><strong>E. coli/coliforms</strong></td>
<td>Nourseothricin</td>
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<tr>
<td></td>
<td>Tetracyclines</td>
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<td>Fluoroquinolones</td>
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<tr>
<td></td>
<td>Extended spectrum beta lactams</td>
<td>1</td>
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<tr>
<td></td>
<td>Gentacyclin, apramycin</td>
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<tr>
<td><strong>STEC</strong></td>
<td>Multiple drug resistance</td>
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<tr>
<td><strong>Streptococci</strong></td>
<td>Tylosin</td>
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Relative rates of culture-confirmed infections with Campylobacter, STEC* O157, Listeria, Salmonella, Vibrio, and Yersinia, compared with 1996–1998 rates
FoodNet 1996–2015

- ~20-30% reduction in *Listeria, Campylobacter, STEC O157*
- ~ 0% change in *Salmonella*
- ~60% reduction in *Yersinia enterocolitica*
% of NT *Salmonella* resistant to ≥3 classes
(NARMS 2013)
Fluoroquinolone resistant Campylobacter

- Best documented circumstance linking a specific antimicrobial used in food animals to occurrence of resistance in an important zoonotic pathogen
  - Several countries including USA
- Led to removal of FQ use in poultry in 2005
  - Removal did not lead to reduction in prevalence
- Extent of impact on public health questioned
  - FQ resistant infections not more severe than sensitive (Wassenaar et al., Int J Antimicrob Agents. 2007; 30:195-201)
Fluoroquinolone-resistant *C. jejuni* in the USA 1982–2001 (Gupta et al, 2004)
Meat-borne infections with antibiotic resistant bacteria: Driving the discussion

- Vancomycin resistant enterococci (VRE)
- ‘Livestock associated’ MRSA
- ESBL Enterobacteriaceae
- Carbapenem resistant Enterobacteriaceae
- Colistin resistant Enterobacteriaceae
Avoparcin and VRE in Europe

- Avoparcin: glycopeptide growth promotant used in pigs and poultry in Europe from early 1970s
  - Never licensed in the USA
- VRE in Europe in 1990s
  - High prevalence in pigs and poultry (avoparcin)
  - ~10% prevalence of VRE carriage in healthy humans
  - VRE clinical infections remained very rare
- Sparse use of vancomycin in human medicine
- Avoparcin banned in EU in 1990s (all by 1997)
Vancomycin use in human medicine in USA vs. Europe (Bonten et al., 2001)
Prevalence of VRE in nosocomial infections in intensive-care patients in the USA (Bonten et al., 2001)
Vancomycin resistance *E. faecium* bacteremias in North America and Europe (1999-2008 SENTRY Program)

*withdrawal of animal growth promoters eg. avoparcin*  
(April 1, 1997 as a precautionary, protective measure)
Avoparcin and VRE

- Avoparcin use led to high VRE prevalence in food animals and healthy humans
- VRE infections in USA attributed to high use of vancomycin in human medicine
  - No glycopeptide antibiotic use in food animals
- VRE infections emerged in Europe post avoparcin
ST398 ‘Livestock associated’ MRSA
Generally accepted ‘facts’

- First recognized in Netherlands in 2004
  - Now reported in livestock species in many countries
- High MRSA exposure risk for people with direct animal contact
  - 20-50% vs. ~ 0.5 - 2% in general populations
- Human cases have been reported, some serious
  - Very few serious infections in healthy livestock workers
  - Several deaths in medically compromised
- Low risk of exposure for the general public
Emergence of ST398 MRSA in Denmark
Meticillin-resistant *Staphylococcus aureus* CC398 is an increasing cause of disease in people with no livestock contact in Denmark, 1999 to 2011

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ST398 ‘has become a major cause of human disease in Europe, posing a serious public health challenge in countries with intensive livestock production’

Suggests substantial dissemination of MRSA CC398 from livestock or livestock workers into the Danish community

Findings strongly suggest foodborne transmission does not play a major role in the MRSA CC398 epidemiology
Incidence of MRSA infections in DK in 2011
(Larsen et al., 2015)

- Pig dense areas
  - All MRSA: **10.9*/100,000 person-years*
  - ST398 **0.7*/100,000 person-years (no pig contact)**

- Other areas
  - All MRSA: **12.8*/100,000 person-years*
  - ST398 **0.3*/100,000 person-years (no pig contact)**
ST398 MRSA risk in DK vs MRSA risk in USA

- Invasive MRSA in USA in 2005 (Klevens et al., 2007)
  - 31.8 invasive MRSA cases/100,000 person-years
  - 6.3 fatal MRSA cases/100,000 person-years

- Invasive MRSA infection 45 X more likely in a US citizen than any ST398 MRSA infection in a Danish citizen in a pig dense area

- Fatal MRSA infection 9 X more likely in a US citizen than any ST398 MRSA infection in a Danish citizen in pig dense area
What we know about antibiotic use (ABU)

- ABU leads to resistance in any setting
- The contribution of ABU in animals is to resistance in human pathogens is >0
- Lack of ‘proof’ of harm is not an argument for ‘injudicious’ use
- The existence of greater abuse in other arenas is not an argument for ‘injudicious’ use
- Room for improved stewardship of antibiotics in food animal industries