Antibiotic Use in Food Animals
What, So What, Now What?

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“For clarity, these are solely my personal views/opinions and do not represent those of any organization to which I am affiliated.”
New CDC Foodborne Illness Estimates

Foodborne Illnesses

We estimate that each year in the United States, 31 pathogens caused 37.2 million (90% CrI 28.4–47.6 million) illnesses, of which 36.4 million (90% CrI 27.7–46.7 million) were domestically acquired; of these, 9.4 million (90% CrI 6.6–12.7 million) were foodborne (Table 2). We estimate that 5.5 million (59%) foodborne illnesses were caused by viruses, 3.6 million (39%) by bacteria, and 0.2 million (2%) by parasites. The pathogens that caused the most illnesses were norovirus (5.5 million, 58%), nontyphoidal Salmonella spp. (1.0 million, 11%), C. perfringens (1.0 million, 10%), and Campylobacter spp. (0.8 million, 9%).

Bacterial Foodborne Disease Trends

Figure 3
Distribution of estimated annual U.S. salmonellosis cases and disease outcomes

93% do not visit a physician and recover fully
746,880 - 3,734,400 cases

5% visit a physician and recover fully
40,320 - 201,600 cases

2% are hospitalized
12,800 - 64,000 cases

94% recover fully
12,000 - 60,000 cases

6% die
800 - 4,000 deaths

Percent of total
93%
5%
1.5%
0.1%
100%

1Percentages are rounded.
Prepared by Economic Research Service, USDA.
Figure 6
Distribution of estimated annual U.S. campylobacteriosis cases and disease outcomes

<table>
<thead>
<tr>
<th>Campylobacteriosis acute illness cases</th>
<th>Percent of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>94% do not visit a physician and recover fully</td>
<td><strong>94.1%</strong></td>
</tr>
<tr>
<td>2,351,770 - 2,352,300 cases</td>
<td></td>
</tr>
<tr>
<td>5.4% visit a physician and recover fully</td>
<td><strong>5.4%</strong></td>
</tr>
<tr>
<td>135,000 cases</td>
<td></td>
</tr>
<tr>
<td>0.6% are hospitalized</td>
<td><strong>0.5%</strong></td>
</tr>
<tr>
<td>12,700 - 13,230 cases</td>
<td></td>
</tr>
<tr>
<td>94.98% recover fully</td>
<td><strong>0.5%</strong></td>
</tr>
<tr>
<td>12,500 cases</td>
<td></td>
</tr>
<tr>
<td>2 - 6% die</td>
<td><strong>&lt;0.1%</strong></td>
</tr>
<tr>
<td>200 - 730 deaths</td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
## US vs. DK
(cases / 100,000)

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>13</td>
<td>61</td>
</tr>
<tr>
<td>Salmonella</td>
<td>15</td>
<td>39</td>
</tr>
</tbody>
</table>

- MMWR / April 16, 2010 / Vol. 59 / No. 14/p 419
- DANMAP 2009
Not All Meat Products...

Figure 2. Percent of Retail Meat Samples Culture Positive for *Salmonella*, 2002-2009
Not All Meat Products...

Figure 18. Percent of Retail Meat Samples Culture Positive for *Campylobacter*, 2002-2009

- Chicken Breasts
- Ground Turkey

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What is the clinical predictive value of *in vitro* susceptibility tests?

- Susceptible or Resistant – what to use?
- “the 90–60 rule”
  - In general, a susceptible result is associated with a favorable therapeutic response in 90 to 95% of patients. When the infecting bacterium has been determined to be resistant, notwithstanding this result, nearly two-thirds of patients can be expected to respond to therapy.
  - These observations apply to immunocompetent patients with mono-microbic bacterial infections who are treated with a single antimicrobial agent which is administered parenterally. [~25% of all cases]

Treatment Outcome

• Meta-analysis of Campylobacteriosis treatment with either a fluoroquinolone or a macrolide
• Our meta-analysis confirms the findings of small randomized, controlled trials that are often cited in guidelines and reviews: that antibiotic treatment shortens the duration of diarrheal illness. Although the effect is evident, our data indicate a mean decrease in diarrheal illness of <2 days with antimicrobial treatment. Antibiotic treatment also shortened the excretion of *Campylobacter species from feces.*

Ternhag et al. CID 2007.44: 696-700
Treatment Outcome

- 12-trial Meta-analysis of Salmonellosis treatment with various antibiotics
- Included infants, children and adults
- Clinical parameters evaluated

Authors’ Conclusions

Implications for practice

Antibiotic therapy has no positive clinical effect on the treatment of salmonella diarrhoea in healthy children and adults with non-severe diarrhoea. Adverse drug reactions, although minimal, do occur with antibiotic treatment. Antibiotic administration, therefore, should not be routinely recommended for this disease in children and adults. For patients with some underlying immunosuppressive disorder, current data are insufficient to guide management: this suggests that they are not indicated outside the context of a randomised, placebo controlled trial.

AMR Bacteria treatment failures?

• ...“antibiotic resistance” is not listed on death certificates as the cause of death; generally, as in the United States, the cause of death would be listed as multiple organ failure, making it difficult to identify deaths caused by antibiotic-resistant infections.
• Note:
  – Not all salmonella or campylobacter infections in humans can be associated with a food animal origin or a food of animal origin
  – Epidemiology?
What?

• AMR foodborne bacteria are a subset!
• Similar antibiotic classes used in both animals and humans are categorized for importance yet there is little connection to human non-foodborne disease treatment uses or resistance.
• Estimated bacterial foodborne disease has decreased and not all isolates are resistant to antibiotics.
Antibiotic Uses in Animals

- Disease treatment
  - Therapeutic
- Disease control
  - Therapeutic
- Disease prevention
  - Therapeutic
- Performance or “Growth promotion”

Draft FDA CVM Guidance 209
### Major Classes of Antimicrobials

(shared human use classes)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
<td>Penicillin, amoxicillin; ceftiofur</td>
</tr>
<tr>
<td><strong>Macrolides &amp; lincosamides</strong></td>
<td>Tylosin; tilmicosin; tulathromycin, lincomycin</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Gentamicin; neomycin</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>Enrofloxacin, danofloxacin</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Tetracycline; oxytetracycline, chortetracycline</td>
</tr>
<tr>
<td><strong>Sulfonamides</strong></td>
<td>Various</td>
</tr>
<tr>
<td><strong>Streptogramins</strong></td>
<td>Virginiamycin</td>
</tr>
<tr>
<td><strong>Polypeptides</strong></td>
<td>Bacitracin</td>
</tr>
<tr>
<td><strong>Phenicols</strong></td>
<td>Florfenicol</td>
</tr>
<tr>
<td><strong>Pleuromutilin</strong></td>
<td>Tiamulin</td>
</tr>
</tbody>
</table>
Antibiotics in Animal Feeds in U.S.

Growth promotion - poultry, swine, and/or cattle

- Arsenicals
- Bacitracin
- Bambermycins
- Carbadox
- Tetracyclines
- Ionophores - monensin, narasin, salinomycin, etc
- Lincomycin
- Penicillin
- Tiamulin
- Tylosin
- Sulfonamide (combination use)
- Virginiamycin

Red-same class use in humans
Black-no human use

Note: Other antibiotics are approved in various other countries
Resistant subset...

- NT-Salmonella ~80% human isolates are pan-susceptible since 2004 (Table 22a)
- NT- Salmonella – <0.1% fluoroquinolone resistant from human isolates, none from retail meat or food animals (Table 7d)
- NT- Salmonella – 3-4% human isolates resistant to ceftriaxone since 2000
- Campylobacter – pan-susceptible since 2005
  - *C. jejuni* – 45-48%
  - *C. coli* – 40-51%

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Major Classes of Antimicrobials
(human use only classes)

- Glycopeptides
- Carbapenems
- Monobactams
- Fidaxomicin
- Lipopeptides (e.g. daptomycin)
- Oxazolidinones
- Glycylcyclines (e.g. tigecycline)
- Ansamycins (e.g. rifampicin)
- Mupirocin
- Mycobacterium anti-infectives
Resistance Gene Transfer from Foodborne Bacteria to Human Pathogens?

- Epidemiological connection?
- Resistance gene transfer in vivo (GI tract)?
- Resistant human pathogen amplification?
- Human **Nosocomial** Pathogens of most AMR concern (Flamm)
  
  - **Gram-positive pathogens**
    - *S. aureus* (MRSA)
    - Enterococci (VRE)
    - *S. pneumoniae* (PenR)
  
  - **Gram-negative pathogens**
    - Enterobacteriaceae
      - *E. coli* (CipR, ESBL)
      - *Klebsiella* spp. (CipR, ESBL, CarbR)
      - *Enterobacter* spp. (CazR, ESBL)
    - Non-fermentative pathogens
      - *P. aeruginosa* (CarbR, MBL)
      - *Acinetobacter* spp. (CarbR, MDR)
AVMA Veterinarians Oath

• "Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge."

Effective 2010
The Issue

• Veterinary need for antibiotics
• Human medical need for antibiotics
• Zoonotic and commensal bacteria may be bystanders during antimicrobial use in food animals
So What?

- Overview of international organizations (WHO, OIE and Codex) risk management strategies which are now being implemented at the national level.
<table>
<thead>
<tr>
<th>Date</th>
<th>Country or International</th>
<th>Report Source</th>
<th>Report Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>United States</td>
<td>National Research Council (NRC)</td>
<td>The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feed</td>
</tr>
<tr>
<td>1981</td>
<td>United States</td>
<td>Institute of Medicine (IOM)</td>
<td>Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed</td>
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<tr>
<td>1989</td>
<td>United States</td>
<td>Committee on Human Health Risk Assessment of Using Subtherapeutic Antibiotics in Animals</td>
<td>Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feeds</td>
</tr>
<tr>
<td>1997</td>
<td>International</td>
<td>World Health Organization (WHO)</td>
<td>The Medical Impact of the Use of Antimicrobials in Food Animals</td>
</tr>
<tr>
<td>1998</td>
<td>United Kingdom</td>
<td>Ministry of Agriculture, Fisheries and Food</td>
<td>A Review of Antimicrobial Resistance in the Food Chain</td>
</tr>
<tr>
<td>1998</td>
<td>United States</td>
<td>Food and Drug Administration (FDA) Center for Veterinary Medicine</td>
<td>A proposed framework for evaluating and assuring the human safety of the microbial effects of antimicrobial new drugs intended for use in food-producing animals</td>
</tr>
<tr>
<td>1999</td>
<td>European Union</td>
<td>The European Agency for the Evaluation of Medicinal products</td>
<td>Antibiotic Resistance in the European Union Associated with Therapeutic Use of Veterinary Medicines</td>
</tr>
<tr>
<td>1999</td>
<td>European Union</td>
<td>EU Scientific Steering Committee</td>
<td>Opinion of the Scientific Steering Committee on Antimicrobial Resistance</td>
</tr>
<tr>
<td>Year</td>
<td>Country</td>
<td>Organization</td>
<td>Document Title</td>
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<tr>
<td>1999</td>
<td>United States</td>
<td>FDA</td>
<td>Risk Assessment on the Human Health Impact of Fluoroquinolone-resistant Campylobacter Associated with Consumption of Chicken</td>
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<tr>
<td>1999</td>
<td>United States</td>
<td>NRC of Sciences Committee on Drug Use in Food Animals and the Panel on Animal Health, Food Safety, and Public Health</td>
<td>The Use of Drugs in Food Animals: Benefits and Risks</td>
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<tr>
<td>1999</td>
<td>United States</td>
<td>U.S. General Accounting Office (GAO)</td>
<td>Food Safety: The Agricultural Use of Antibiotics and its Implications for Human Health</td>
</tr>
<tr>
<td>1999</td>
<td>United Kingdom</td>
<td>Advisory Committee on the Microbiological Safety of Food</td>
<td>Report on Microbial Antibiotic Resistance in Relation to Food Safety</td>
</tr>
<tr>
<td>1999</td>
<td>Australia</td>
<td>Joint Expert Advisory Committee on Antibiotic Resistance</td>
<td>The Use of Antibiotics in Food-Producing Animals: Antibiotic Resistant Bacteria in Animals and Humans</td>
</tr>
<tr>
<td>1999</td>
<td>European Union</td>
<td>European Commission</td>
<td>Opinion of the Scientific Steering Committee on Antimicrobial Resistance,</td>
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<td>1999</td>
<td>International</td>
<td>WHO</td>
<td>The Medical Impact of the Use of Antimicrobials in Food Animals</td>
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<tr>
<td>2000</td>
<td>United States</td>
<td>Centers for Disease Control and Prevention Interagency Task Force on Antimicrobial Resistance</td>
<td>A Public Action Health Plan to Combat Antimicrobial Resistance</td>
</tr>
<tr>
<td>2000</td>
<td>International</td>
<td>WHO</td>
<td>WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food</td>
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<tr>
<td>2000</td>
<td>International</td>
<td>Food and Agriculture Organization of the United Nations (FAO)/WHO Codex Committee on Residues of Veterinary Drugs in Foods</td>
<td>Antimicrobial Resistance and the Use of Antimicrobials in Animal Production</td>
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<tr>
<td>Year</td>
<td>Region</td>
<td>Organization/Group</td>
<td>Activity</td>
</tr>
<tr>
<td>------</td>
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<td>----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<tr>
<td>2001</td>
<td>International</td>
<td>Office International Des Epizooties (OIE)</td>
<td>Antimicrobial Resistance: Reports prepared by the OIE Ad Hoc Group of Experts on Antimicrobial Resistance</td>
</tr>
<tr>
<td>2001</td>
<td>International</td>
<td>WHO</td>
<td>WHO Global Strategy for Containment of Antimicrobial Resistance</td>
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<tr>
<td>2001</td>
<td>International</td>
<td>WHO</td>
<td>Monitoring Antimicrobial Usage in Food Animals for the Protection of Human Health</td>
</tr>
<tr>
<td>2002</td>
<td>United States</td>
<td>Alliance for the Prudent Use of Antibiotics</td>
<td>The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences (“FAAIR Report”)</td>
</tr>
<tr>
<td>2003</td>
<td>International</td>
<td>WHO Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens</td>
<td>Impacts of Antimicrobial Growth Promoter Termination in</td>
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<tr>
<td>2004</td>
<td>United States</td>
<td>GAO</td>
<td>Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals</td>
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<tr>
<td>2005</td>
<td>United States</td>
<td>FDA CVM</td>
<td>Withdrawal Order for Baytril Soluble for Poultry</td>
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<td>Year</td>
<td>Location</td>
<td>Organization</td>
<td>Description</td>
</tr>
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<td>------------</td>
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<tr>
<td>2006</td>
<td>International</td>
<td>FAO, OIE, and WHO</td>
<td>Third Joint FAO/OIE/WHO Expert Workshop on Antimicrobial Use in Aquaculture and Antimicrobial Resistance</td>
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<tr>
<td>2007</td>
<td>International</td>
<td>FAO, OIE and WHO</td>
<td>Fourth Joint FAO/OIE/WHO Expert Workshop on Critically Important Antimicrobials</td>
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<tr>
<td>2011</td>
<td>United States</td>
<td>GAO report</td>
<td>Antibiotic Resistance – Agencies Have Made Little Progress in Addressing Antibiotic Use in Animals</td>
</tr>
</tbody>
</table>
Global Reports on Animal Antibiotic Use since 1997

- WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture, AGISAR)
- OIE Terrestrial Code
- Codex –various (TFAMR)
- Europe (CVMP, EFSA, ECDC; EU commission)
- Australia (JETACAR)
- U.S. (NRC, CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
- Canada (Adv. Com. Report, CCAR)
- Other reports from APUA, IFT, Pew
Summary of Actions and Recommendations
International and National Level

• Responsible Use
  – Appropriate veterinary antibiotic use practices described; education, disease prevention

• Resistance Monitoring

• Antibiotic sales Monitoring

• Regulatory Controls
  – Risk assessment-based regulatory decisions on microbial food safety guide decisions on product use:
    • Approval with appropriate label indications and use, prescription

• Research
  – New products
Food Chain Intervention Points

- **Food Animals**
- **Retail Meat**
- **Patients**

**Release** → **Exposure** → **Consequence**

- **Data useful to determine appropriate intervention points and the subsequent effectiveness of actions to protect human and animal health**

- **Guide Responsible Use, Regulatory support, Food Safety, Risk Assessment, etc.**
Now What?

• Implications – risk management actions will re-shape veterinarians access to antibiotics and the practice of veterinary medicine with an unknown impact on public health and food safety.
Denmark Human AMR effect

- Danish officials told us that Denmark’s resistance data have not shown a decrease in antibiotic resistance in humans after implementation of the various Danish policies, except for a few limited examples. Specifically, officials said that the prevalence of vancomycin-resistant *Enterococcus faecium* from humans has decreased since *avoparcin* was banned for use in animals in 1995. Resistance has been tracked for other types of bacteria and antibiotics, but similar declines have not been seen.
Ciprofloxacin Resistance

Figure 20. Percent of *Campylobacter jejuni* Isolates from Humans, Chicken Breasts, and Chickens Resistant to Ciprofloxacin, by Year, 1997-2009

1 Data for ground turkey, ground beef, and pork chops are not included due to the small number of *C. jejuni* isolates from these sources. Table 50 contains resistance data for *C. jejuni* isolates from each source, by year.

NARMS Executive Report 2009

Sept. 2005 Baytril withdrawal
Figure 21. Percent of *Campylobacter jejuni* Isolates from Humans, Chicken Breasts, and Chickens Resistant to Erythromycin by Year, 1997-2009

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1 Data for ground turkey, ground beef, and pork chops are not included due to the small number of *C. jejuni* isolates from these sources. Table 50 contains resistance data for *C. jejuni* isolates from each source, by year.
Denmark C. *jejuni* susceptibility

Table 18. Comparison of resistance (%) among Campylobacter jejuni from food animals, food of Danish or imported origin and human cases categorized as acquired domestically or reported as associated with travel (DANMAP 2009)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cattle Danish</th>
<th>Cattle Danish</th>
<th>Broiler meat Danish</th>
<th>Broiler meat Imported</th>
<th>Humans Domestically acquired</th>
<th>Humans Travel abroad reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>2</td>
<td>12</td>
<td>4</td>
<td>52</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Ciprofloxacin</td>
<td>20</td>
<td>13</td>
<td>0</td>
<td>56</td>
<td>24</td>
<td>61</td>
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<tr>
<td>Nalidixic acid</td>
<td>20</td>
<td>13</td>
<td>0</td>
<td>56</td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td><strong>Number of isolates</strong></td>
<td><strong>87</strong></td>
<td><strong>75</strong></td>
<td><strong>26</strong></td>
<td><strong>62</strong></td>
<td><strong>62</strong></td>
<td><strong>31</strong></td>
</tr>
</tbody>
</table>
• Preventing development of new forms of resistance should rely, in part, on prudent use of antibiotics with an eye to the ecologies of pathogens and other microorganisms.

• If science and medicine cannot win a war against antibiotic resistance, what CAN be done? We have to find a way to co-exist with resistance. To minimize the loss of life, we can develop strategies to prevent new resistance from spreading and, where resistance already exists, identify the strains we need to protect against, find ways to treat resistant infections effectively in patients, and manage reservoirs of antibiotic resistant strains in the environment.
Food Economics and Consumer Choice

An overview of the challenge ahead

Key Data

In 50 years, the world population will require 100% more food,¹ and 70% of this food must come from efficiency-improving technology²


TECHNOLOGY’S ROLE IN THE 21ST CENTURY
Tipping Point

• Science-based risk-benefit assessment vs. political decision
• Human health and food safety vs. animal health needs
  – Future animal protein availability and affordability
• Therapeutic use vs. performance use
• Veterinarian oversight vs. lay person use
• Shared-class vs. non-human class food borne AMR
  – Animal-use only
• Unintended consequences vs. desired outcome
  – Risk-risk analysis
  – Risk-benefit analysis