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

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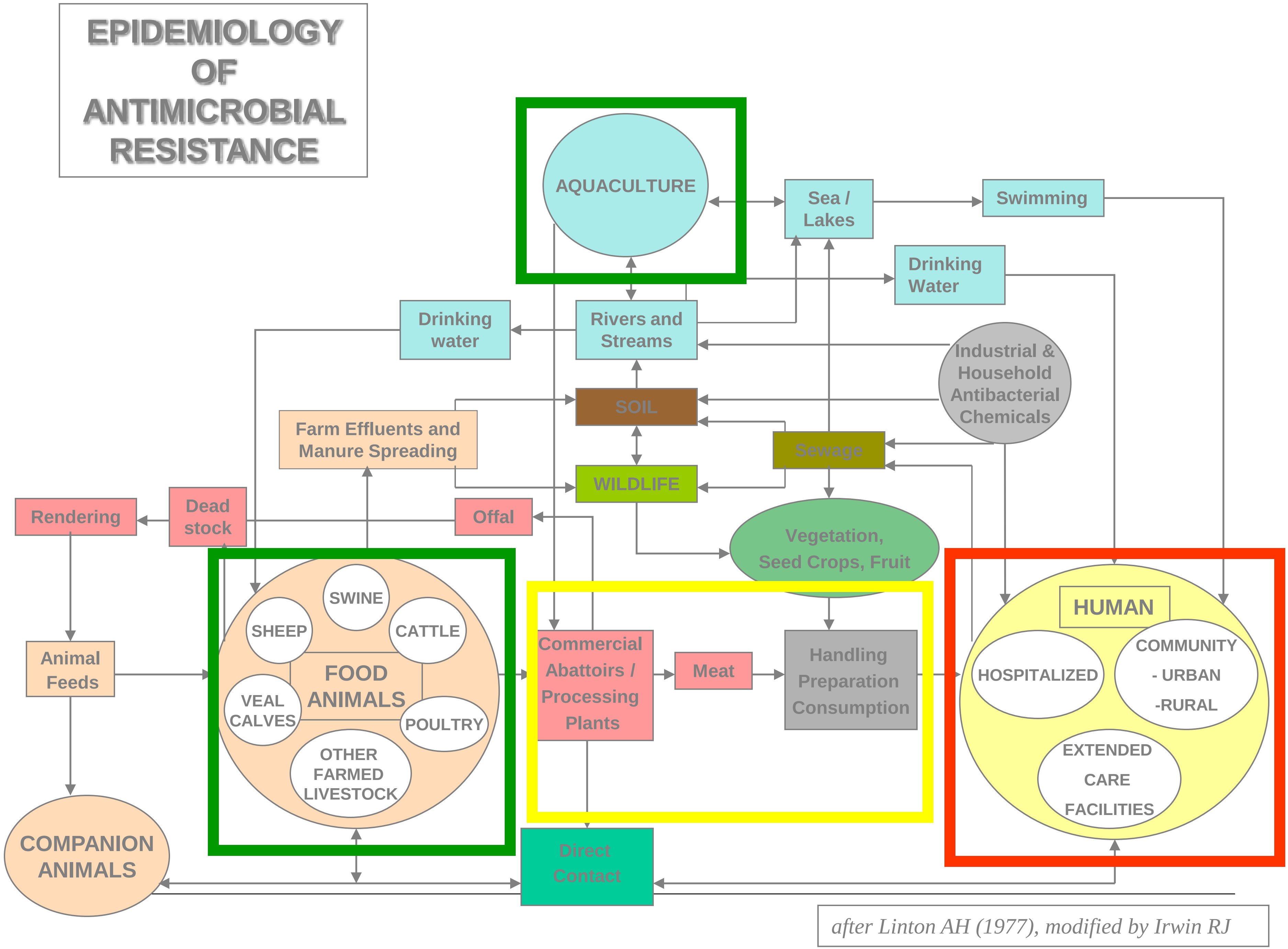
"For clarity, these are solely my personal views/opinions and do not represent those of any organization to which I am affiliated."


EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE
AQUACULTURE
Sea / Lakes
Swimming
Drinking Water
Drinking water
Rivers and Streams
Industrial & Household Antibacterial Chemicals
SOIL
Farm Effluents and Manure Spreading
Sewage
WILDLIFE
Rendering
Dead stock
Offal
Vegetation, Seed Crops, Fruit
SWINE
SHEEP
CATTLE
FOOD ANIMALS
VEAL CALVES
POULTRY
OTHER FARMED LIVESTOCK
Animal Feeds
Commercial Abattoirs / Processing Plants
Meat
Handling Preparation Consumption
HUMAN
HOSPITALIZED
COMMUNITY - URBAN -RURAL
EXTENDED CARE FACILITIES
COMPANION ANIMALS
Direct Contact
after Linton AH (1977), modified by Irwin RJ

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%).

Scallan, 2010. Emerg. Inf. Dis.

Bacterial Foodborne Disease Trends

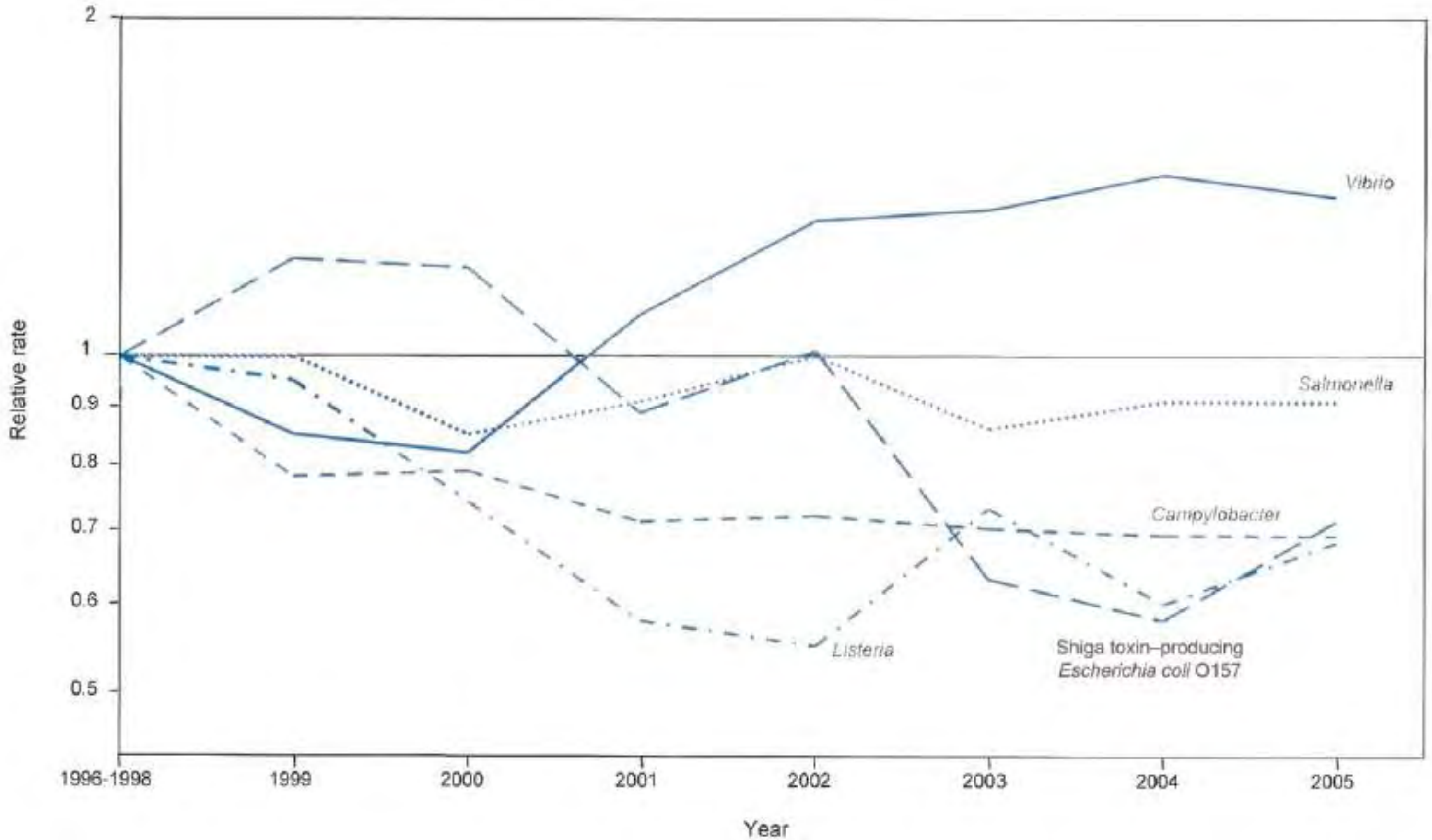
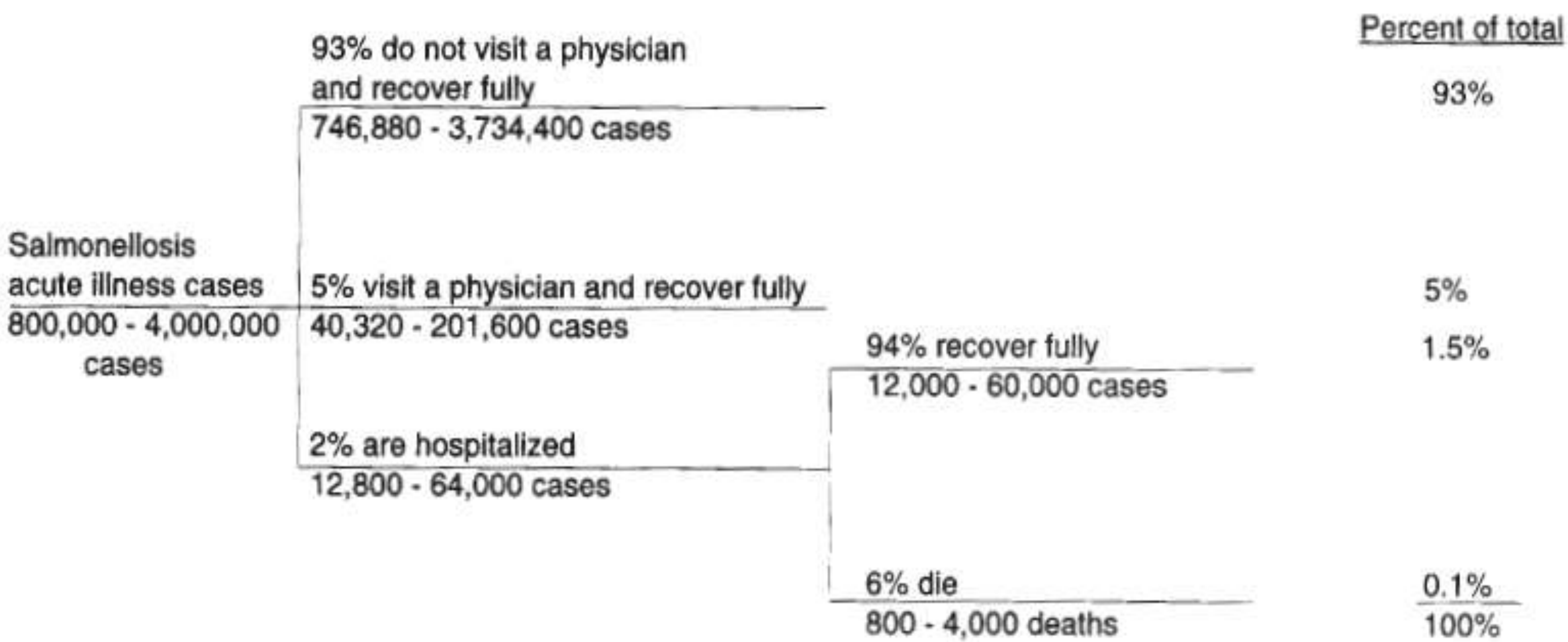


Figure 3. Relative rates, compared with 1996–1998 baseline period of laboratory-diagnosed cases of *Campylobacter*, Shiga-toxin–producing *Escherichia coli* O157, *Listeria*, *Salmonella*, and *Vibrio* infection, by year, Foodborne Diseases Active Surveillance Network, United States, 1996–2005.

Scallan. Clinical Infectious Diseases 2007. 44:718–25

Figure 3

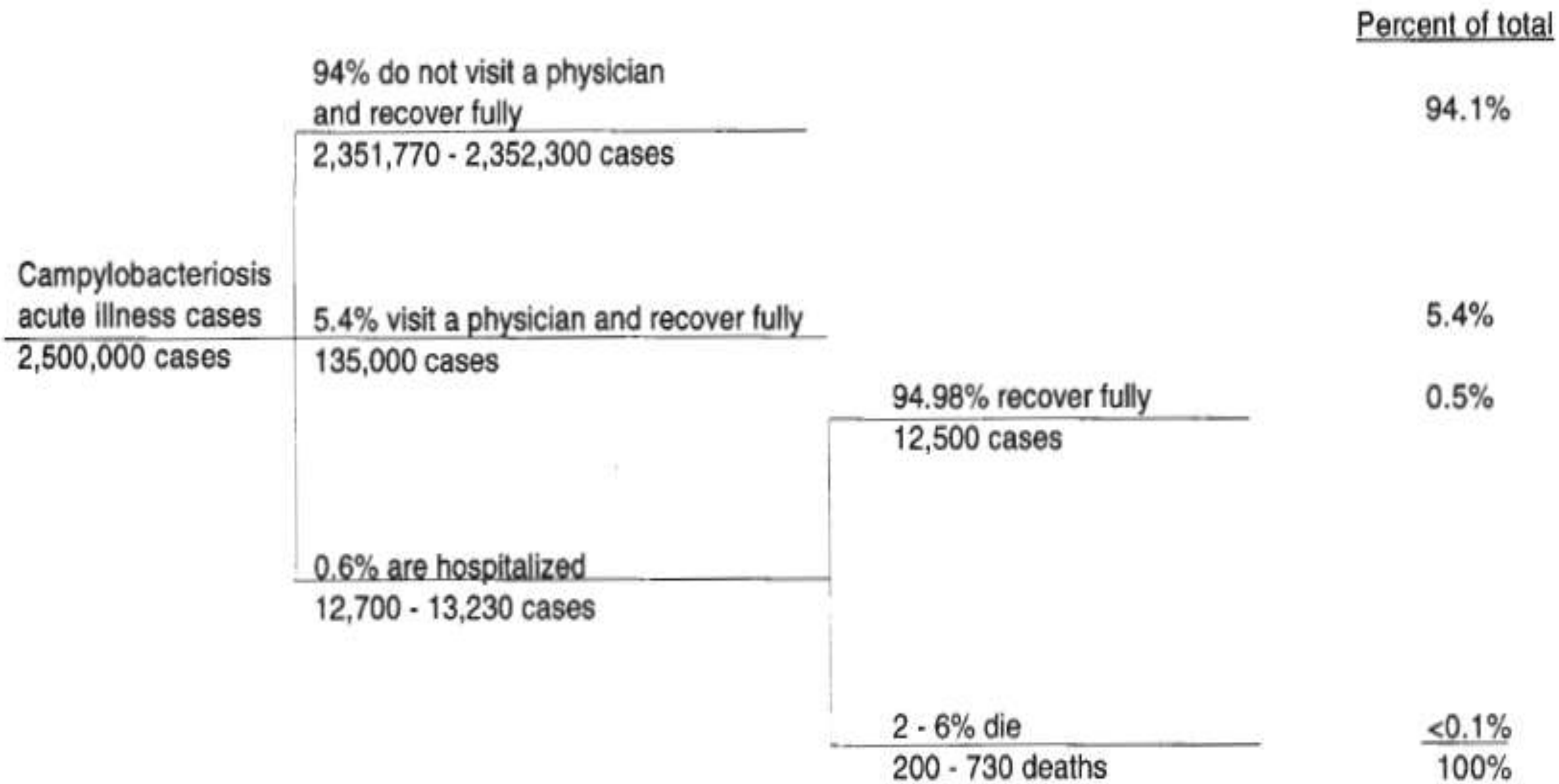
Distribution of estimated annual U.S. salmonellosis cases and disease outcomes[1]



[1] Percentages are rounded.
Prepared by Economic Research Service, USDA.

Figure 6

Distribution of estimated annual U.S. campylobacteriosis cases and disease outcomes[1]



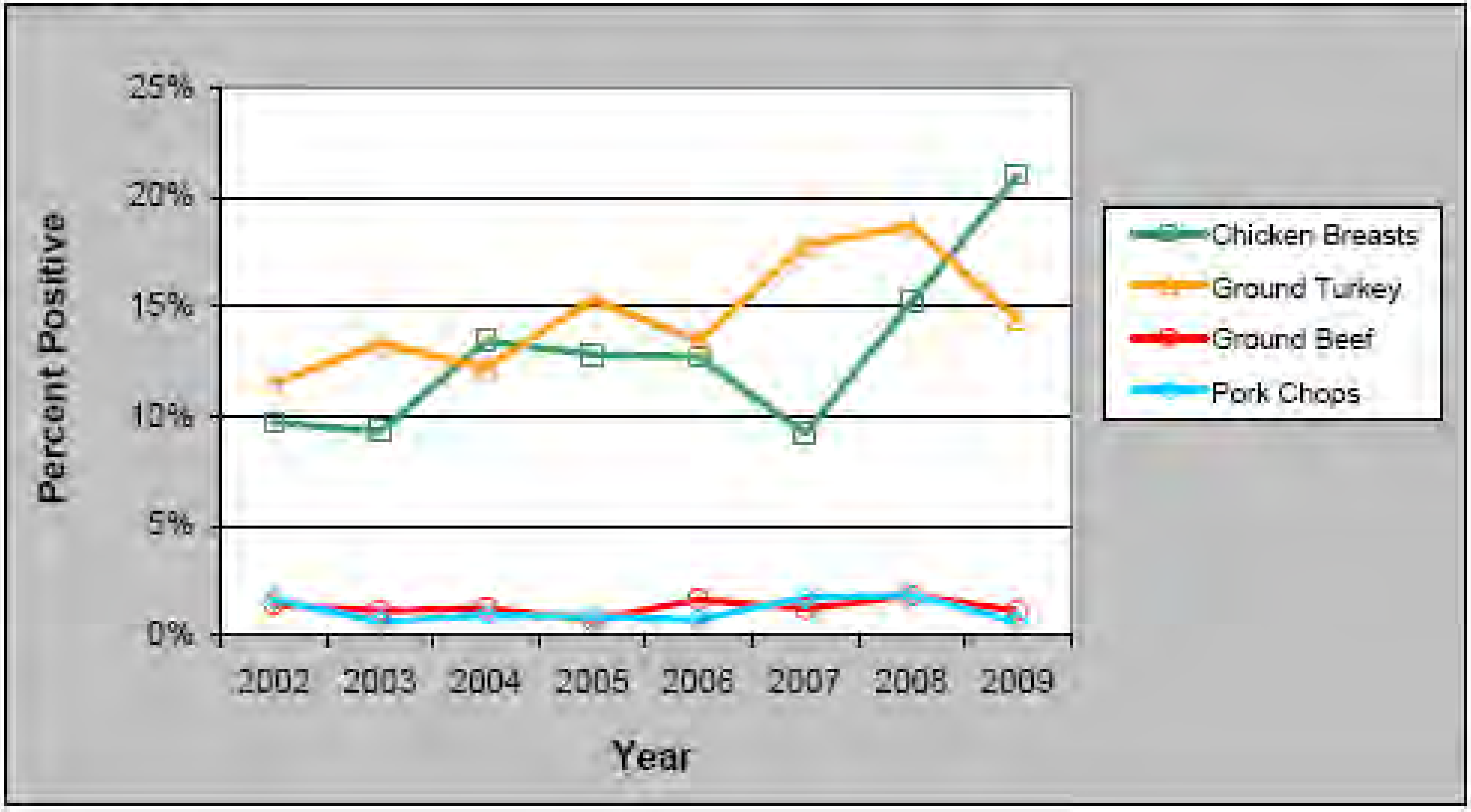
US vs. DK
(cases / 100,000)

	United States	Denmark
Campylobacter	13	61
Salmonella	15	39

- 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



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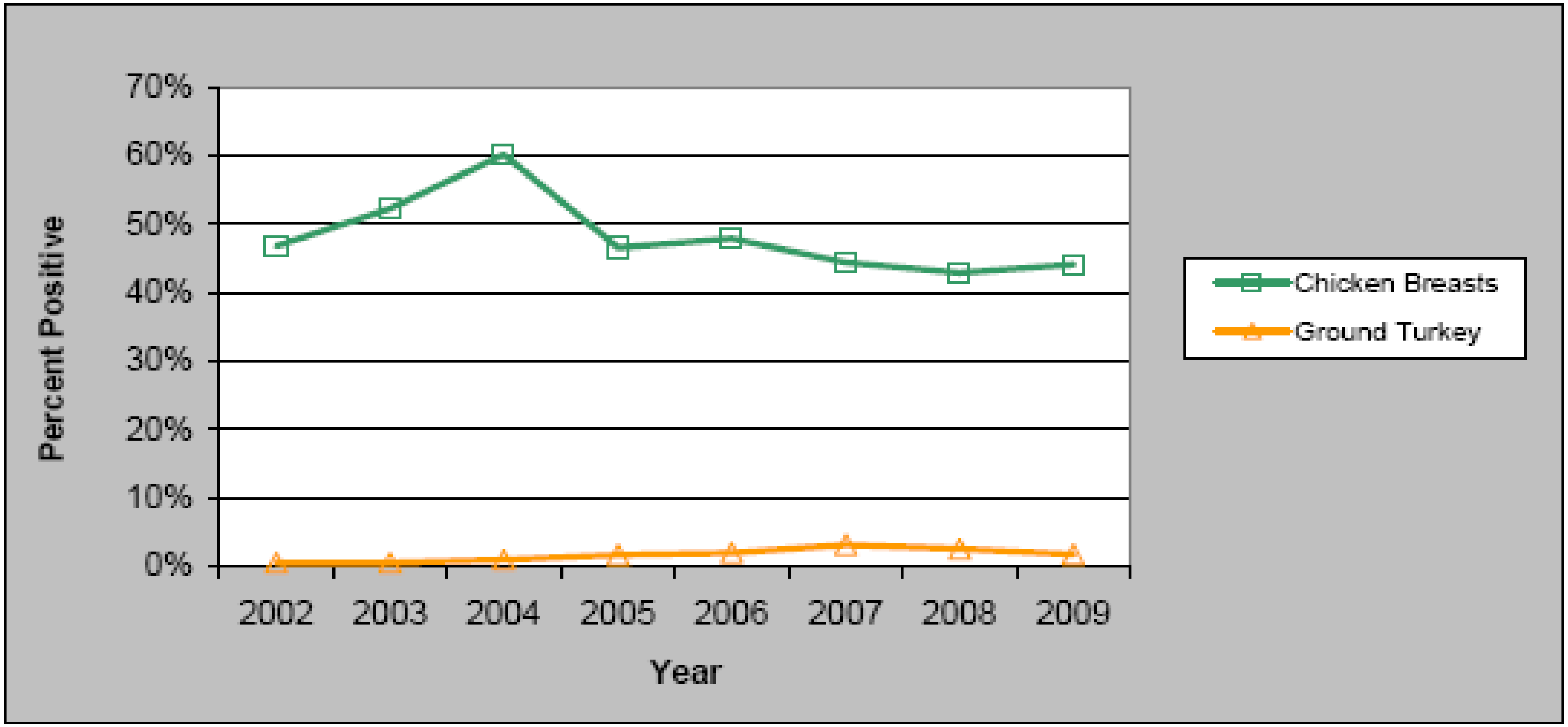
Not All Meat Products…

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



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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}

Doern and Brecher. 2011. J. Clin. Micro. 49 (9 Suppl.):S11–S14

Treatment Outcome

- Meta-analysis of Campylobacterosis 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.

S Sirinavin, P Garner. Antibiotics for treating salmonella gut infections
Cochrane Database of Systematic Reviews 2008 Issue 2 (Status: *Unchanged*)
The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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.

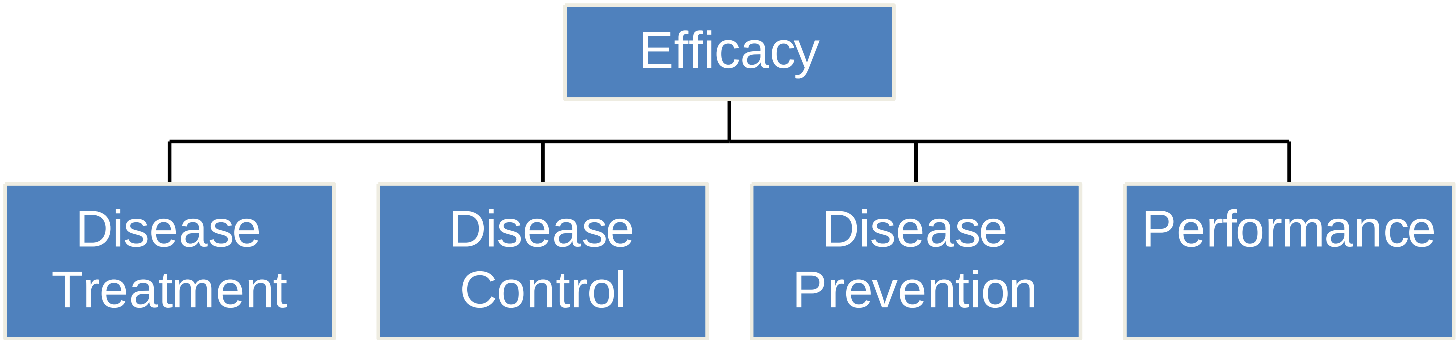
Attribution?

- 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)

β-lactams	Penicillin, amoxicillin; ceftiofur
Macrolides & lincosamides	Tylosin; tilmicosin; tulathromycin, lincomycin
Aminoglycosides	Gentamicin; neomycin
Fluoroquinolones	Enrofloxacin, danofloxacin
Tetracyclines	Tetracycline; oxytetracycline, chortetracycline
Sulfonamides	Various
Streptogramins	Virginiamycin
Polypeptides	Bacitracin
Phenicols	Florfenicol
Pleuromutilin	Tiamulin

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)

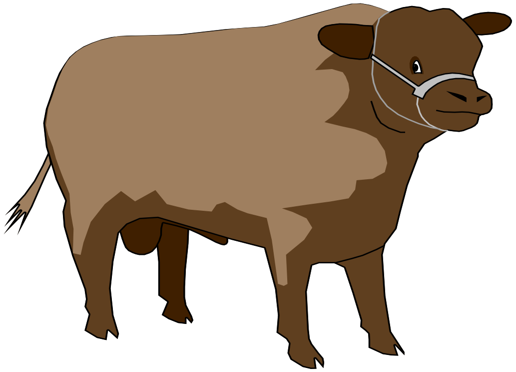
AVMA Veterinarians Oath

- "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.

Date	Country or International	Report Source	Report Title
1969	United Kingdom	English Parliament	The Report to Parliament by the Joint Committee on Antibiotic Uses in Animal Husbandry and Veterinary Medicine ("Swann Report")
1980	United States	National Research Council (NRC)	The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feed
1981	United States	Council for Agricultural Science & Technology	Antibiotics in Animal Feeds, Report 88
1981	United States	Institute of Medicine (IOM)	Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed
1989	United States	*Committee on Human Health Risk Assessment of Using Subtherapeutic Antibiotics in Animals*	Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feeds
1997	International	World Health Organization (WHO)	The Medical Impact of the Use of Antimicrobials in Food Animals
1998	United Kingdom	Ministry of Agriculture, Fisheries and Food	A Review of Antimicrobial Resistance in the Food Chain
1998	United States	Food and Drug Administration (FDA) Center for Veterinary Medicine	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
1998	International	WHO	Use of Quinolones in Food Animals and Potential Impact on Human Health: Report and Proceedings of a WHO Meeting
1999	European Union	The European Agency for the Evaluation of Medicinal products	Antibiotic Resistance in the European Union Associated with Therapeutic Use of Veterinary Medicines
1999	European Union	EU Scientific Steering Committee	Opinion of the Scientific Steering Committee on Antimicrobial Resistance

1999	United States	FDA	Risk Assessment on the Human Health Impact of Fluoroquinolone-resistant Campylobacter Associated with Consumption of Chicken
1999	United States	NRC *of Sciences Committee on Drug Use in Food Animals and the Panel on Animal Health, Food Safety, and Public Health*	The Use of Drugs in Food Animals: Benefits and Risks
1999	United States	U.S. General Accounting Office (GAO)	Food Safety: The Agricultural Use of Antibiotics and its Implications for Human Health
1999	United Kingdom	Advisory Committee on the Microbiological Safety of Food	Report on Microbial Antibiotic Resistance in Relation to Food Safety
1999	Australia	Joint Expert Advisory Committee on Antibiotic Resistance	The Use of Antibiotics in Food-Producing Animals: Antibiotic Resistant Bacteria in Animals and Humans
1999	European Union	European Commission	Opinion of the Scientific Steering Committee on Antimicrobial Resistance,
1999	International	WHO	The Medical Impact of the Use of Antimicrobials in Food Animals
2000	United States	Centers for Disease Control and Prevention *Interagency Task Force on Antimicrobial Resistance*	A Public Action Health Plan to Combat Antimicrobial Resistance
2000	International	WHO	WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food
2000	International	Food and Agriculture Organization of the United Nations (FAO)/WHO *Codex Committee on Residues of veterinary Drugs in Foods*	Antimicrobial Resistance and the Use of Antimicrobials in Animal Production

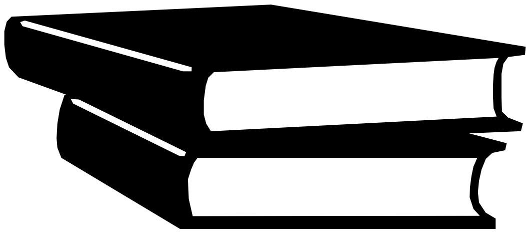
2001	International	Office International Des Epizooties (OIE)	Antimicrobial Resistance: Reports prepared by the OIE Ad Hoc Group of Experts on Antimicrobial Resistance
2001	International	WHO	WHO Global Strategy for Containment of Antimicrobial Resistance
2001	International	WHO	Monitoring Antimicrobial Usage in Food Animals for the Protection of Human Health
2002	United States	Alliance for the Prudent Use of Antibiotics	The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences ("FAAIR Report")
2002	Canada	Veterinary Drugs Directorate, Health *Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health*	Uses of Antimicrobials in Food Animals in : Impact on Resistance and Human Health
2003	International	WHO *Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens*	Impacts of Antimicrobial Growth Promoter Termination in
2004	International	FAO, OIE, and WHO	Joint FAO/OIE/WHO Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment
2004	International	FAO, OIE, and WHO	Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options
2004	United States	GAO	Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals
2005	United States	FDA CVM	Withdrawal Order for Baytril Soluble for Poultry

2006	International	FAO, OIE, and WHO	Third Joint FAO/OIE/WHO Expert Workshop on Antimicrobial Use in Aquaculture and Antimicrobial Resistance
2007	International	FAO, OIE and WHO	Fourth Joint FAO/OIE/WHO Expert Workshop on Critically Important Antimicrobials
2007-2010	International	Codex *Ad hoc Intergovernmental Task Force on Antimicrobial Resistance*	Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance
2009, 2010	International	WHO	Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
2011	United States	GAO report	Antibitotic Resistance – Agencies Have Made Little Progress in Addressing Antibiotic Use in Animals

Global Reports on Animal Antibiotic Use

since 1997

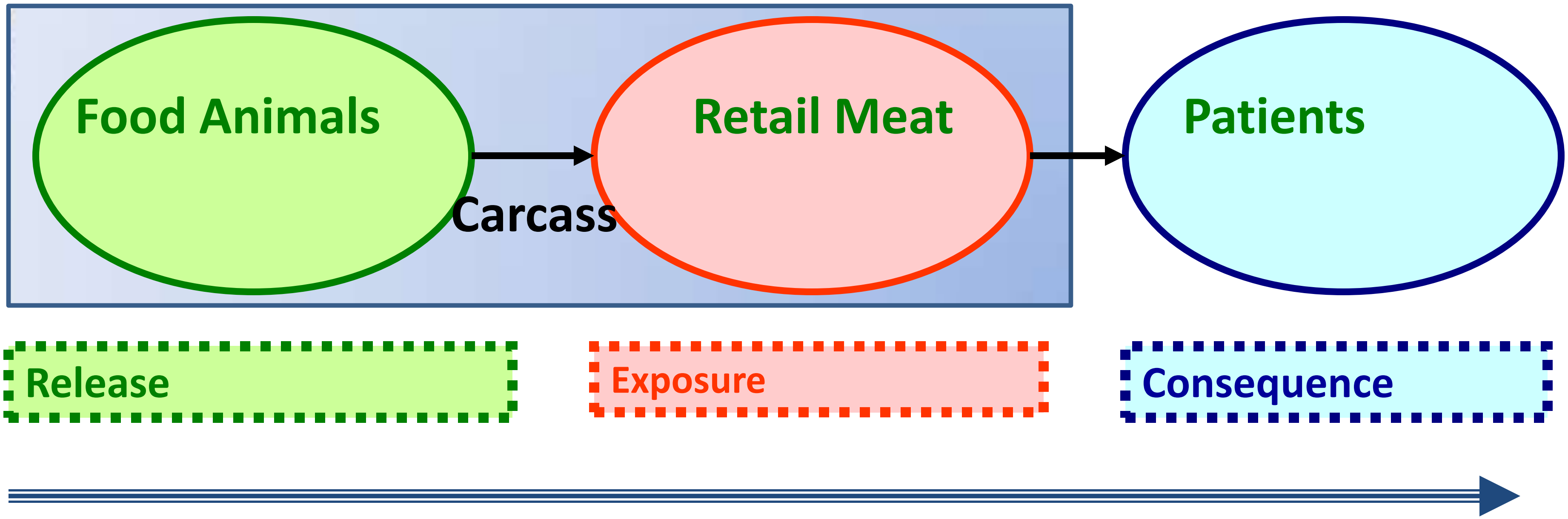
- WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture, AGISAR)
- OIE Terrestrial Code
- Codex –various (TFAMR)
- Europe (CVMP, EFSA, ECDC; EU commission)
- Australia (JETACAR)
- U.S. (NRC, CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
- Canada (Adv. Com. Report, CCAR)
- Other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



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?

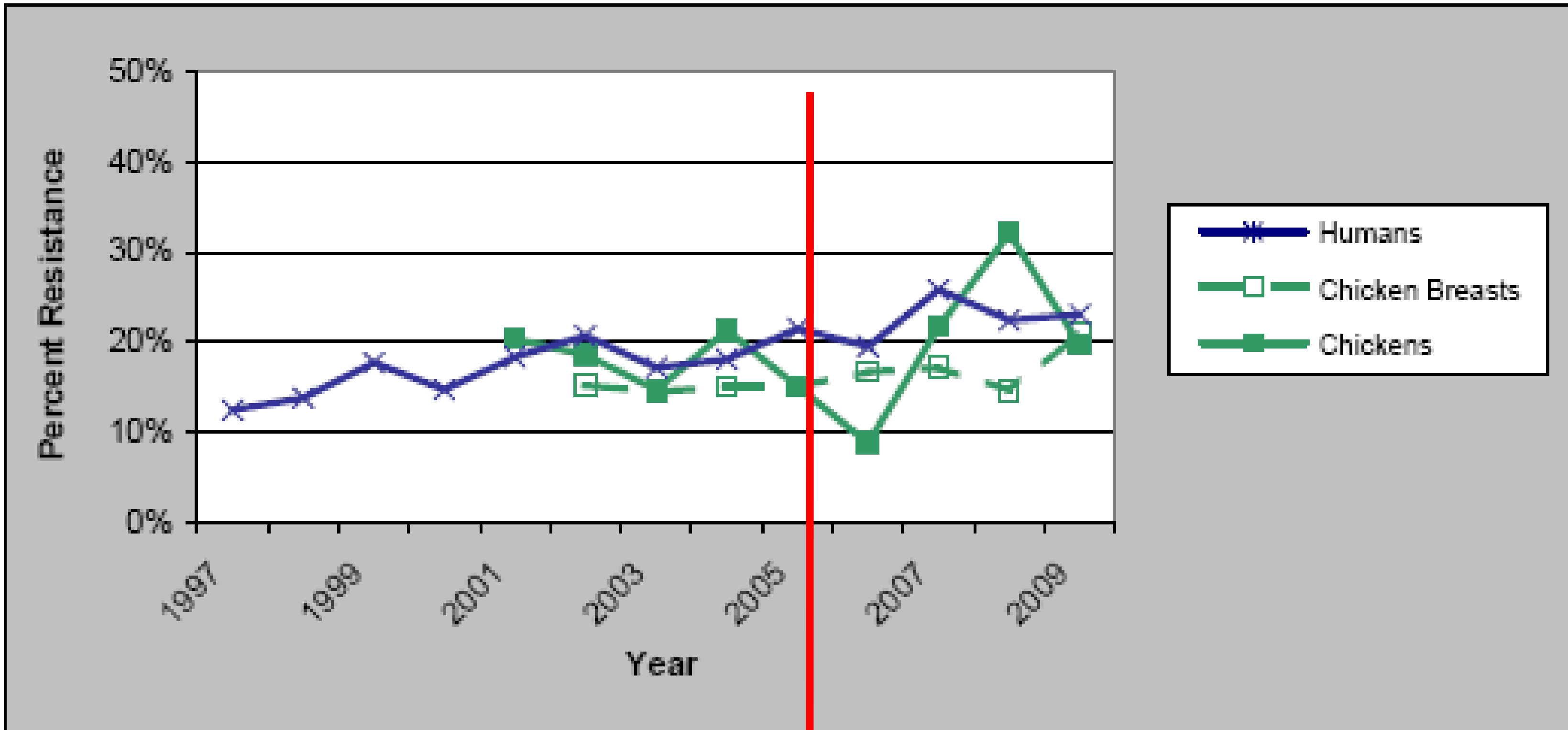
- Implications – risk management actions will re-shape veterinarians access to antibiotics and the practice of veterinary medicine with an unknown impact on public health and food safety.

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]



[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

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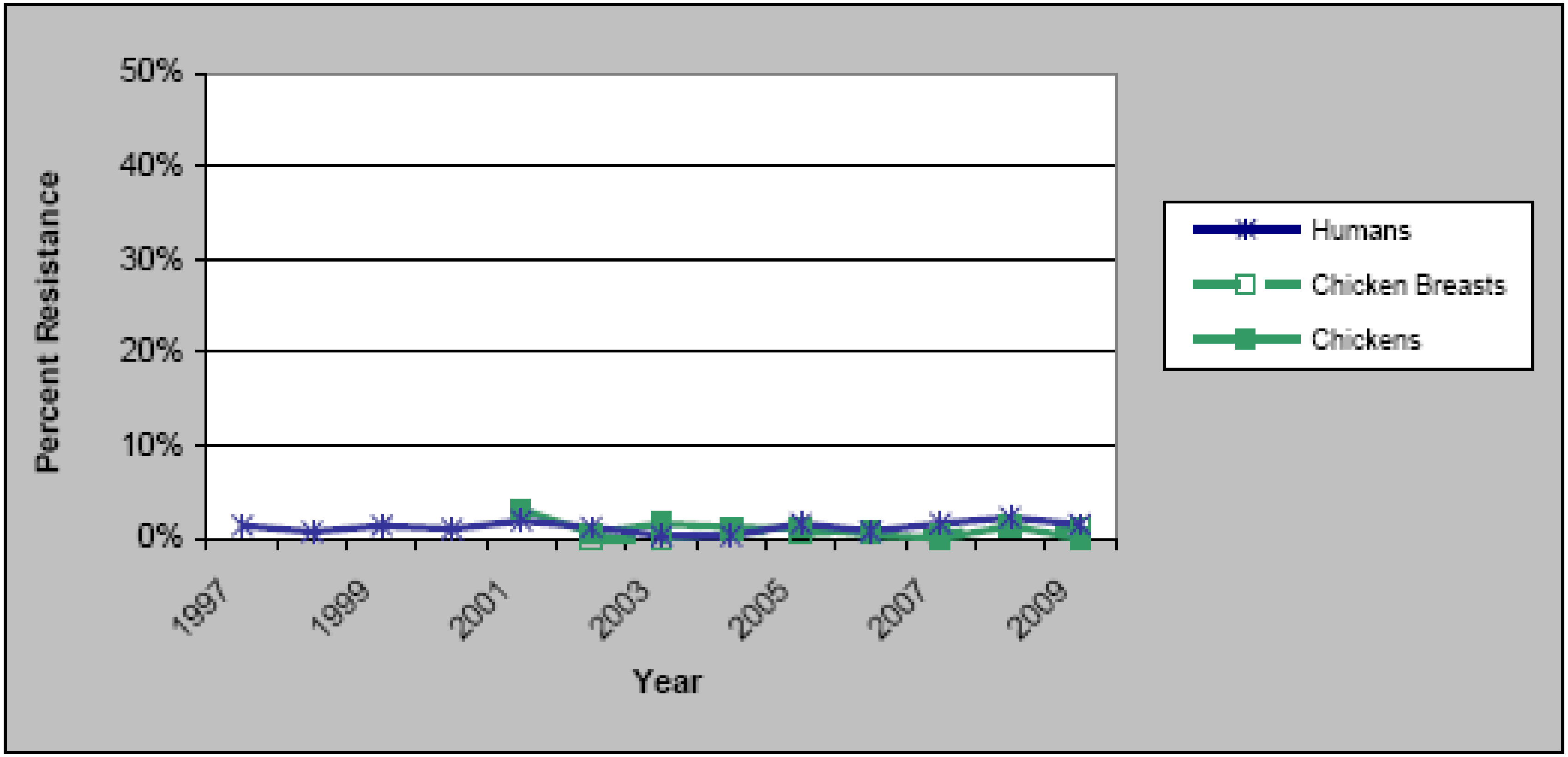
Sept. 2005 Baytril withdrawal

Erythromycin Resistance

Figure 21. Percent of *Campylobacter jejuni* Isolates from Humans, Chicken Breasts, and Chickens Resistant to Erythromycin by Year, 1997-2009[1]



[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

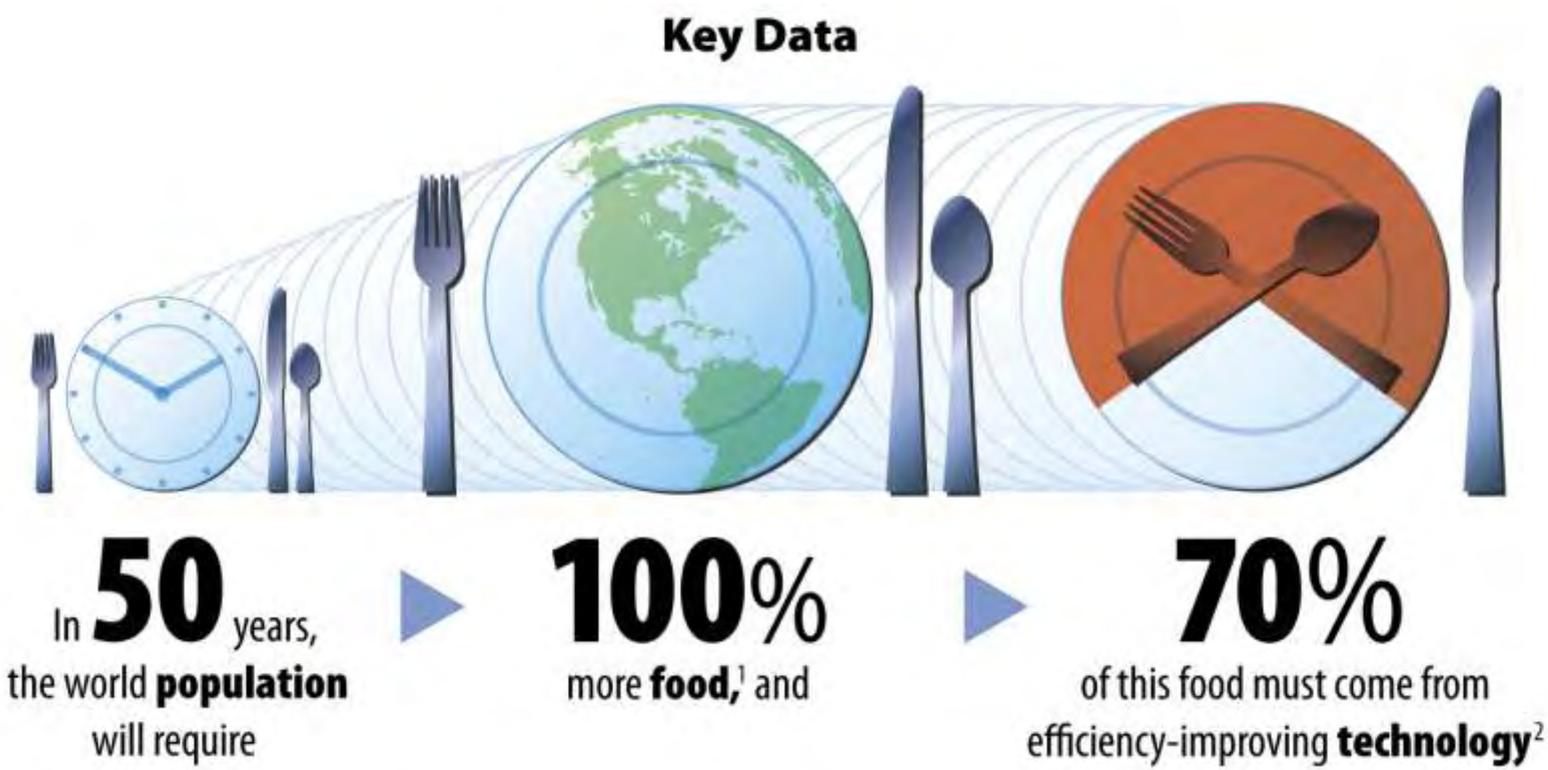
Substance	Cattle	Broilers	Broiler meat		Humans	
	Danish	Danish	Danish	Imported	Domestically acquired	Travel abroad reported
	%	%	%	%	%	%
Tetracycline	2	12	4	52	11	39
Chloramphenicol	0	0	0	0	0	0
Erythromycin	0	0	0	0	0	0
Gentamicin	0	0	0	0	0	3
Streptomycin	5	1	0	0	2	7
Ciprofloxacin	20	13	0	58	24	61
Nalidixic acid	20	13	0	58	24	61
Number of isolates	87	75	28	62	62	31

American Academy of Microbiology
Colloquium Report 2008
"An Ecological Approach to an Old Problem"

- 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



1 Green, R. et al. January 2005. "Farming and the Fate of Wild Nature." Science 307.5709: 550-555; and Tilman, D. et al. August 2002. "Agricultural sustainability and intensive production practices." Nature 418.6898: 671-677.

2 "World Agriculture: toward 2015/2030." 2002. United Nations Food and Agriculture Organization, Rome. Accessed 12/8/08. <ftp://ftp.fao.org/docrep/fao/004/y3557e/y3557e.pdf>.

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