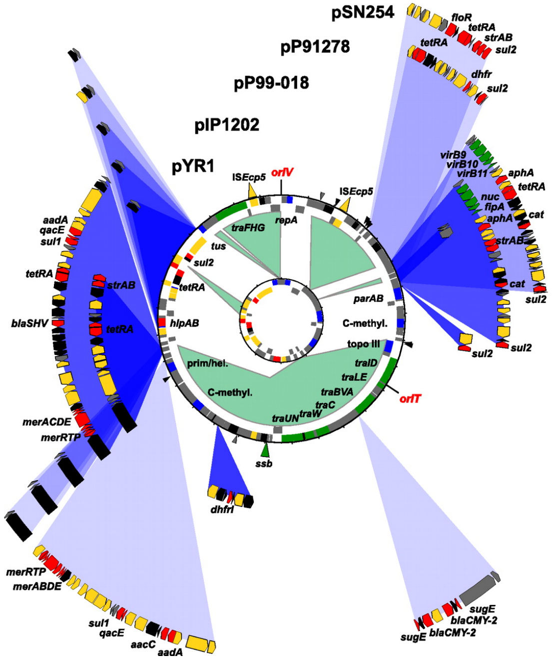
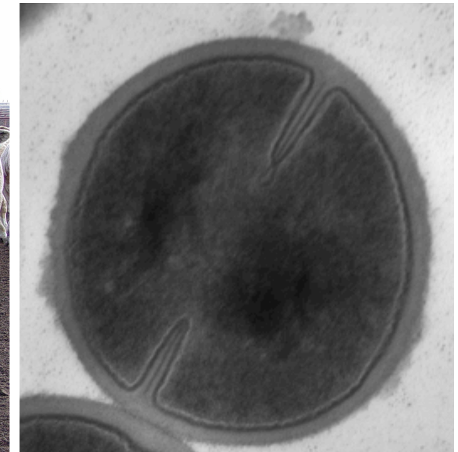
Antimicrobial Resistant Bacteria and Food Safety



(Fricke *et al.*, *J. Bacteriology*, 191:4750, 2009)



2014 Nebraska Manure Demonstration Day

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United States Meat Animal Research Center
Meat Safety and Quality Research Unit
Clay Center, NE

Infectious Disease and Antibiotics

- **WHO has estimated that premature deaths would be 40% higher if antibiotics did not exist.**

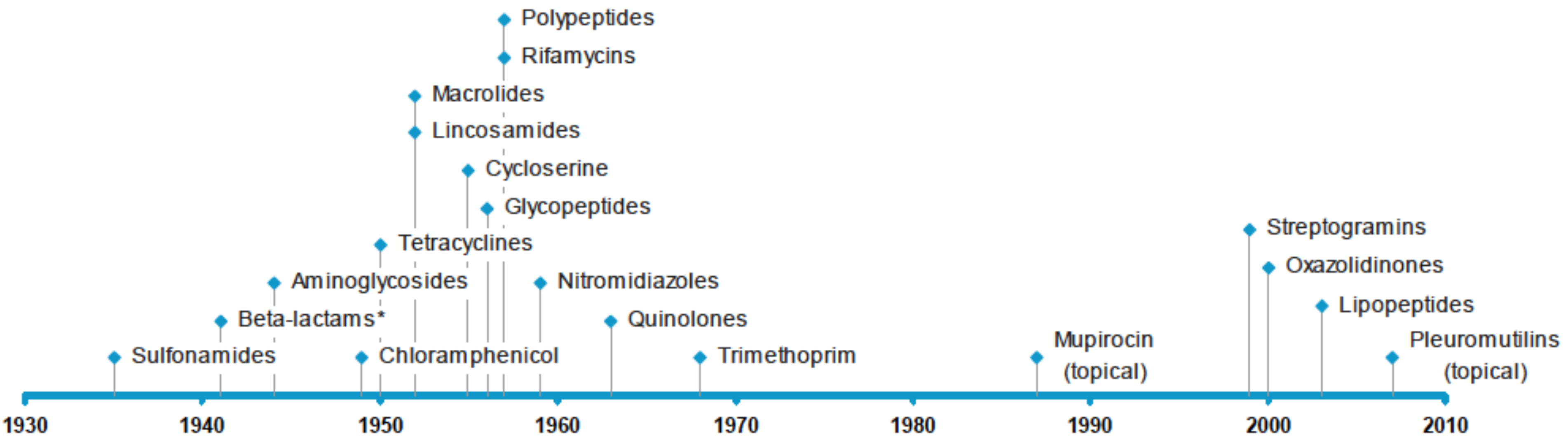
- **Increasing prevalence of several antibiotic resistant diseases identified as high priority by Thomas R. Frieden, CDC Director, in congressional testimony (4/28/10).**
  - **Methicillin-resistant *Staphylococcus aureus* (MRSA)**
  - **MDR *Mycobacterium tuberculosis***
  - **MDR Gram negatives (*E. coli*, *Klebsiella, Acinetobacter*)**
  - **MDR *Neisseria gonorrhoeae***
  - **Cephalosporin-resistant *Salmonella***
  - **Fluoroquinolone-resistant *Campylobacter***

- **Many declarations of "critical threat to public health."**

- **Fears of "return to pre-antibiotic era."**

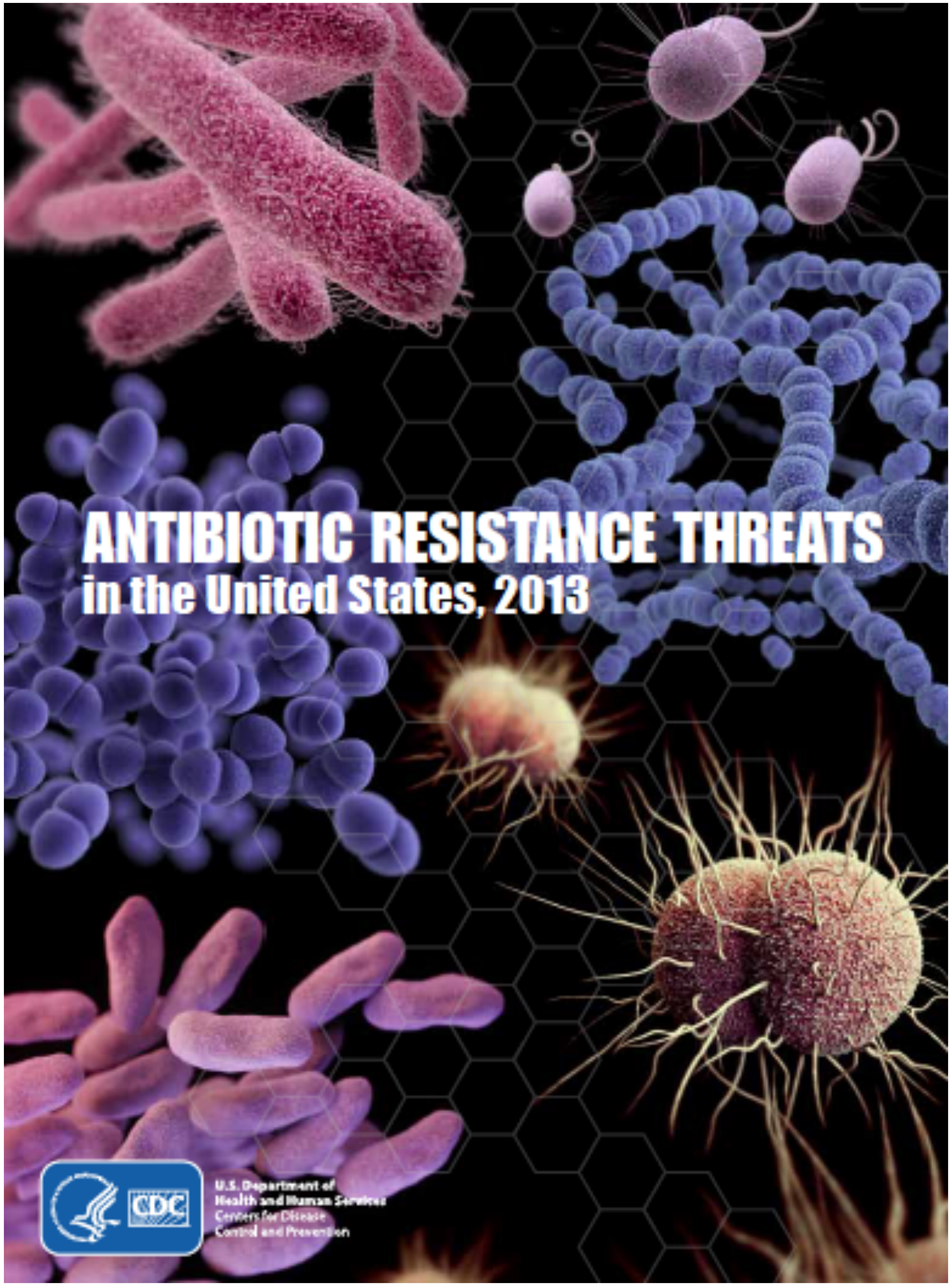
No Novel Antibiotics on Horizon

Timeline of introduction of antibiotic classes to clinical use



- **Discovery programs have largely yielded compounds in the same class or that target the same function as known antibiotics.**
- **Discovery, development, and regulatory costs are extremely high with extremely high failure rates.**
- **Drugs with highest ROI treat chronic diseases (diabetes, etc.).**

Antibiotic Resistance Threats, CDC



CDC Report on Antibiotic Resistance Threats

But only a portion are due to bacterial infections with a plausible link to animal agriculture…

CDC Report on Antibiotic Resistance Threats

Microorganism	CDC Threat Level	CDC Report Links to Animal Ag	Others Link to Animal Ag	US Infections/ year	US Deaths/year
Clostridium difficile	**Urgent**	No	No	250,000	14,000
Carbapenem-resistant Enterobacteriaceae (CRE)	**Urgent**	No	No	9,000	600
Drug-resistant *Neisseria gonorrhoeae*	**Urgent**	No	No	246,000	N/A
MDR *Acinetobacter*	**Serious**	No	No	7,300	500
Drug-resistant *Campylobacter*	**Serious**	**Yes**	**Yes**	310,000	120
Fluconazole-resistant *Candida*	**Serious**	No	No	3,400	220
Extended-spectrum β-lactamase producing Enterobacteriaceae (ESBLs)	**Serious**	No	**Yes**	26,000	1,700
Vancomycin-resistant *Enterococcus* (VRE)	**Serious**	No	No	20,000	1,300
MDR *Psueudomonas aeruginosa*	**Serious**	No	No	6,700	440
Drug-resistant non-typhoidal *Salmonella*	**Serious**	**Yes**	**Yes**	100,000	450
Drug-resistant *Salmonella* Typhi	**Serious**	No	No	3,800	Not Reported
Drug-resistant *Shigella*	**Serious**	No	No	27,000	40
Methicillin-resistant *Staphylococcus aureus* (MRSA)	**Serious**	No	No	80,461	11,285
Drug-resistant *Streptococcus pneumoniae*	**Serious**	No	No	1,200,000	7,000
Drug-resistant tuberculosis	**Concerning**	No	No	1,042	Not Reported
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	**Concerning**	No	No	< 2	Usually Fatal
Erythomycin-resistant Group A *Strepotococcus* (GAS)	**Concerning**	No	No	1,300	160
Clindamycin-resistant Group B Streptococcus	**Concerning**	No	No	7,600	440
			TOTALS	**2,300,000**	**38,000**

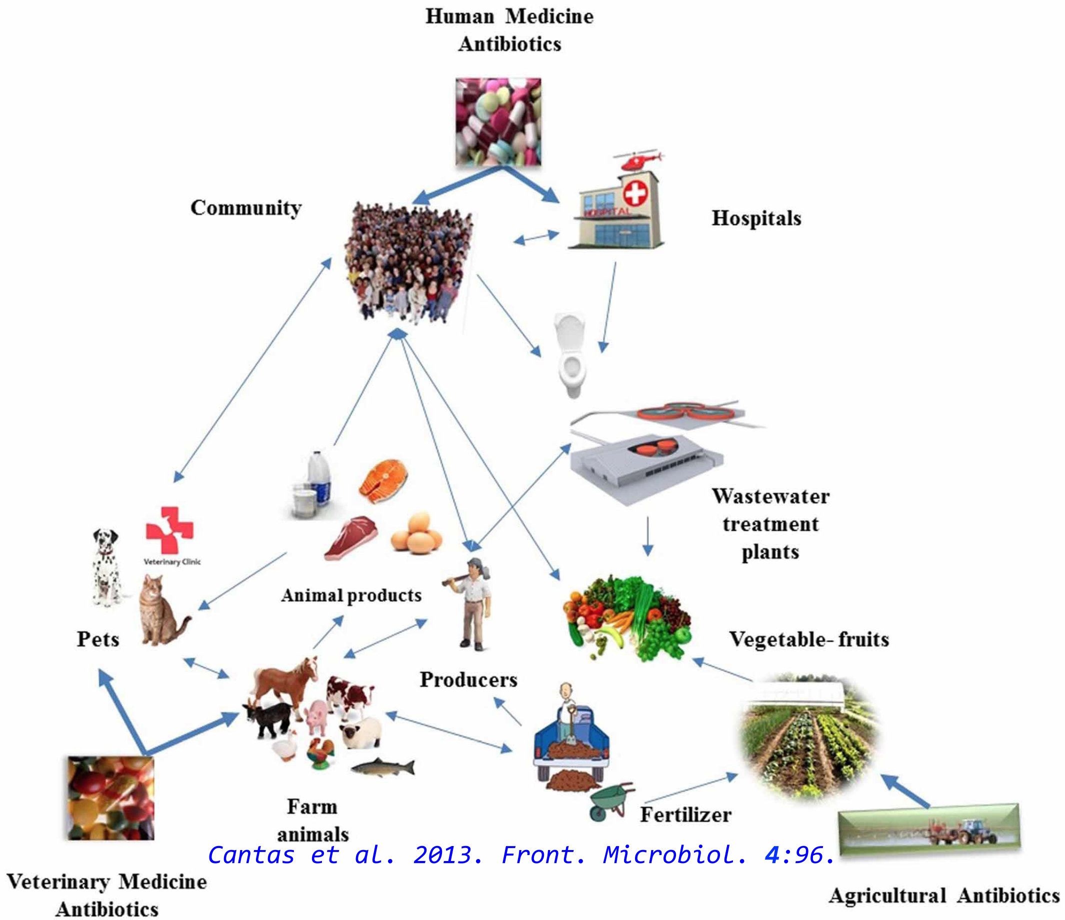
- **The entire bacterial groups with a link to animal ag. account for 436k (19 %) of the estimated 2.3 million antibiotic-resistant infections in the US per year and 2,270 (6 %) of the estimated 38,000 deaths due to antibiotic-resistant infections in the US per year.**
- **Problem is far larger than animal agriculture and will not be solved by only addressing animal uses of antibiotics.**

CDC Report on Antibiotic Resistance Threats

The use of antibiotics is the single most important factor leading to antibiotic resistance around the world. Antibiotics are among the most commonly prescribed drugs used in human medicine. However, up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed. Antibiotics are also commonly used in food animals to prevent, control, and treat disease, and to promote the growth of food-producing animals. The use of antibiotics for promoting growth is not necessary, and the practice should be phased out. Recent guidance from the U.S. Food and Drug Administration (FDA) describes a pathway toward this goal.[2] It is difficult to directly

Antibiotics, Human Health, and Animal Ag.

- **The extremely complex relationship between antibiotics, animal health, human health and environmental health is driven by two premises:**
  1) **Antibiotic resistance is a *naturally occurring phenomenon* that is present with or without the use of antibiotics.**
  2) **Anytime an antibiotic enters the ecosystem, it contributes to the presence of antibiotic resistance.**



Cantas et al. 2013. Front. Microbiol. 4:96.

Bacterial Antibiotic Resistance Is Ancient

- **Bacterial antibiotic resistance is an ancient, natural, and dynamic process that pre-dates the human use of antibiotics.**

LETTER

doi:10.1038/nature10388

Nature, 477:457-61 (2011).

Antibiotic resistance is ancient

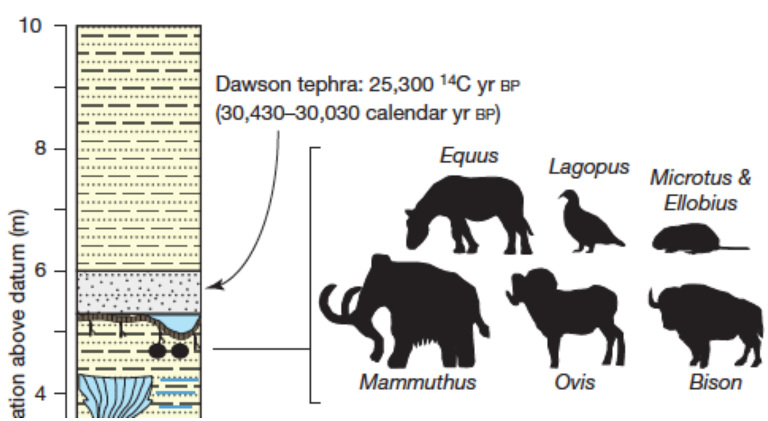
Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes[1,2]. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics[3]. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Recent studies of modern environmental and human commensal microbial genomes have a much larger concentration of antibiotic resistance genes than has been previously recognized[4–6]. In addition,

with high concentrations of *Escherichia coli* harbouring the *gfp* (green fluorescent protein) gene from *Aequorea victoria* (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase



Bacterial Antibiotic Resistance Is Ancient and *Natural*

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- Many bacterial species synthesize antibiotics, and these species must possess a resistance mechanism to avoid their own demise.
- Genetic analysis indicates that bacteria have possessed antibiotic resistance genes for more than 2 billion years.
- Bacterial resistance to penicillin was first reported in 1940, pre-dating the first therapeutic uses in 1942.

Low Impact of Ag. Antibiotic Use on Human Health ?

- **Several quantitative assessments have demonstrated that the risks to human health posed by antibiotic use in animal production are low.**

Risk Analysis, Vol. 28, No. 3, 2008 DOI: 10.1111/j.1539-6924.2008.01054.x

A Stochastic Assessment of the Public Health Risks of the Use of Macrolide Antibiotics in Food Animals

H. Scott Hurd[1]* and Sasidhar Malladi[2]

FOODBORNE PATHOGENS AND DISEASE
Volume 7, Number 11, 2010
© Mary Ann Liebert, Inc.
DOI: 10.1089/fpd.2010.0550

Quantitative Risk from Fluoroquinolone-Resistant *Salmonella* and *Campylobacter* Due to Treatment of Dairy Heifers with Enrofloxacin for Bovine Respiratory Disease

H. Scott Hurd,[1] Michael B. Vaughn,[2] Derald Holtkamp,[1] James Dickson,[3] and Lorin Warnick[4]

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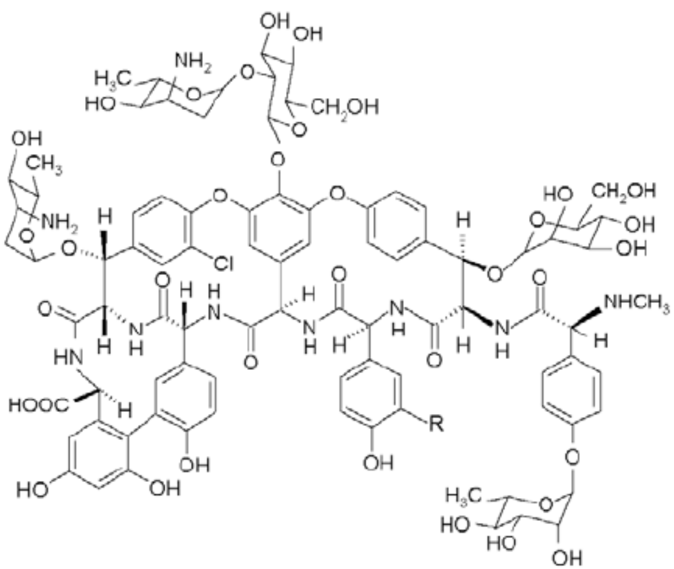
ScienceDirect
Preventive Veterinary Medicine 79 (2007) 186–203
PREVENTIVE VETERINARY MEDICINE
www.elsevier.com/locate/prevetmed

Modeling the relationship between food animal health and human foodborne illness

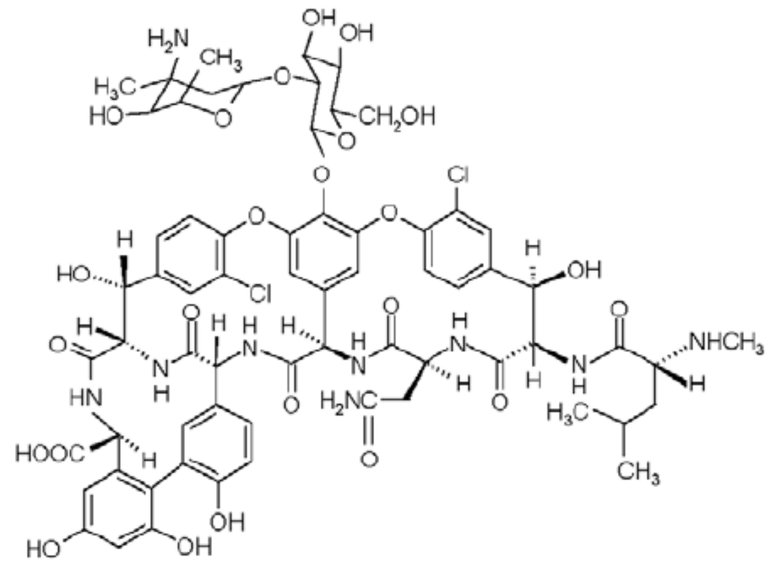
Randall S. Singer[a,b,*], Louis A. Cox Jr.[c], James S. Dickson[d], H. Scott Hurd[e], Ian Phillips[f], Gay Y. Miller[g]

So Why Restrict Agricultural Uses of Antibiotics? Denmark, EU, Avoparcin, and VRE

- **Avoparcin and vancomycin are glycopeptide antibiotics with similar structures and methods of action.**



α – Avoparcin R=H
β – Avoparcin R=Cl



Vancomycin

Denmark, EU, Avoparcin, and VRE

- Avoparcin was used for growth promotion in Europe but was never used in the US.
- US use of vancomycin in humans was higher than in Europe.
- Levels of Vancomycin-Resistant Enterococci (VRE) in EU food animals, meat, and human commensal flora were higher than in US.
- Concluded that avoparcin use for growth promotion caused the higher levels of VRE. To lower VRE levels Denmark banned avoparcin use in 1995 and the EU banned avoparcin use in 1997.
- Following the bans levels of VRE dropped in food animals, meat, and human commensal flora.

This Success Lead To The “Precautionary Principle”

- **Additional bans were enacted by Denmark and the EU not to reduce levels of specific antibiotic resistant bacterial groups but based on the “Precautionary Principle.”**

Year	Action
1998	Denmark bans all growth promoting antibiotics.
1999	EU bans growth promoting uses of tylosin, spiramycin, bacitracin, virginiamycin, carbadox, and olaquindox.
2002	Denmark bans most uses of fluoroquinolones.
2005	Denmark increases oversight of swine veterinarians.
2006	EU bans growth promoting uses of all remaining antibiotics.
2007	Denmark increases oversight of food animal veterinarians.
2010	Denmark sets limits on therapeutic antibiotic use on swine farms.

The Precautionary Principle states “where there are threats of serious or irreversible damage lack of scientific certainty should not postpone cost-effective measures to reduce risks to humans.”

Bans Have Not Had Desired Impact on Human Health

- **Denmark's comprehensive antibiotic resistance monitoring program (DANMAP) has not observed decreases in antibiotic resistant infections in humans.**

Figure 8.1. Resistance (%) in *Escherichia coli* blood isolates from humans, Denmark

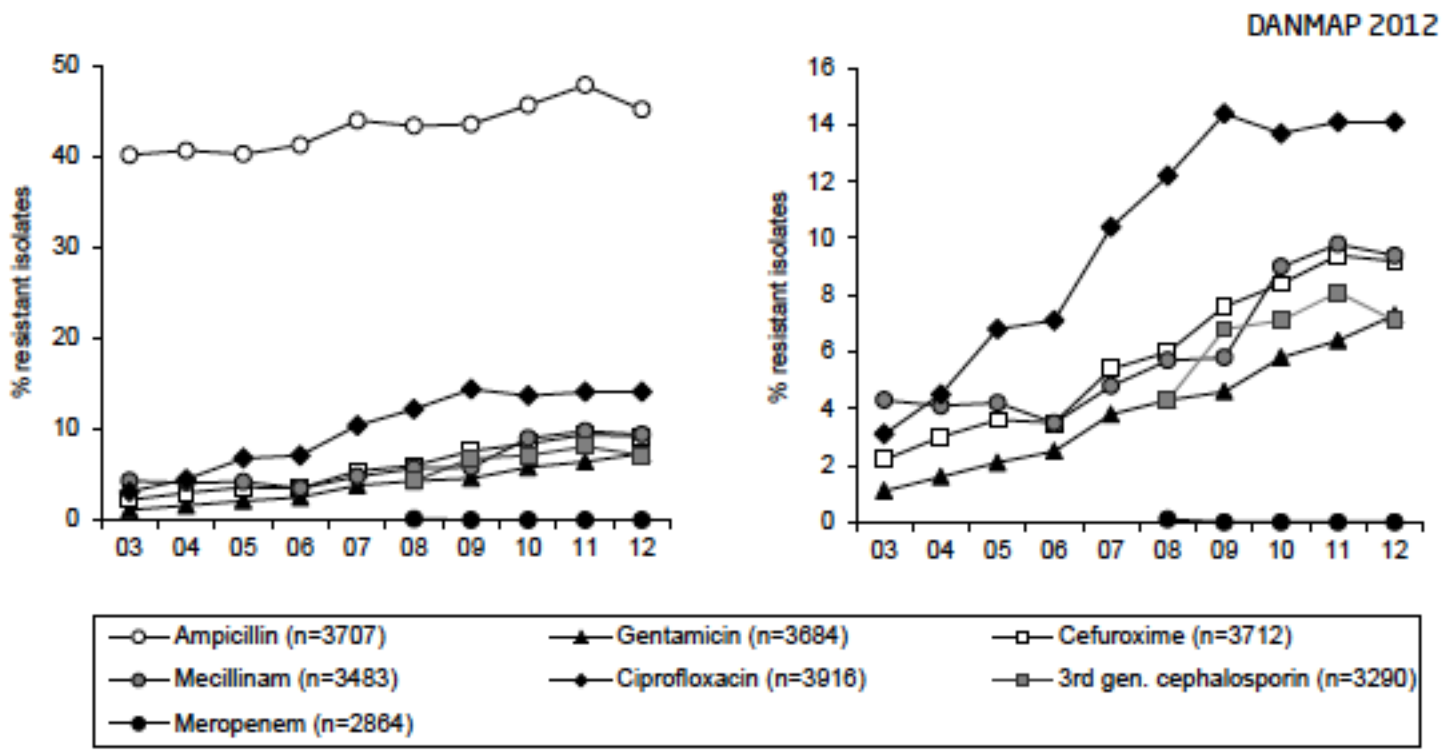


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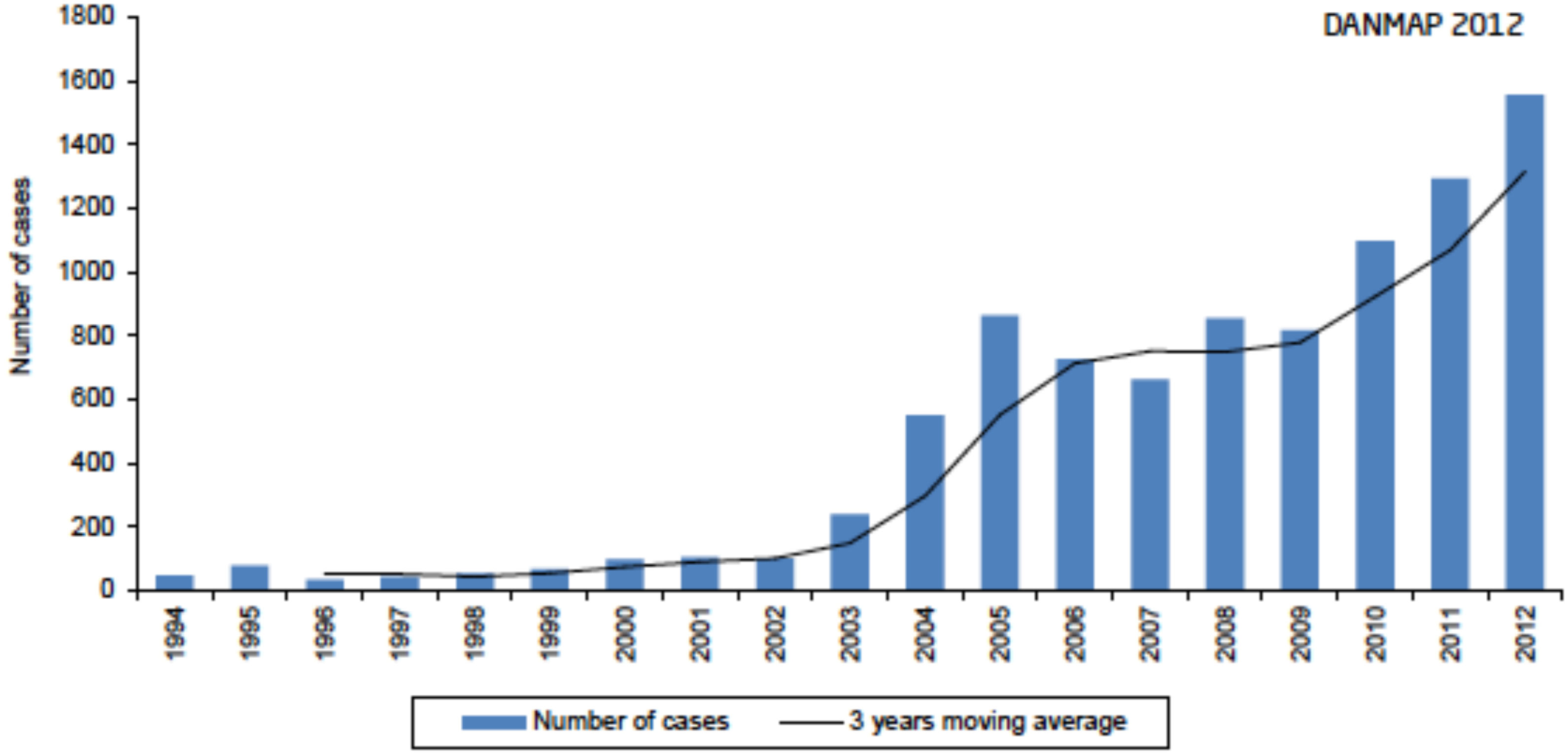
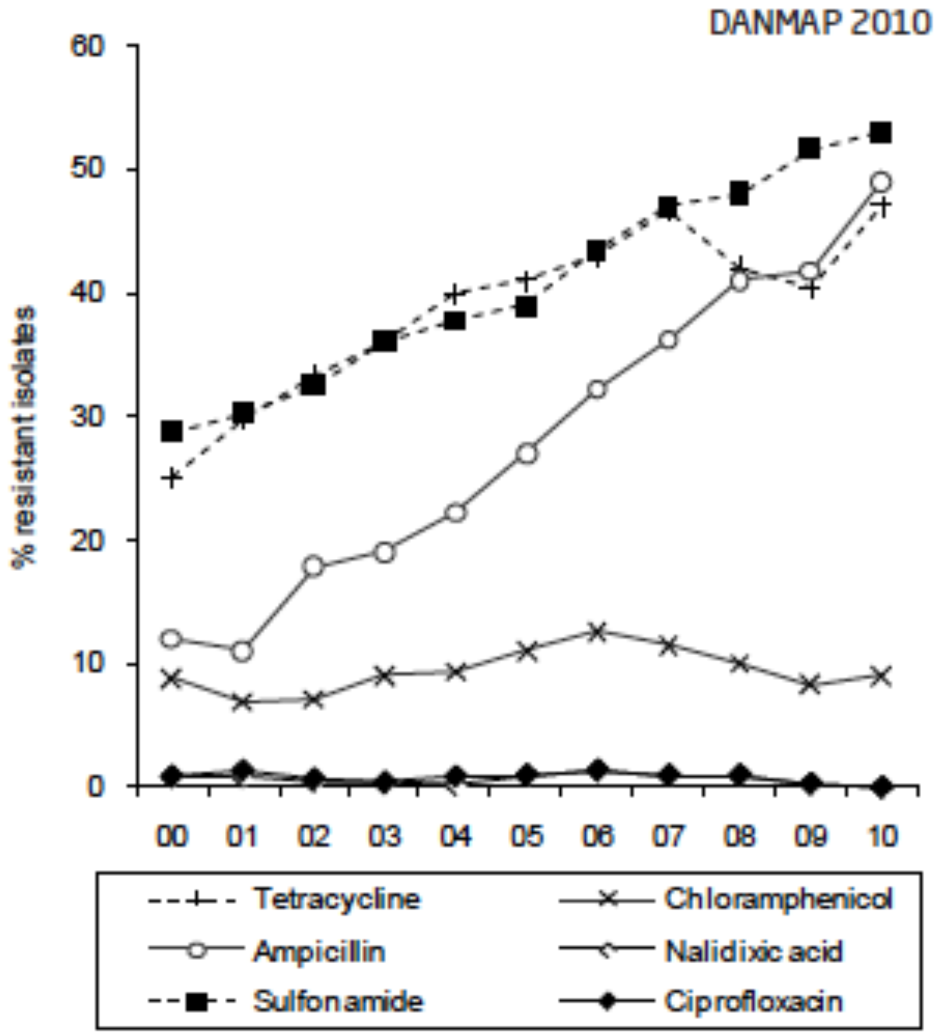
Figure 8.7. Number of MRSA cases, with a three years moving average, Denmark



Antibiotic Resistance in Animals Increased

Figure 6.1. Resistance (%) in *Salmonella* Typhimurium[(a)] from pigs, Denmark



Simple bans will not solve the problem, no easy answers.

Conclusions

- The use of antibiotics in animal agriculture is *perceived* to contribute significantly to the occurrence of human infections caused by antibiotic-resistant bacteria in spite of scientific evidence that antibiotic resistance is ancient, occurs naturally, and that comparable levels of antibiotic resistance genes are found in environments with varying exposures to anthropogenic antibiotics.

- Antibiotic use in animal agriculture continues to be blamed for human infections caused by antimicrobial resistant bacteria because *of a lack of studies directly examining the relative occurrences of antimicrobial resistant bacteria and genes in conventional production environments and other environments*.

Objectives of USMARC Antibiotic Resistance Research

The overall objectives of the USMARC antibiotic resistance research program address the most critical data gaps relating to meat animals by:

1) Determining the baseline levels of antibiotic-resistant bacteria in meat animal production environments and meat animal final products.

2) Increasing scientific understanding of the persistence of antibiotic-resistant bacteria in meat animal production environments in the absence of antibiotic use.

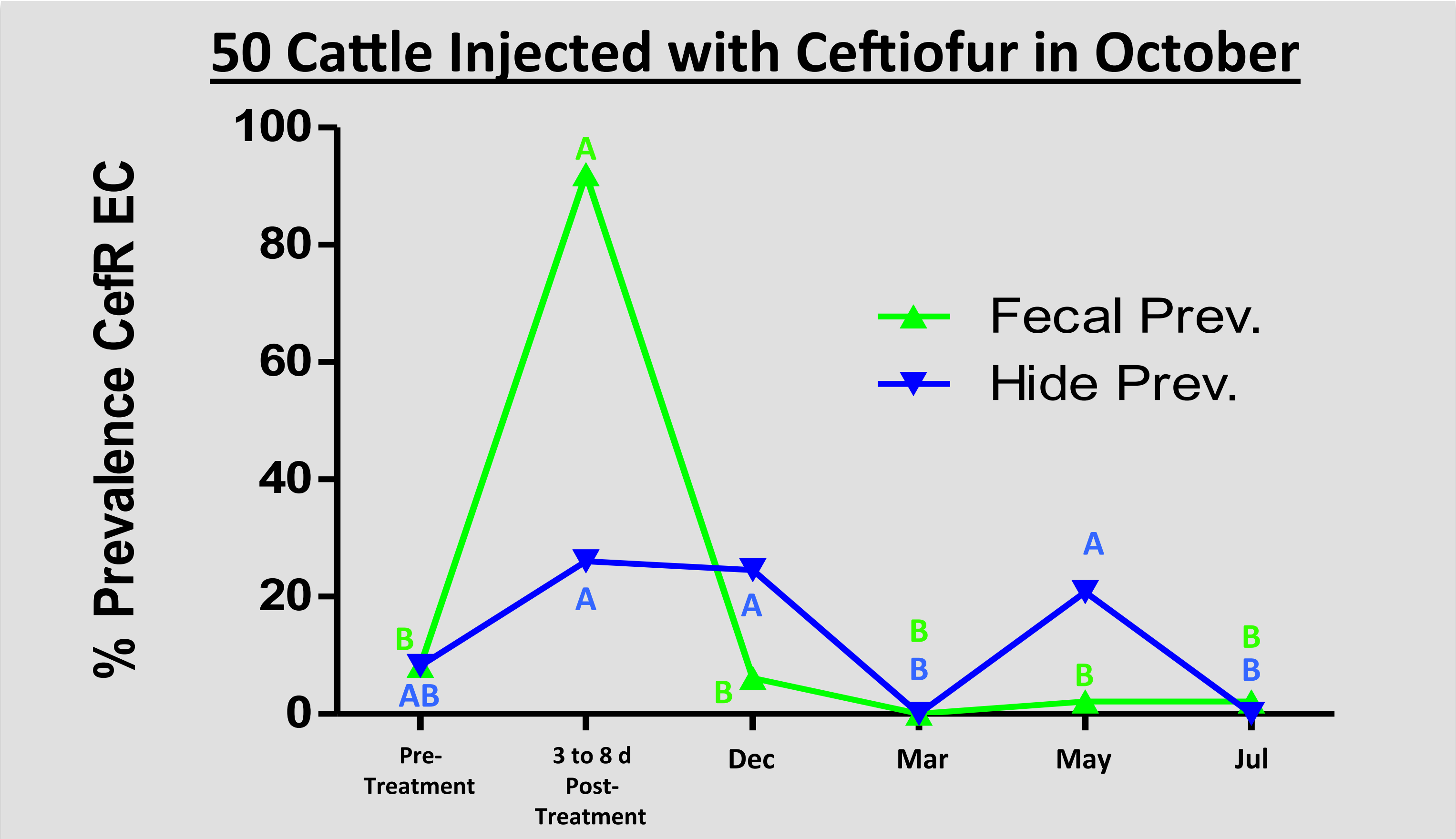
3) Determining the impact of agricultural antibiotic uses on resistance and evaluating methods to mitigate antibiotic-resistant bacteria in meat animal production environments.

Ceftiofur use in Beef Cattle Does Not Increase Resistance at Harvest

- **Ceftiofur (Excede, Naxcel) is a cephalosporin used in cattle to treat several diseases.**

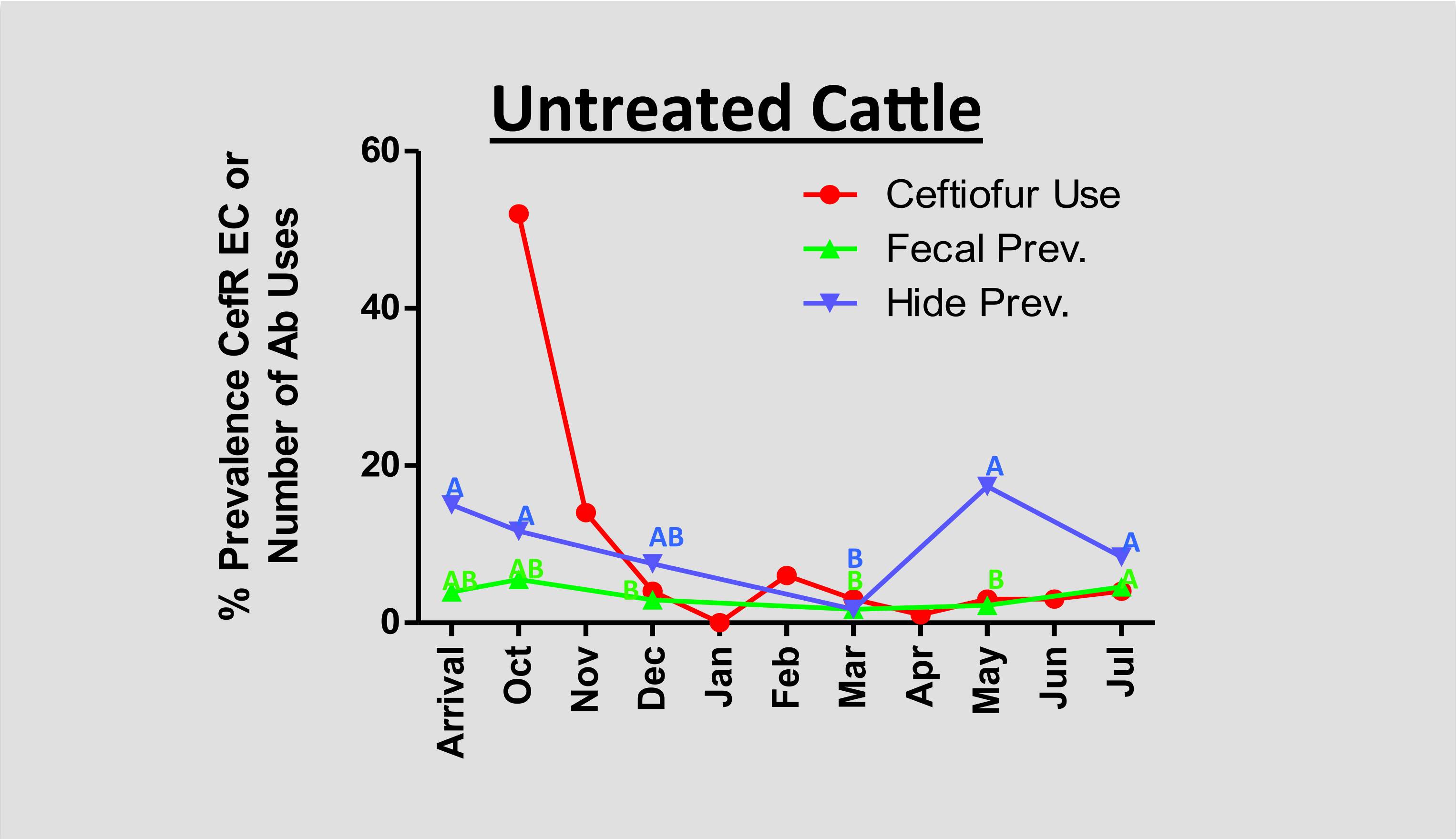
- **Cephalosporins are considered critically important to human medicine since they are currently a front-line treatment for serious *Salmonella* and *E. coli* infections.**

Ceftiofur use in Beef Cattle Does Not Increase Resistance at Harvest



- **Fecal prevalences of cephalosporin-resistant *E. coli* *transiently increase following* ceftiofur treatment then return to pretreatment levels.**
- **Hide prevalences do not increase significantly.**

Ceftiofur use in Beef Cattle Does Not Increase Resistance at Harvest

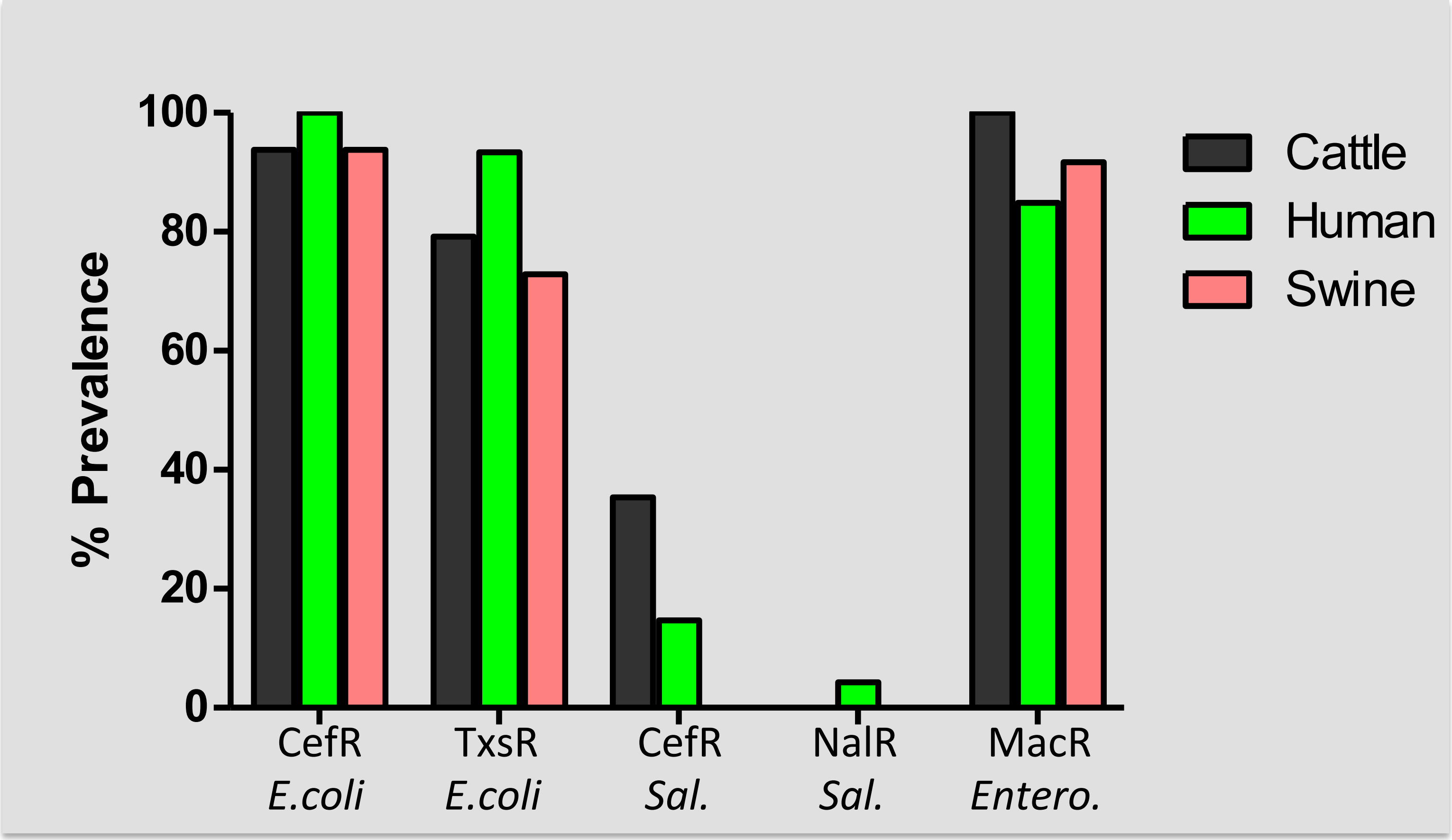


- **Fecal and hide prevalences of cephalosporin-resistant *E. coli* *do not increase* when cattle reside at a feedlot using ceftiofur.**

Antibiotic-Resistant Bacteria in Human and Animal Waste

- **Antibiotic-resistant bacteria have been identified in a variety of habitats.**
- **Lack of research examining if levels of clinically important antibiotic-resistant bacteria in animal and human wastes (some of which are applied to fields).**

Antibiotic-Resistant Bacteria in Human and Animal Waste



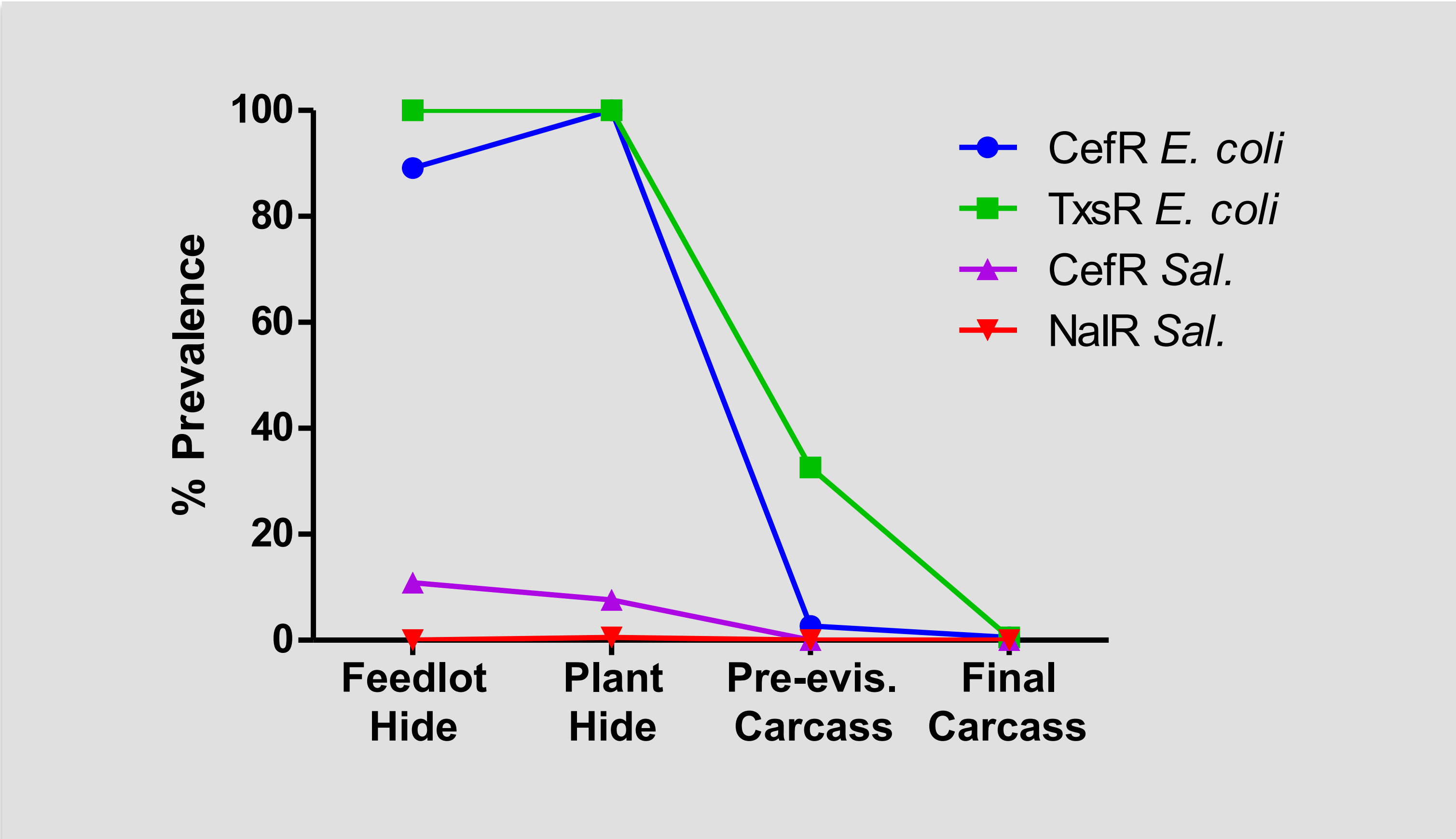
- **Antibiotic-resistant bacteria prevalences *were similar* between cattle, human, and swine sources.**

Beef Processing Interventions Remove Antibiotic-Resistant Bacteria

- **Concerns have been raised that antibiotic-resistant bacteria may persist through beef processing, potentially contemning final products and impacting human health.**




Beef Processing Interventions Remove Antibiotic-Resistant Bacteria



- **Almost all cattle leave the feedlot and begin processing with antibiotic-resistant bacteria on hides.**
- **Currently employeed processing interventions are effective sine antibiotic resistant bacteria were detected on < 1 % of final carcasses.**

Current and Future Research

- **Comparison of antibiotic-resistant bacteria and resistance genes in feces of cattle "raised without antibiotics" and "conventionally raised."**
- **Comparison of antibiotic-resistant bacteria in meat "raised without antibiotics" and "conventionally raised."**


- **Quantitative microbial risk assessment of antibiotic uses in beef cattle on public health risk.**
- **Investigation into the roles of antibiotic residues and feedlot pen soil in the persistence of antibiotic resistant bacteria in the absence of antibiotic use.**
- **Study the survival of antibiotic-resistant bacteria in manure and municipal solid waste applied to crops.**

USDA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- Dr. Dennis Burson
- Dr. Xi Li
- Dr. Dan Snow
- Dr. Bing Wang

Questions

- 35,000 acres
- 6,500 cattle
- 4,000 sheep
- 700 swine litters/year

- Genetics, Breeding, & Animal Health
- Nutrition & Environmental Management
- Meat Safety & Quality
- Reproduction

- 45 Scientists
- 12 Post-docs