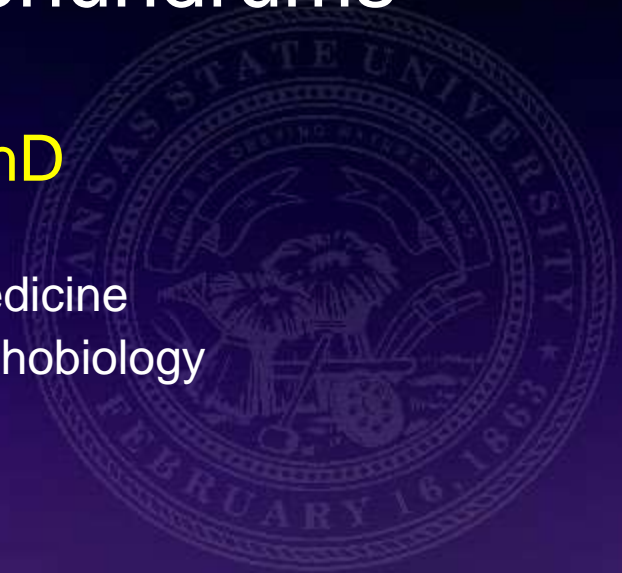


Risk management approaches to antimicrobial resistance in the U.S. and abroad

Expectations, results and conundrums

H. Morgan Scott DVM, PhD

E.J. Frick Professor of Veterinary Medicine
Department of Diagnostic Medicine / Pathobiology
Kansas State University



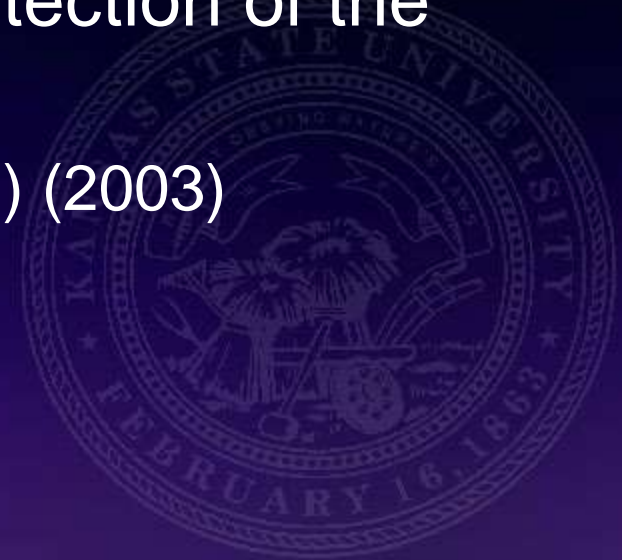
Outline

- **How surveillance is used...**
 - both to inform risk management decision-making and, ideally, to monitor any resulting changes to the bacterial populations
- **The underlying scientific principles...**
 - that should guide risk management and intervention at the animal, farm, industry and national levels
- **The conflicting pressures that are brought to bear...**
 - when attempting to conserve "*critically important*" antimicrobials for human medicine while at the same time restricting access to less important, but widely used, antimicrobial options in animal agriculture



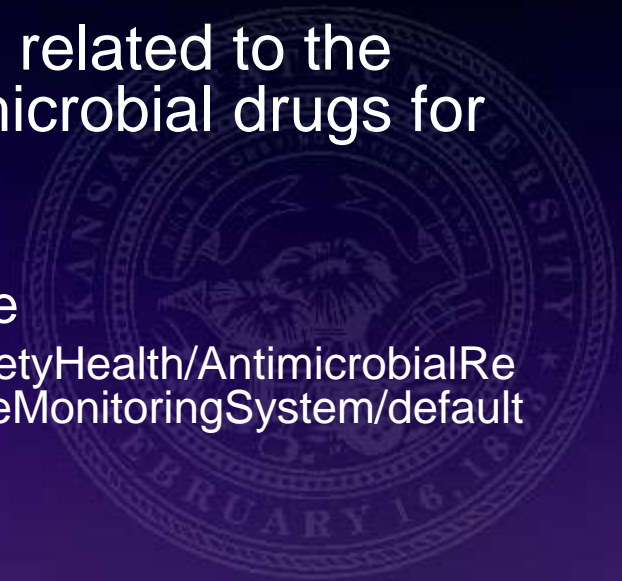
How surveillance is used: definitions

- One definition of surveillance:
 - An ongoing formal and systematic process aimed at early detection of a specific disease or agent in a population with a pre-specified action that would follow the detection of the agent or disease
 - Adapted from Salman, M.D. (ed.) (2003)

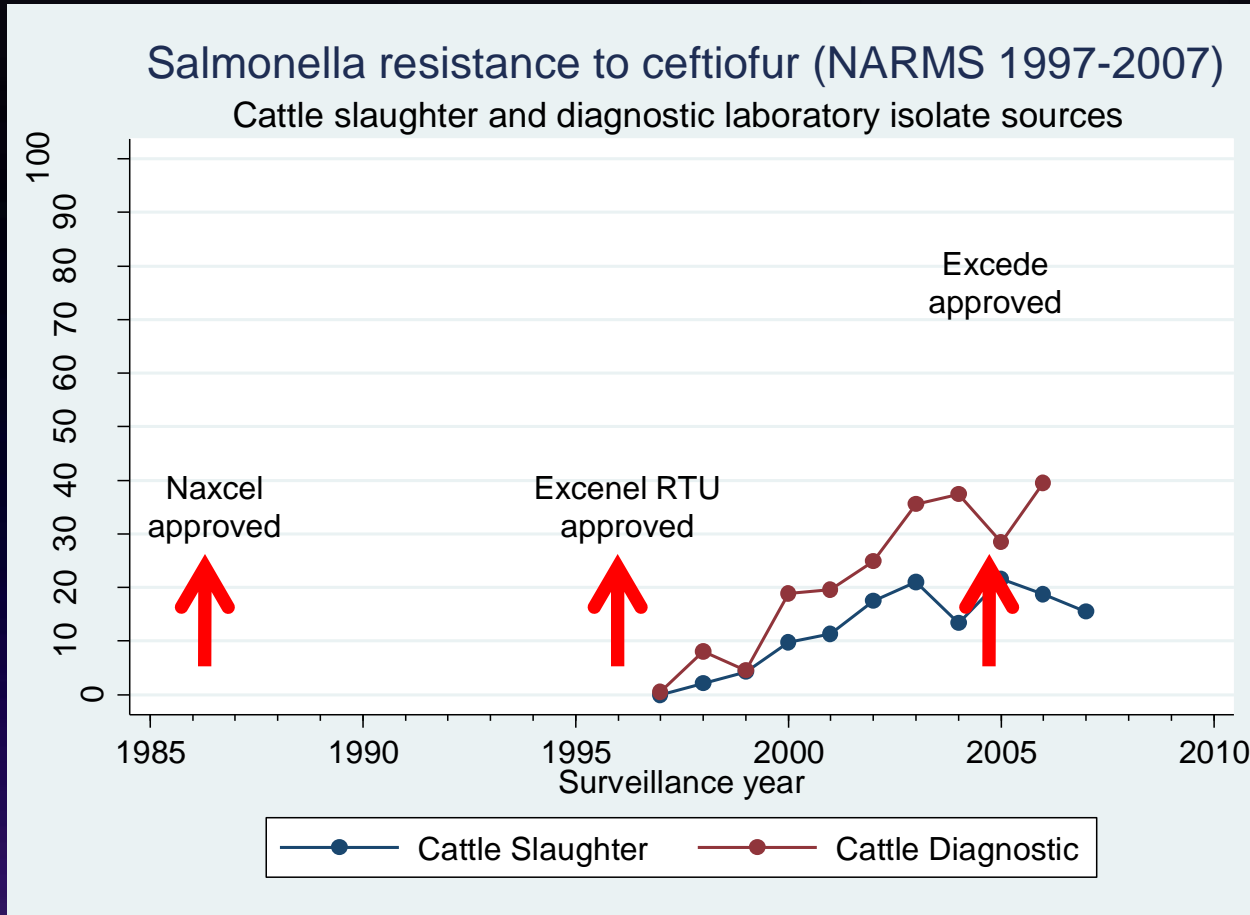


How 'monitoring' is used: definitions

- Among the primary objectives of NARMS are to:
 - Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
 - Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals
 - Adapted from the FDA NARMS website
 - <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm>



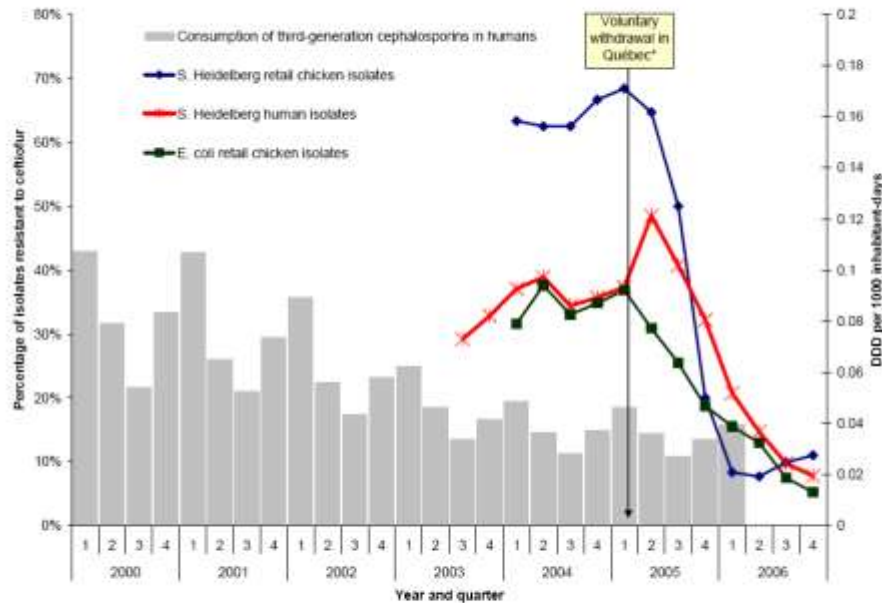
Monitoring trends in resistance: example of ceftiofur resistance



Source: USDA-NARMS

Monitoring trends in resistance: CIPARS ceftiofur resistance

Figure 1. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S. Heidelberg* isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (IMS² Health) in Québec.



¹ Extra-label involves use other than what is on the label such as use for a different species, different age class, different indication, or at a different dose/duration. This use is considered unapproved although veterinarians have the legal authority to use drugs in this manner if the situation is warranted.

² IMS=Intercontinental Medical Statistics



Assist in decision-making: example of ceftiofur resistance

- Pending (since 2008) final rule of the U.S. Food and Drug Administration (FDA) to ban extra-label use of cephalosporins in food-producing animals

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
21 CFR Part 530
[Docket No. FDA-2008-N-0326]

Display Date: 7-2-08
Publication Date: 7-3-08
Dennis A. Corbett

**New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use;
Order of Prohibition**

AGENCY: Food and Drug Administration, HHS.
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order prohibiting the extralabel use of cephalosporin antimicrobial drugs in food-producing animals. We are issuing this order based on evidence that extralabel use of these drugs in food-producing animals will likely cause an adverse event in humans and, as such, presents a risk to the public health.

DATES: This rule becomes effective [insert date 90 days after date of publication in the Federal Register]. Submit written or electronic comments on this document by [insert date 60 days after date of publication in the Federal Register].

ADDRESSES: You may submit comments, identified by [Docket No. FDA-2008-N-0326], by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions:

cv0840
FDA-2008-N-0326
NFR

FDA broiler hatchery survey

Table 1. Use of Antimicrobial Injections in 27 Hatcheries in the 30 Days Prior to Inspection: Line-Listing of Data

Record	State	Hatchery Type	Size	Egg Injections	Bird Injections	Dose (mg)
1*		Chicken	Medium	Unknown*	None	N/A
2		Chicken	Large	None	None	N/A
3		Chicken	Small	Gentamicin	None	0.2
4		Chicken	Small	None	None	N/A
5		Chicken & Turkey	Small	None	None	N/A
6		Chicken	Small	None	Ceftiofur	0.4
7		Chicken	Small	None	Ceftiofur	0.0312
8		Chicken	Very Large	Ceftiofur	None	0.1
9		Chicken	Small	None	Ceftiofur	0.2
10		Chicken	Medium	Gentamicin	None	0.2
11		Turkey	Small	None	Gentamicin	1.0
12		Chicken	Very Large	None	None	N/A
13		Chicken	Large	Gentamicin	None	0.16
14		Chicken	Medium	Ceftiofur	None	0.0625
15		Chicken	Medium	Ceftiofur	None	0.0625
16		Chicken	Small	None	Gentamicin	0.2
17		Chicken	Medium	Gentamicin	None	0.194
18		Chicken	Large	None	Gentamicin	0.2
19		Chicken	Very Large	Gentamicin	None	0.051
20		Chicken	Very Large	None	None	N/A
21		Turkey	Small	None	Gentamicin	0.16
22		Chicken	Medium	Gentamicin	None	0.16
23		Chicken	Very Large	Ceftiofur	None	0.0833
24		Chicken	Large	None	Gentamicin	0.2
25		Chicken	Large	None	Gentamicin	0.16
26		Chicken	Medium	None	None	N/A
27**		Turkey	Small	None	Ceftiofur & Gentamicin**	0.4 & 1.0

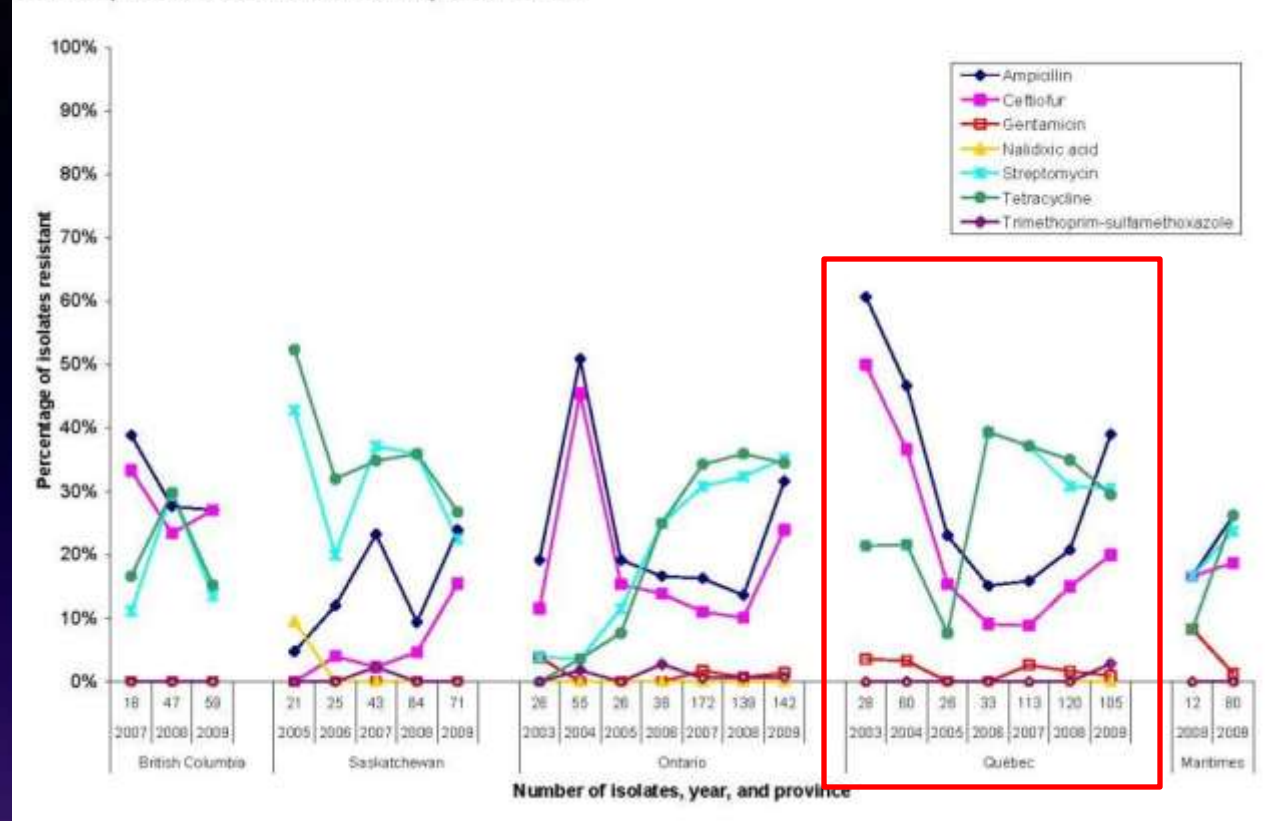
*This hatchery injected eggs with gentamicin (and Marek's vaccine), but had recently discontinued this practice. Since no records were kept, it was unclear if the hatchery used gentamicin in the 30 days prior to inspection.

**This turkey hatchery used both ceftiofur and gentamicin (not in the same poult).



CIPARS: reciprocal response to older antimicrobials (tet, str, sul)

Figure 13. Temporal variation in resistance to selected antimicrobials in *Salmonella* isolates from chicken; Retail Meat Surveillance, 2003–2009.



Source: PHAC-CIPARS

Beware the Tao of resistance; or, you can't have one without the other

A lot of a little



Susceptible

Resistant

A little of a lot



Underlying scientific principles...

- Risk management and interventions in the aggregate:
 - Animal
 - Farm
 - Industry
 - National
 - International

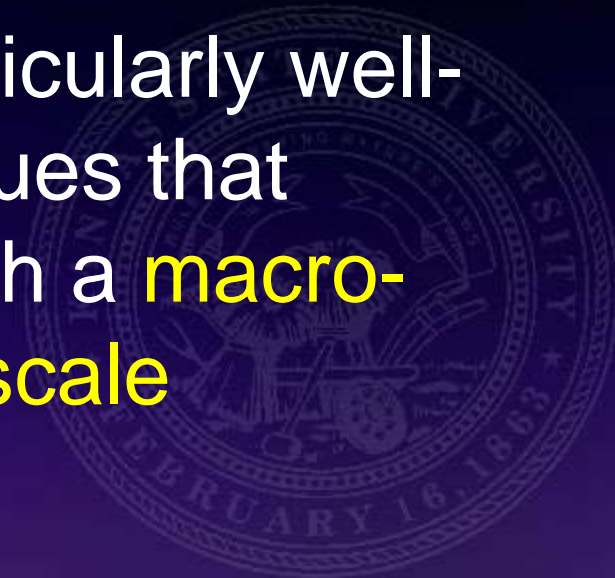


Risk analysis: the NRC paradigm



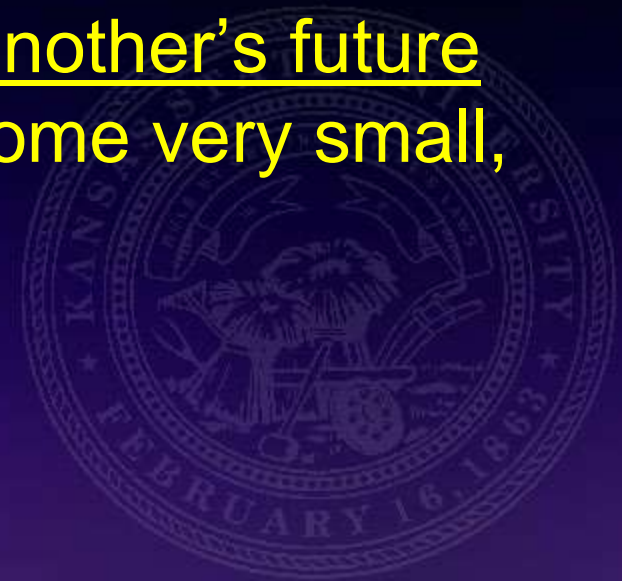
Quantitative risk assessment and antimicrobial resistance

- **Risk assessments** are well-suited to releases of toxic substances (NRC), and microbial safety in certain contexts (e.g., animal and food importation risk: OIE)
- My opinion: they are not particularly well-suited to microbial safety issues that develop and progress on both a **macro-ecological and evolutionary scale**



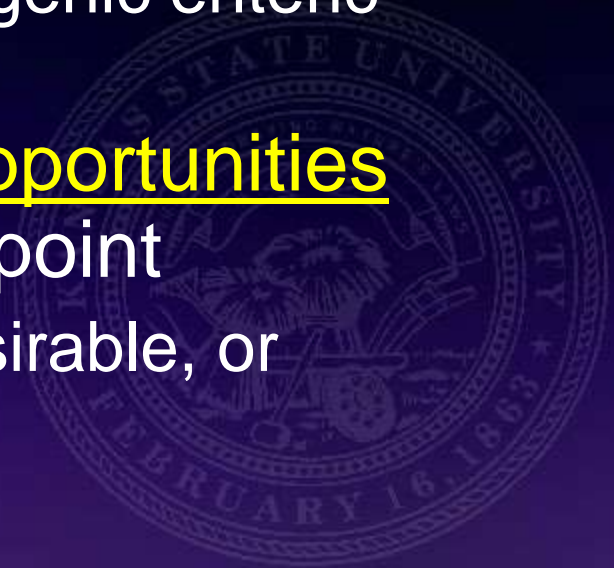
Not a simple risk management problem

- Bacterial resistance is a uniquely non-linear process with biological, economic, and social/philosophical consequences:
 - One person's use of an antibiotic may diminish the effectiveness of another's future use of the same antibiotic in some very small, yet incremental way

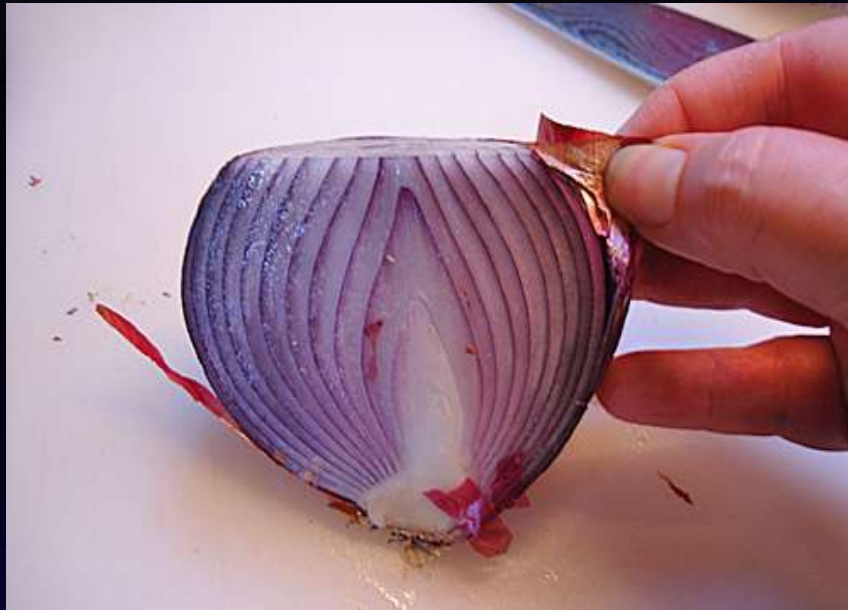


Unintended consequences...

- Concern in **human medicine** 'generally' focuses on 'target' pathogens
- Concern in **animal agriculture** 'generally' focuses on 'non-targeted' bacteria
 - Typically, commensal and pathogenic enteric bacteria
- This offers both barriers and opportunities from a risk management standpoint
 - Effect on gut bacteria can be desirable, or problematic



Peeling back the layers of the onion...



- I call the first layer: **“Irony”** ...
- No measurable effect of low dose CTC on gut, but likely the desired effect
- Measurable effect of CTC at 22 mg/kg on gut but not the desired effect
- I call the second layer: **“Opportunity”** ...

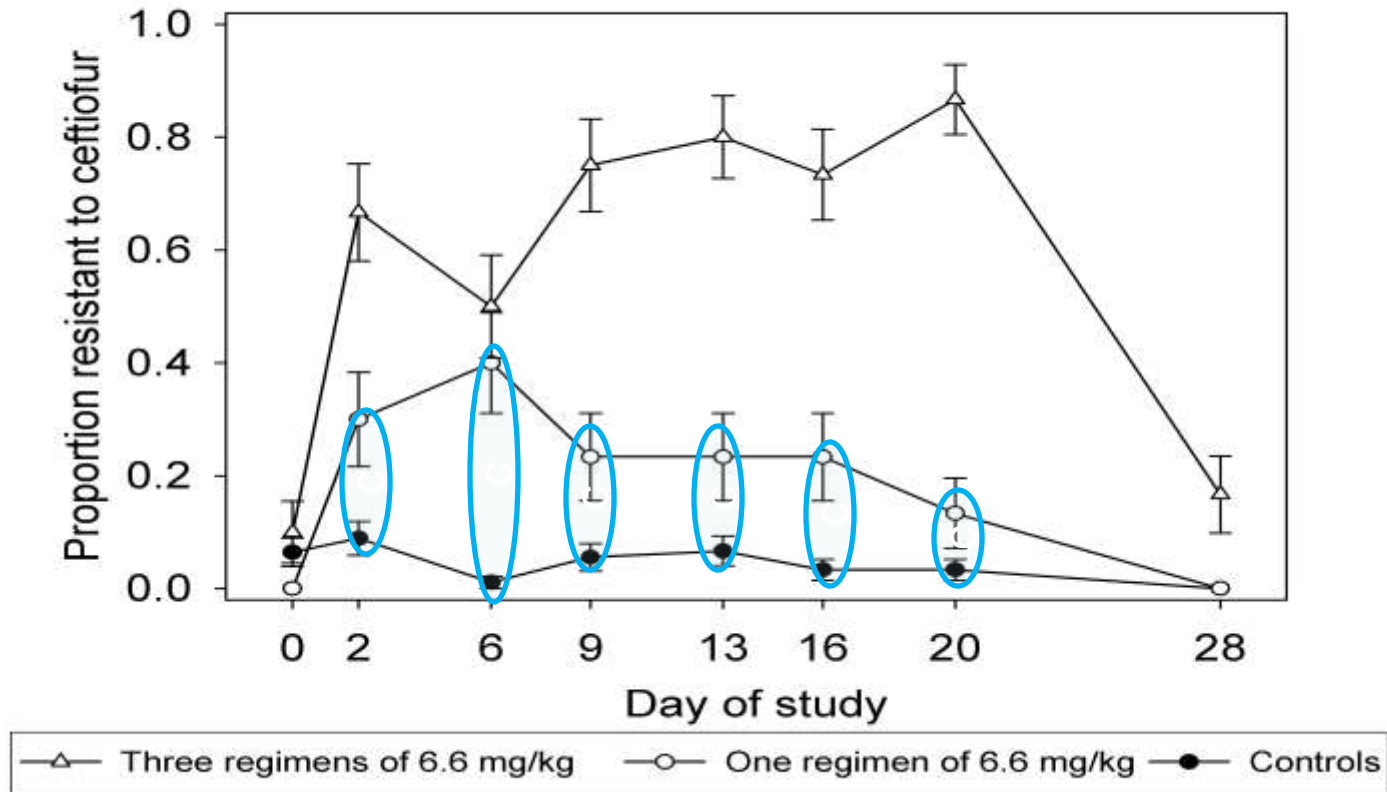
Two deceptively '*simple*' risk management questions: Q1

- If we start using an antibiotic (or, use more of it), will resistance to that antibiotic appear; or else, increase from current levels?
- Answer: it depends...



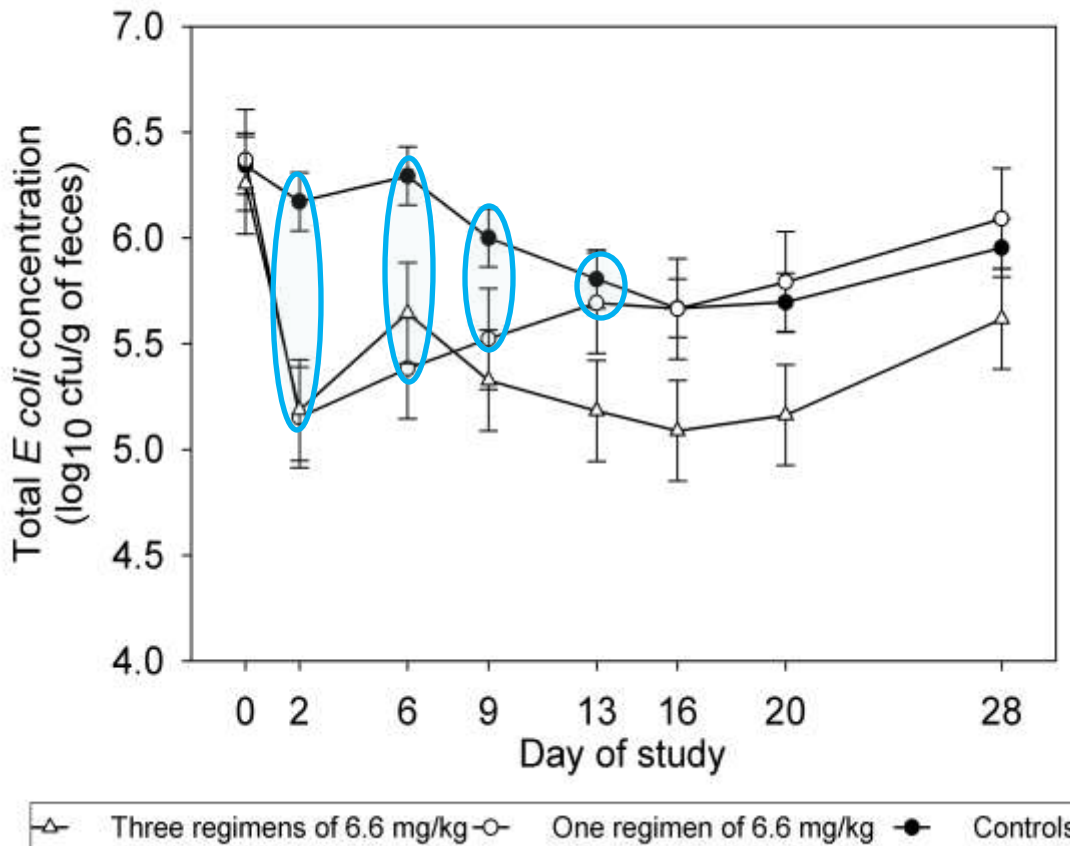
Antibiotic resistance: apparent short term effects

Adapted from Lowrance et al., 2007



Antibiotic resistance: actual short term effects

Adapted from Lowrance et al., 2007



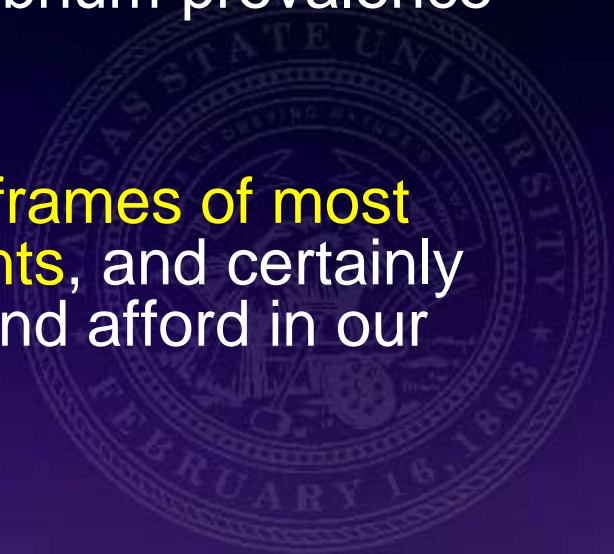
So why does this matter?

- Available evidence supports theories suggesting that the use of antimicrobials in animal agriculture leads to the favorable selection of resistant strains of bacteria within treated animals and within aggregated groups of treated animals
- However, the measurable effect applies largely to periods while animals are being treated, and for a short time thereafter

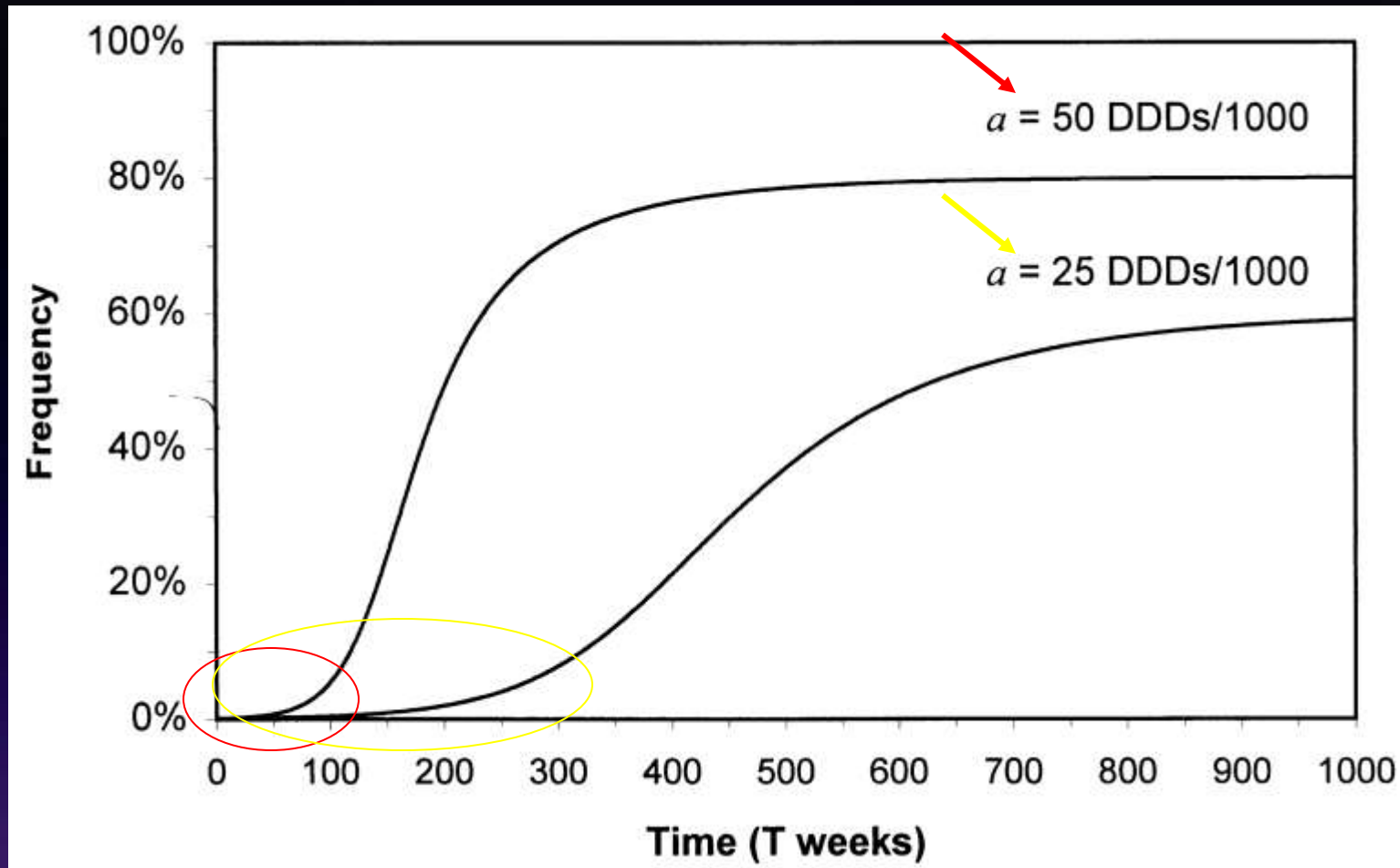


Long-term effects

- Longer-term effects* reflect the **cumulative impacts of multiple uses in many animals and farms** over extended periods of time
 - *Longer-term effects such as shown in NARMS data
- These likely lead to **major shifts in bacterial population** features that gradually 'reset' the equilibrium prevalence of competing strains
- These are **not well studied in the time frames of most empirical research and risk assessments**, and certainly not on a scale we can easily operate and afford in our funding cycles



Long-term models of expansion of community-based bacterial resistance



Austin, D. J. et al. (1999) Proc. Natl. Acad. Sci. USA 96, 1152-1156

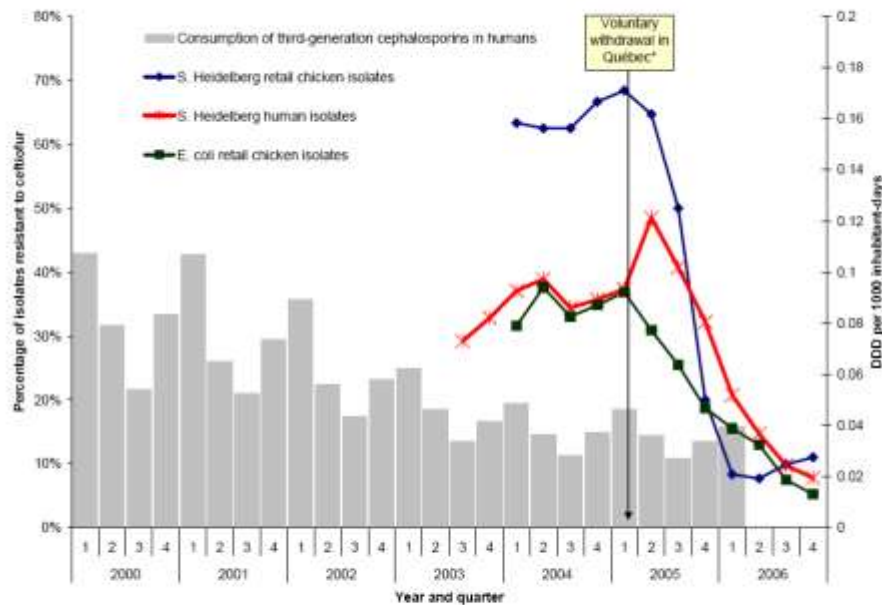
Two deceptively '*simple*' risk management questions: Q2

- If we stop using an antibiotic (or, use less of it), will resistance to that antibiotic disappear; or else, decrease from current levels?
- Answer: it depends...



Voluntary withdrawal of ceftiofur *in ovo* injections in broiler hatcheries

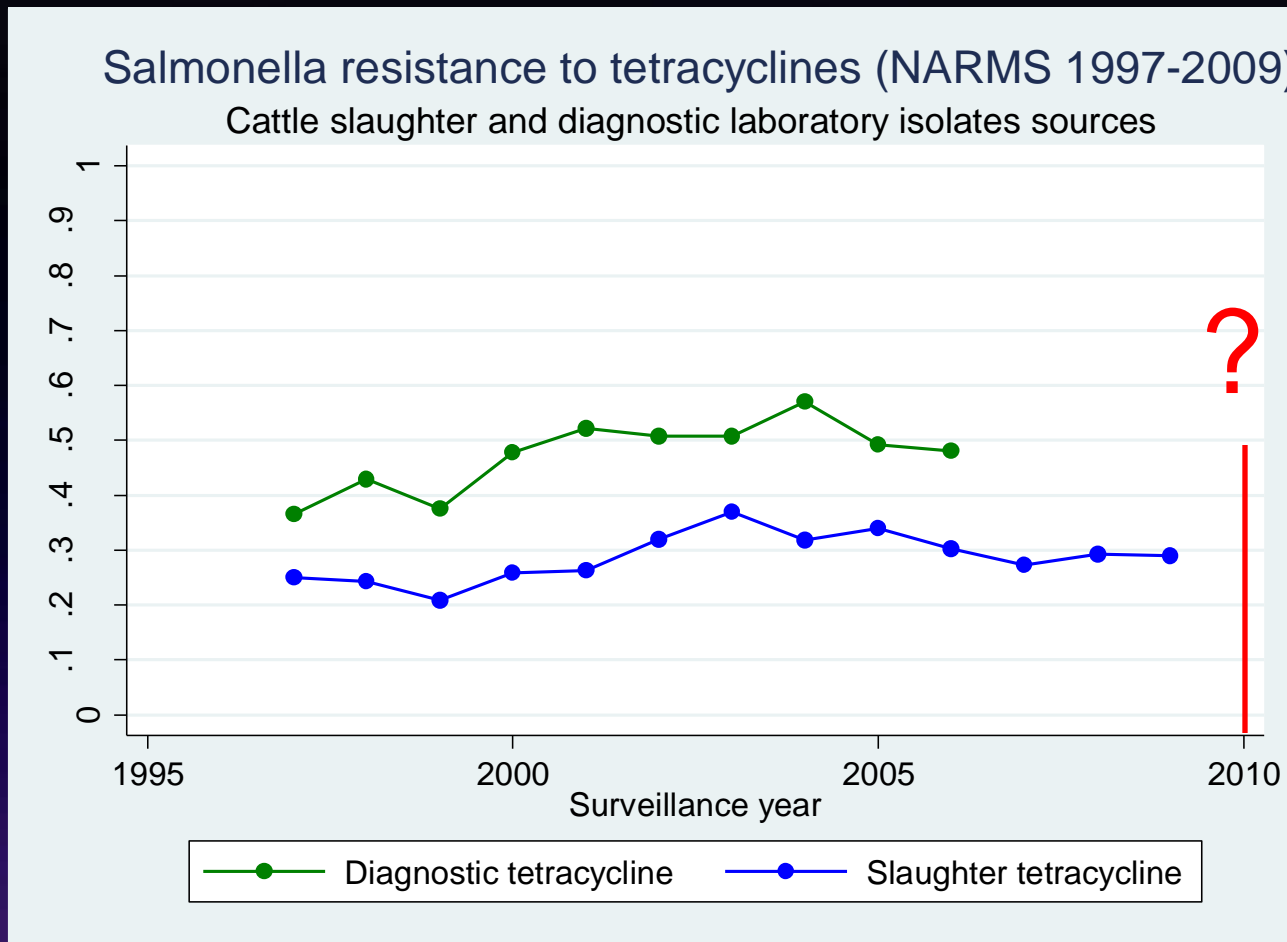
Figure 1. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S. Heidelberg* isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (IMS² Health) in Québec.



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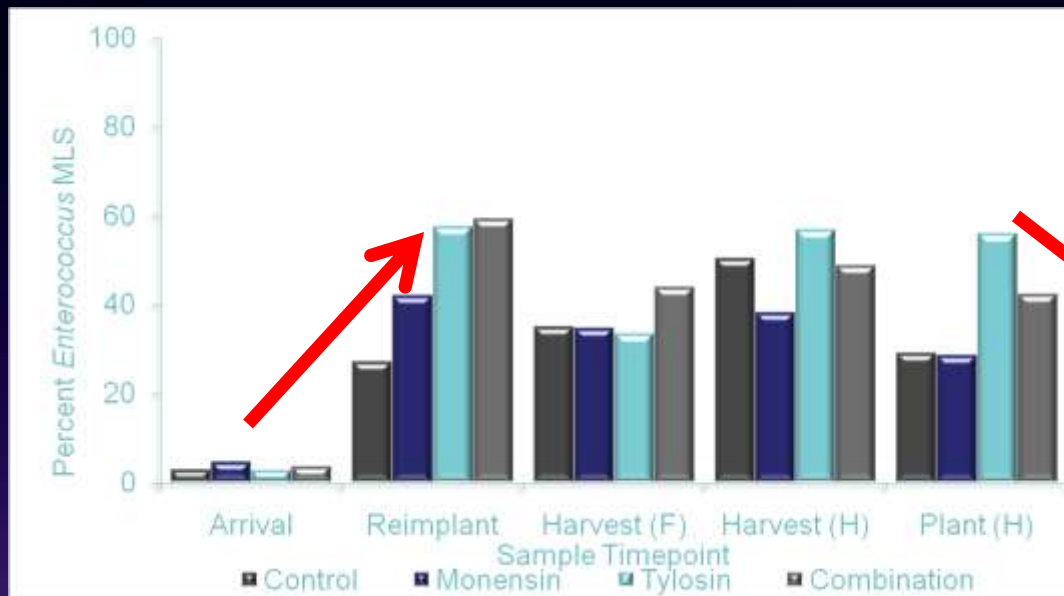
² IMS=Intercontinental Medical Statistics

Likely effect of cessation of tetracycline use?

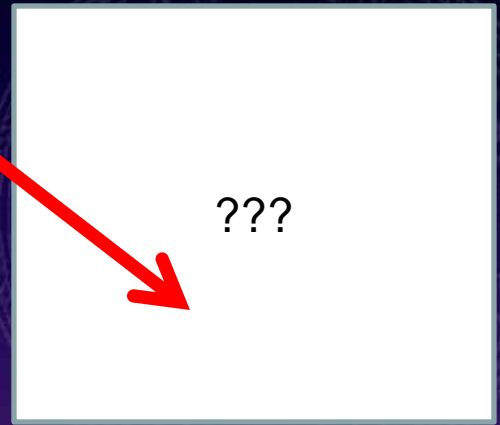


Possibility for 'environmental' interventions

- Are the drivers of these long-term changes reversible?



?



Slide courtesy Dr. Guy Loneragan

Impact of cessation of antimicrobial use on human health endpoints?

- The critical question
 - Quebec broilers and human cases of Salmonella Heidelberg is likely to be the exception, rather than the rule
 - “Waterfall effects” are rare...



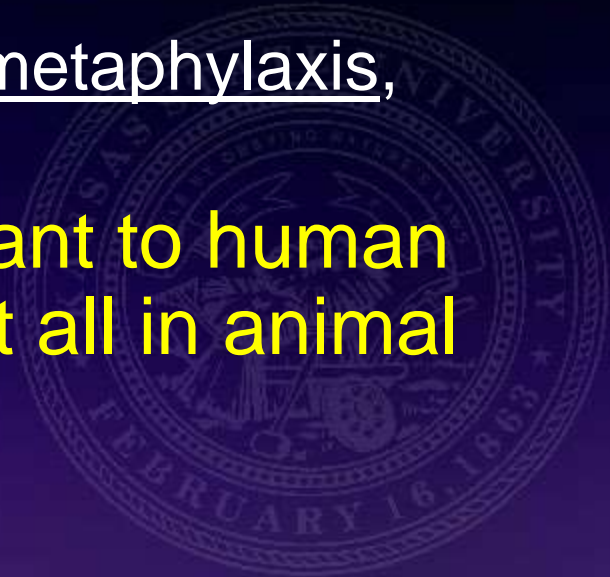
Conflicting pressures brought to bear: shared perspectives

- Antibiotics are essential for enhancing the health and well-being of humans and animals
- There is recognition of overuse/misuse of antibiotics in both human and animal settings
- Protecting the efficacy of antibiotics for future generations is considered a desirable objective



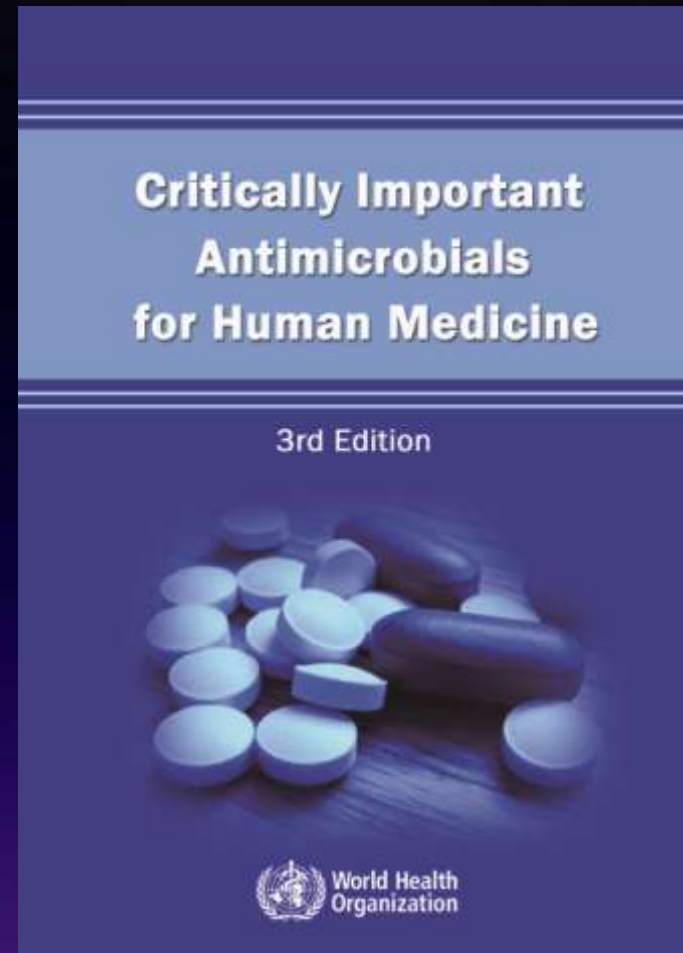
Conflicting pressures brought to bear: risk averse perspective

- Human medicine takes precedence over veterinary medicine and animal agriculture; therefore, the precautionary principle suggests that all but the most urgent uses in animals should be curtailed in this order:
 - Growth promotion, prophylaxis, metaphylaxis, therapy
- Drugs deemed critically important to human medicine should not be used at all in animal agriculture



Critically Important Antimicrobials: the 'other' CIA

- World Health Organization (WHO) list of “Critically Important Antimicrobials” for use in human medicine
- A work in progress
 - Can be very reactive to changing conditions
 - NDM-1 has brought colistin / polymixin B to foreground



The First NDM-Positive *Salmonella* spp. Identified in the United States

Patrice Savard^{1,2*}, Ramya Gopinath^{3*}, Wenming Zhu⁴, Brandon Kitchel⁴, J. Kamile Rasheed⁴,
Tsigereda Tekle⁵, Ava Roberts⁵, Tracy Ross⁵, Jafar Razeq⁶, B. Mark Landrum³, Lucy E.
Wilson⁷, Brandi Limbago⁴, Trish M. Perl^{1,2} and Karen C. Carroll⁵

Antimicrobial/ Isolate	<i>Klebsiella pneumoniae</i>	<i>Salmonella</i> Senftenberg
Amikacin	>32	>32
Ampicillin	>16	>16
Ampicillin-sulbactam	>16/8	>16/8
Aztreonam	>16	>16
Cefazolin	>16	>16
Cefepime	>16	>16
Cefoxitin	>16	>16
Ceftriaxone	>32	>32
Ciprofloxacin	>2	>2
Colistin	0.12*	-
Ertapenem	>8	>8
Gentamicin	>8	>8
Imipenem	>8	>8
Meropenem	>8	2
Moxifloxacin	>4	>4
Pip/tazobactam	>64/4	>64/4
Tetracycline	8	4
Ticarcillin/ clav	>64/8	>64/2
Tigecycline	>8	2
Tobramycin	>8	>8
TMP-SMX	>2/38	<0.5/9.5



Top 3 CIA: U.S. examples of human versus food animal molecules

- **Fluoroquinolones**
 - (ciprofloxacin versus enrofloxacin)
- **3rd generation cephalosporins**
 - (ceftriaxone versus ceftiofur)
 - Ceftiofur formulated to extend half-life
- **Macrolides**
 - (erythromycin versus tylosin)
 - Only feedgrade class of CIA in U.S.



The Independent: June 17, 2011

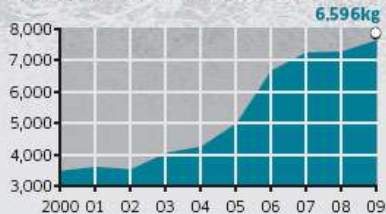
HOW ANTIBIOTIC USE HAS SOARED ON BRITISH FARMS

Use of cephalosporins and fluoroquinolones in UK veterinary medicine, 2000-2009



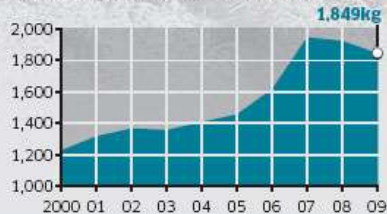
ALL CEPHALOSPORINS

KGS ACTIVE INGREDIENT IN VETERINARY MEDICINE



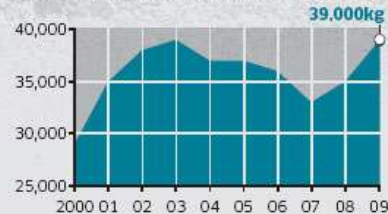
FLUOROQUINOLONES

KGS ACTIVE INGREDIENT IN VETERINARY MEDICINE

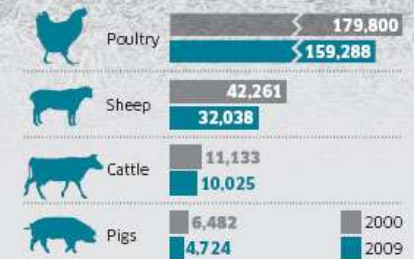


MACROLIDES

KGS ACTIVE INGREDIENT IN VETERINARY MEDICINE

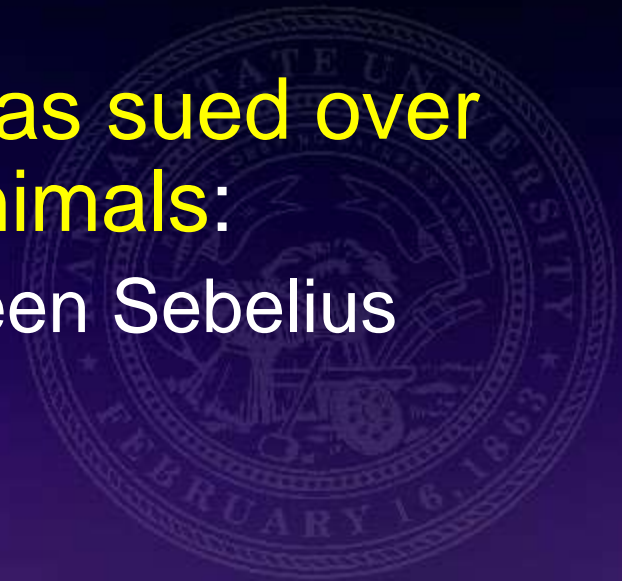


LIVESTOCK NUMBERS



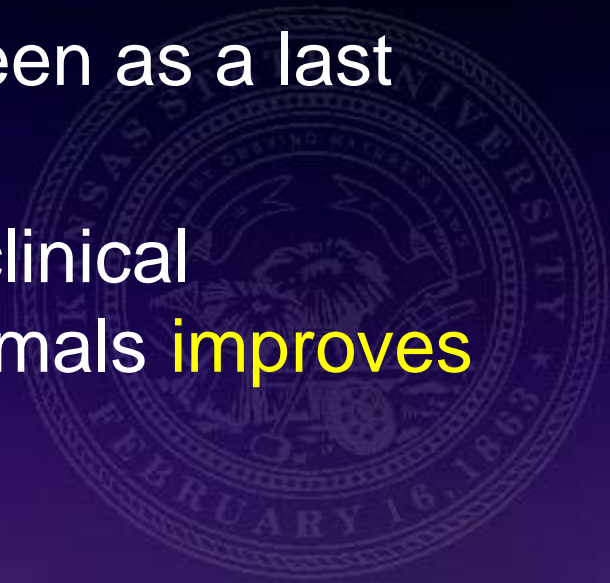
Restricting antibiotic use: antibiotic class versus use

- On March 17, 2009, Rep. Louise Slaughter introduced HR 1549, The **Preservation of Antibiotics for Medical Treatment Act (PAMTA)** in the House of Representatives
- On May 25, 2011 the **FDA was sued over antibiotics allowed in farm animals:**
 - Margaret Hamburg and Kathleen Sebelius named as co-defendants



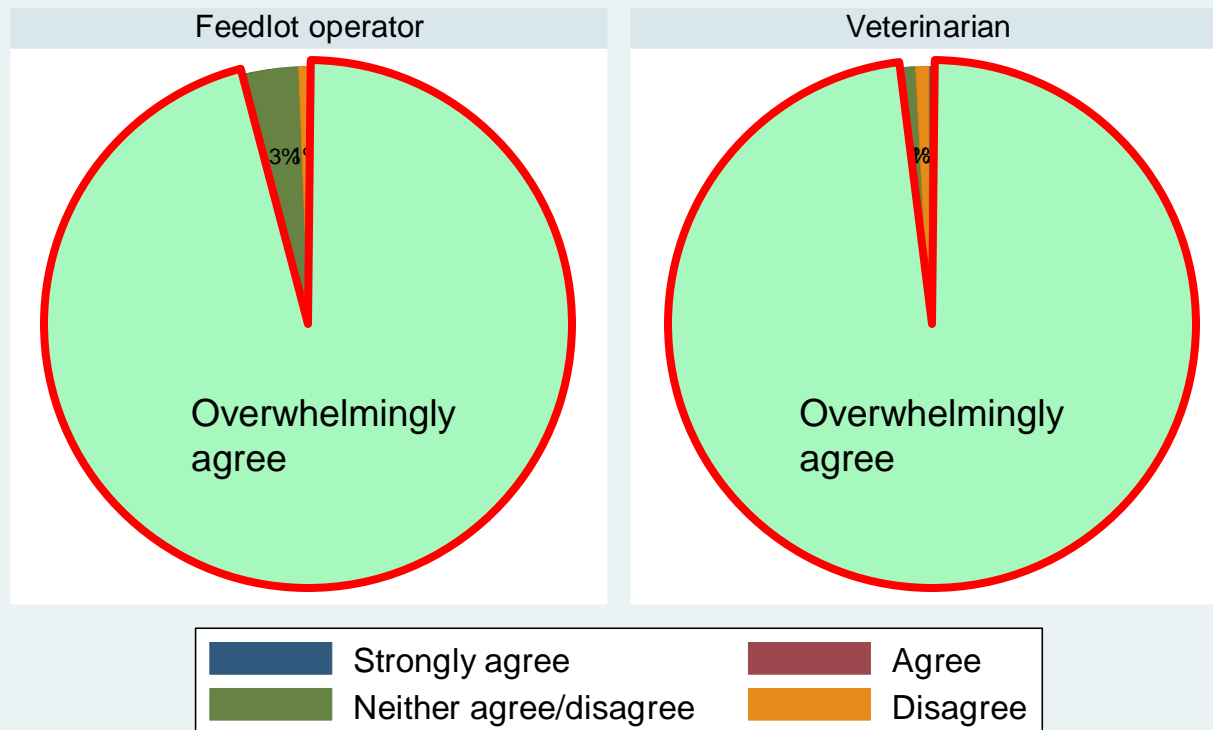
Overview of the issues: risk tolerant perspective

- Providing safe, nutritious food products at a reasonable price is **also a moral imperative**; to do this sometimes requires the judicious use of antibiotics
 - Antibiotic therapy should be seen as a last resort
 - **Prevention** of clinical and subclinical infectious diseases in food animals **improves both animal and human health**



I have a moral duty to treat acutely ill cattle

Level of respondent agreement with the statement:
I have a moral duty to treat acutely ill feeder cattle with antimicrobials

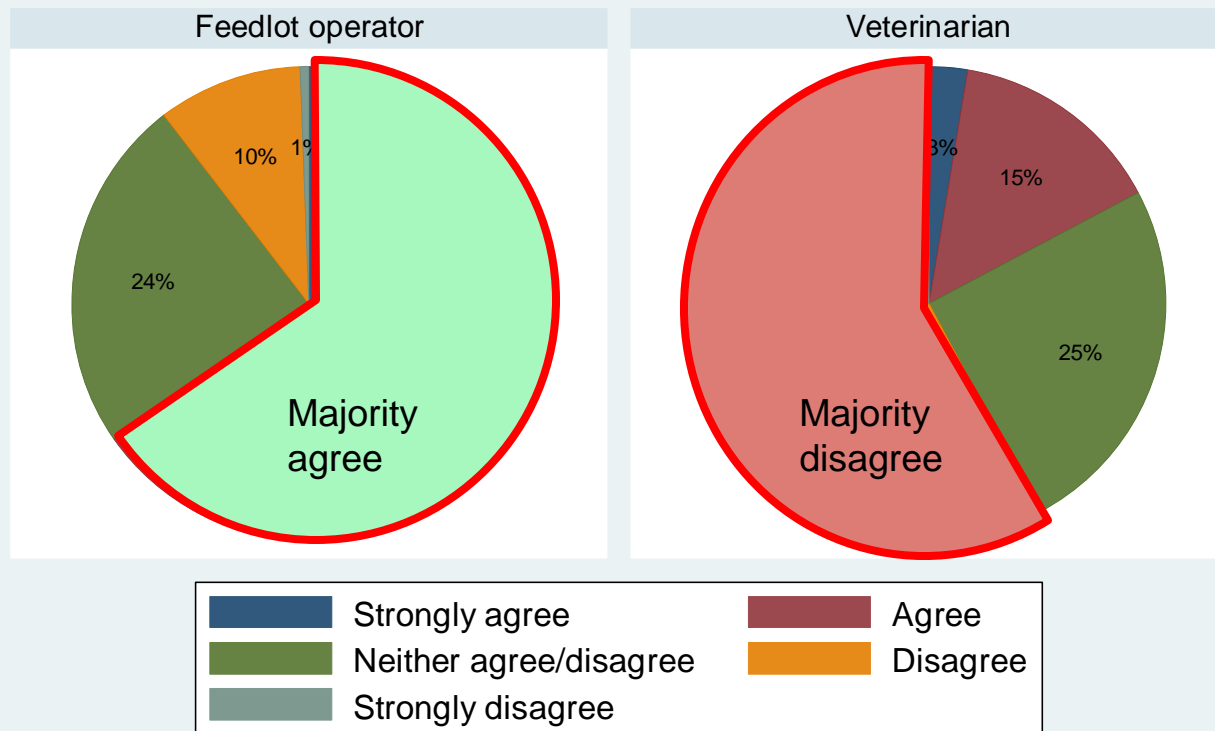


Graphs by respondent type

Responses do not differ at $P = 0.413$

I have a moral duty to use subtherapeutic antimicrobials

Level of respondent agreement with the statement:
I have a moral duty to use subtherapeutic antimicrobials in 'at-risk' feeder cattle



Graphs by respondent type

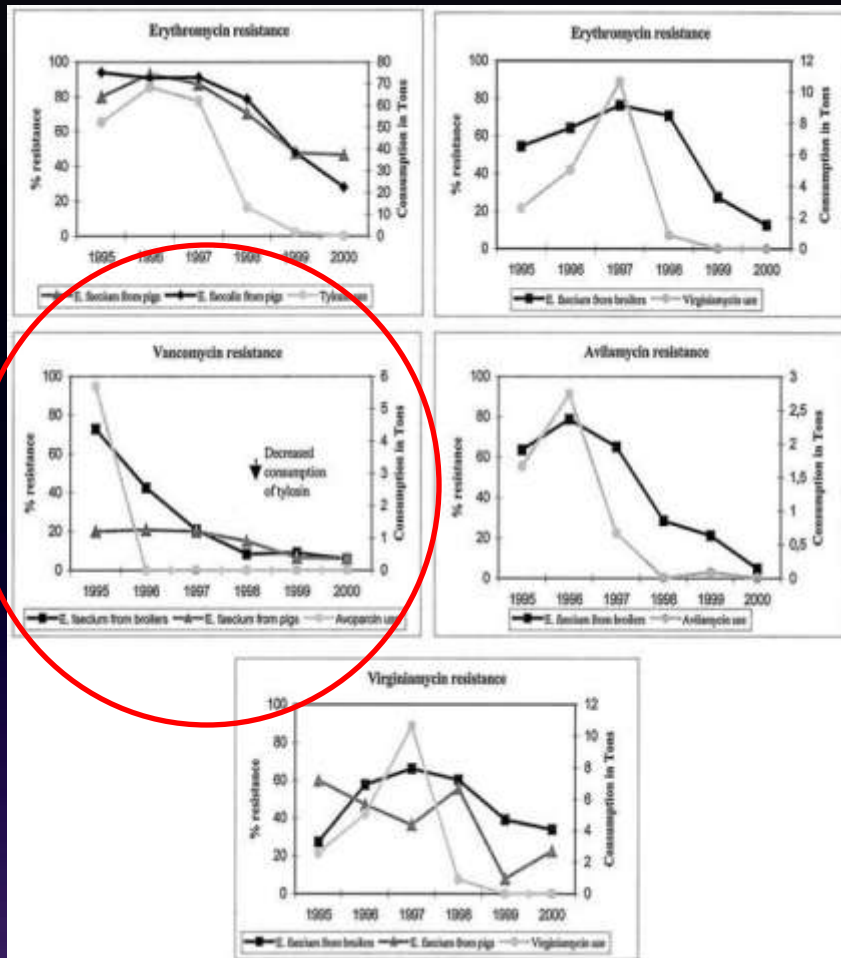
Responses differ at $P < 0.0001$

Risk management in Europe: EU ban on AGPs

- European Union (EU) ban on the use of antibiotics as growth promoters since 2006
 - Followed earlier actions by Sweden (1986) and Denmark (1996)



VRE: Danish and Swedish experiences



Journal of Antimicrobial Chemotherapy (2009) 63, 868–872
doi:10.1093/jac/dkp045
Advance Access publication 24 February 2009

JAC

Spread without known selective pressure of a vancomycin-resistant clone of *Enterococcus faecium* among broilers

O. Nilsson¹*, C. Greko¹, J. Top², A. Franklin¹ and B. Bengtsson¹

¹National Veterinary Institute, Uppsala, Sweden; ²University Medical Center, Utrecht, The Netherlands

Received 14 November 2008; returned 12 December 2008; revised 29 January 2009; accepted 30 January 2009

Objective: The aim of this paper was to describe an increased occurrence of vancomycin-resistant enterococci (VRE) in Swedish broilers since 2000 and to investigate the genetic relatedness of isolates.

Methods: Caecal content from slaughtered broilers was cultured for VRE on medium supplemented with vancomycin (16 mg/L). Species identification, antibiotic susceptibility determination, vancomycin resistance genotyping, multilocus sequence typing (MLST) and characterization of Tn1546 were performed.

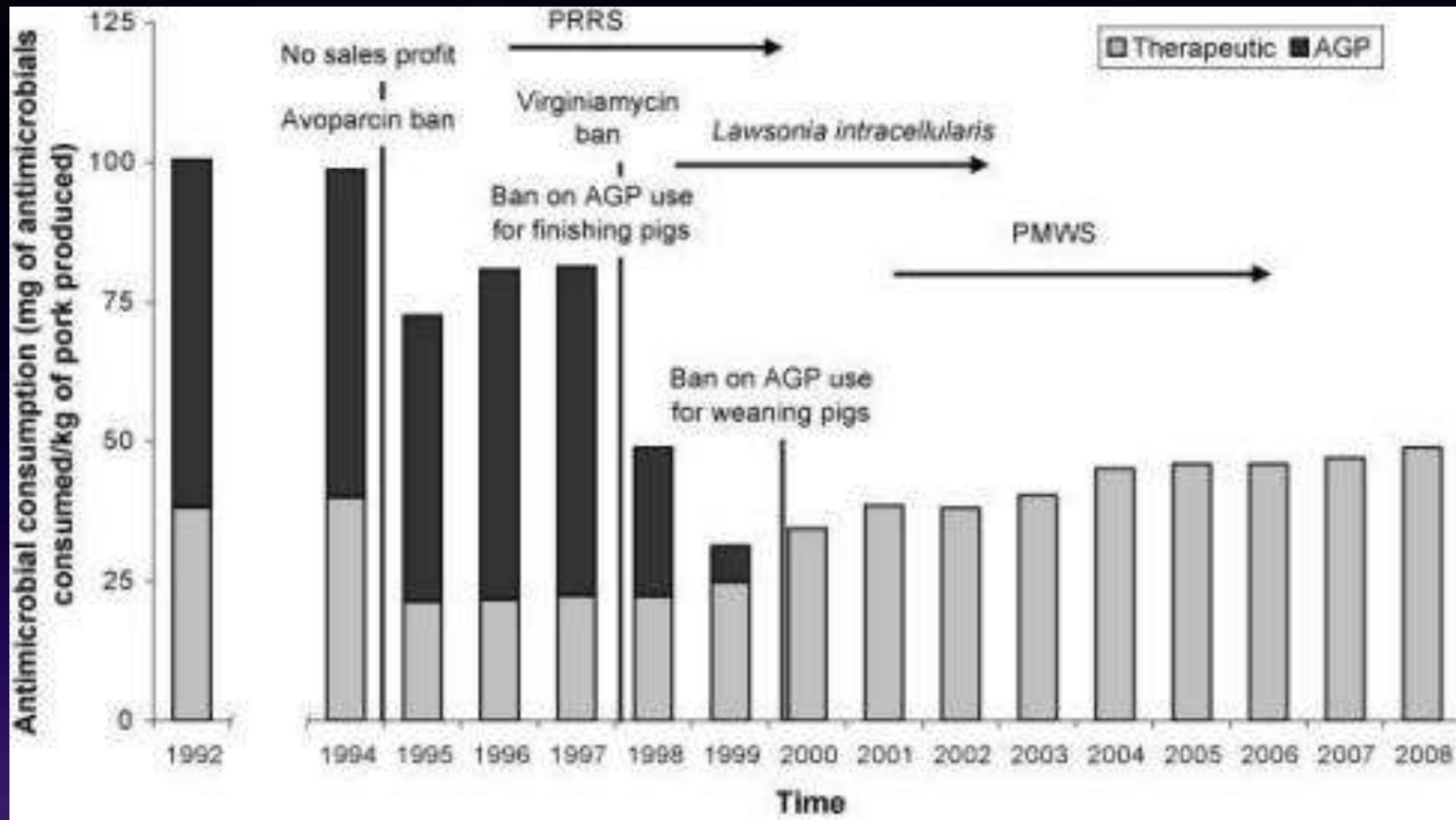
Results: The proportion of VRE-positive samples increased gradually from <1% in 2000 to slightly over 40% in 2005. Between 2005 and 2006, the proportion of VRE-positive samples decreased and between 2006 and 2007, it was stable at just below 30%. All isolates tested were *Enterococcus faecium* and carried the *vanA* gene. A majority of the isolates had similar antibiograms, the same MLST sequence type and Tn1546 transposon.

Conclusions: The proportion of VRE-positive samples from broilers has increased since 2000, and this is due to the spread of one major clone. Moreover, this has taken place in an environment without any obvious selective pressure.

Keywords: epidemiology, MLST, *vanA*

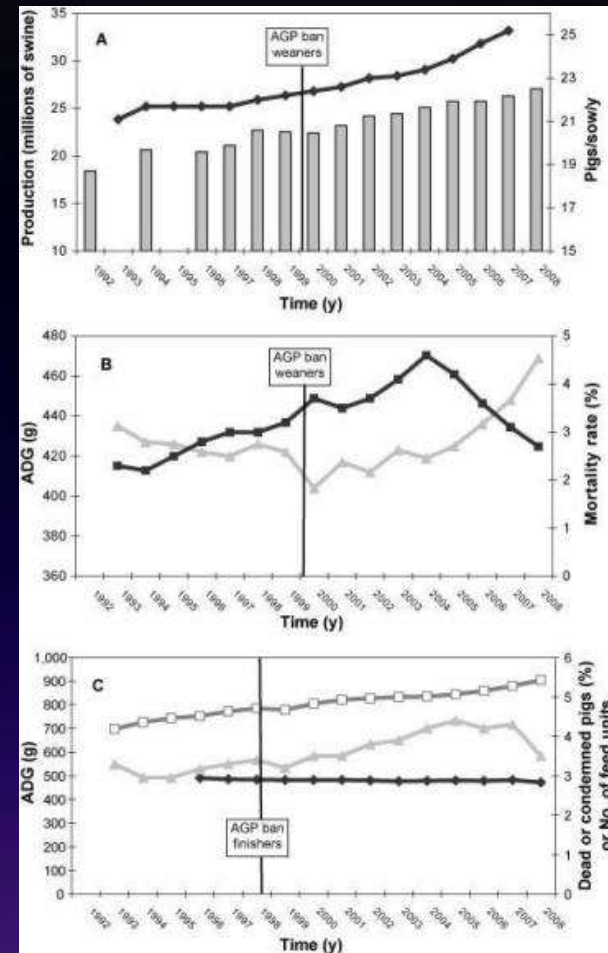
Nilsson et al 2009

The Danish experience: Aarestrup et al AJVR 2009



The Danish experience: Aarestrup et al AJVR 2009

- Before/after
 - Number of swine, pigs per sow
 - ADG and mortality rate
 - ADG, feed units and condemnations



“Rule by obeying Nature’s laws”

