Physicians, Farmers, and the Politics of Antibiotic Resistance: A One Health Analysis

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The One Health Concept

- One Health: a concept that recognizes the links between human, animal, and environmental health.
- Because they are linked, issues such as antibiotic resistance must be analyzed using a holistic One Health approach.
- The One Health Initiative: http://www.onehealthinitiative.com

A One Health Analysis

- United Kingdom
- Sweden
- Denmark
- European Union
- United States

- History of Ban of Low Dose Antibiotics
- Antibiotic Use
- Antimicrobial Resistance (AMR)
- Livestock Production
- Healthcare Costs
- Global AMR
- Environmental AMR
- Antibiotic R & D Issues

Disclaimer: I do not represent any of these country's governments!
All analyses and conclusions from government data are my own work.

Inherent Costs With Agriculture

Disease	Animal
Measles	Cattle
Influenza	Wild Waterfowl
Q fever	Sheep, Goats
Nipah virus	Fruit bats to Pigs
BSE (Prion)	Cattle
Camplylobacter	Poultry
E. Coli 0157:H7	Cattle

Eating wild animals presents its own risks—SARS, Ebola, HIV, etc.

Evolution of Medicine and Agriculture in the 20th century

Medicine

- Increasingly specialized
- Technology driven
- Dependent on antibiotics
- Price of medical care increased

Agriculture

- Increasingly specialized
- Technology driven
- Dependent on antibiotics
- Price of food decreased

Uses of Antibiotics

- Livestock
  - Growth
  - Prevention
  - Treatment
- Humans
  - Prevention
  - Treatment

All uses lead to antibiotic resistance

Defining Terms

- Low dose
- Sub-therapeutic
- Non-therapeutic
- Growth promoting

All mean essentially the same thing.

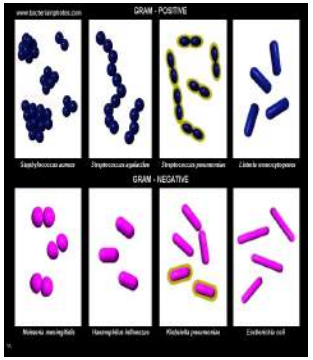
- Typically mean levels as low as 1-2 parts per million in feed.
- Higher doses, up to 100 parts per million or higher used to treat sick animals.

Resistant *Salmonella typhimurium* and *Enterococcus faecium* drove policy

Zoonotic Bacteria

- Cause illness in both livestock and people. Major cause of food-borne illness.
- *Salmonella* enterica (subspecies: Salmonella typhimurium)
- *Campylobacter species.*

Gram negative: Stain pink
S. Typhimurium
Campylobacter
E. coli



Indicator Bacteria

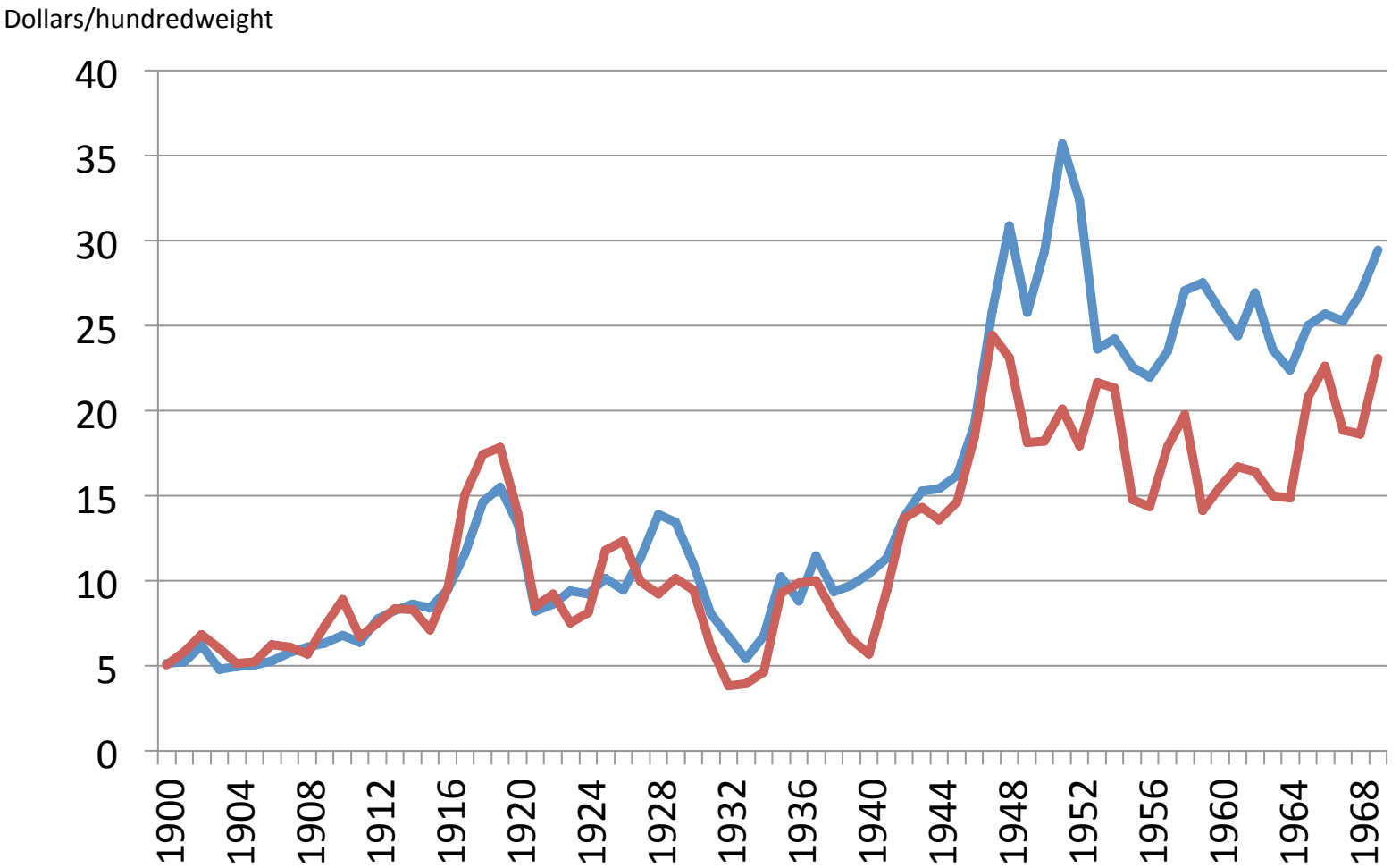
- Part of normal intestinal microbiome in both animals and people. Can cause life-threatening illnesses.
- *Escherichia coli* (*E. coli*)
- *Enterococcus* (*Enterococcus faecium* and *Enterococcus faecalis*)

Gram positive: Stain blue
Enterococcus

One Health Analysis Conclusions on Vancomycin Resistant Enterococcus (VRE)

- VRE in hospitalized humans is genetically distinct from VRE in livestock.
- Growth promoter ban had no effect on VRE rates in hospitalized humans, but possibly decreased pig meat yield in E.U.
- VRE rates in hospitalized humans strongly correlated with vancomycin use in humans.
- American used much more vancomycin in hospitals than Europeans.
- Genomic data revealed a surprising culprit.

Why were antibiotics used as growth promoting agents?
Price of Beef and Pork in U.S., 1900-1969



Before WWII, U.S. relied on fishmeal and cod liver oil to supplement feed.

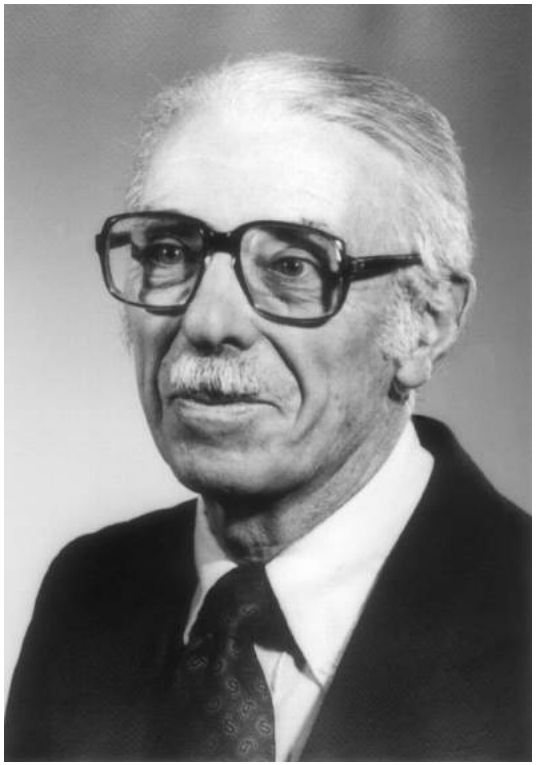
Olmstead, Alan L. and Paul W. Rhode , "Beef, veal, pork, and lamb – slaughtering, production, and price: 1899–1999." Table Da995-1019 in *Historical Statistics of the United States, Earliest Times to the Present: Millennial Edition,* edited by Susan B. Carter, Scott Sigmund Gartner, Michael R. Haines, Alan L. Olmstead, Richard Sutch, and Gavin Wright. New York: Cambridge University Press, 2006. http://dx.doi.org/10.1017/ISB

Accidental Discovery of Antibiotics as Growth Promoting Agents in 1940's

Work at Lederle Labs, Division of American Cyanamid Company

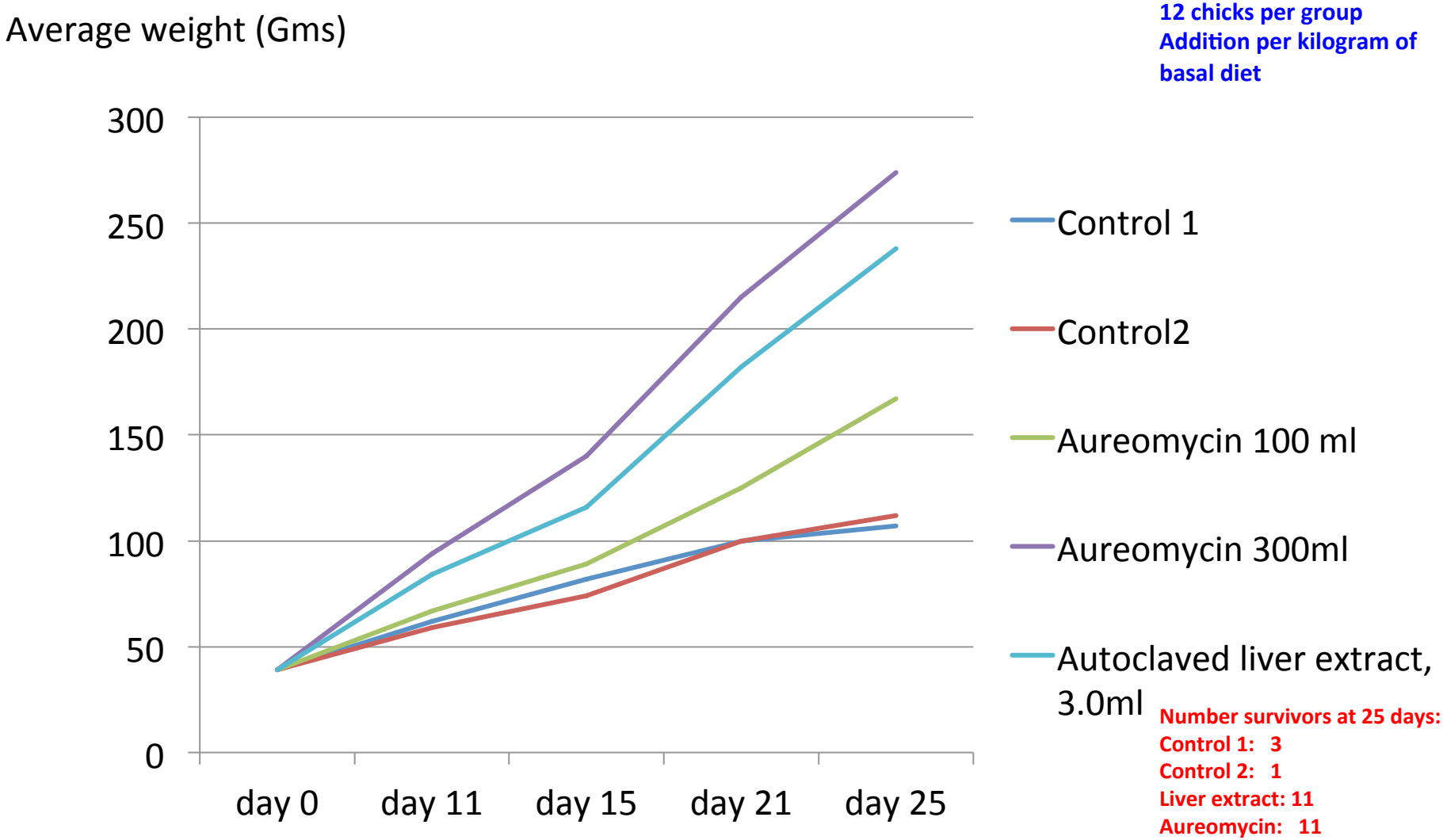
- Fed vitamin B12 to chicks and piglets
- Growth rates increased
- Residues from chlortetracycline
- Increased efficiency in agriculture.
- Adopted in many countries

Thomas H. Jukes, PhD (1906-1999)
Biochemist and nutritionist



Effect of Aureomycin (chlortetracycline) on Chick Growth

5 groups of chicks
12 chicks per group
Addition per kilogram of basal diet



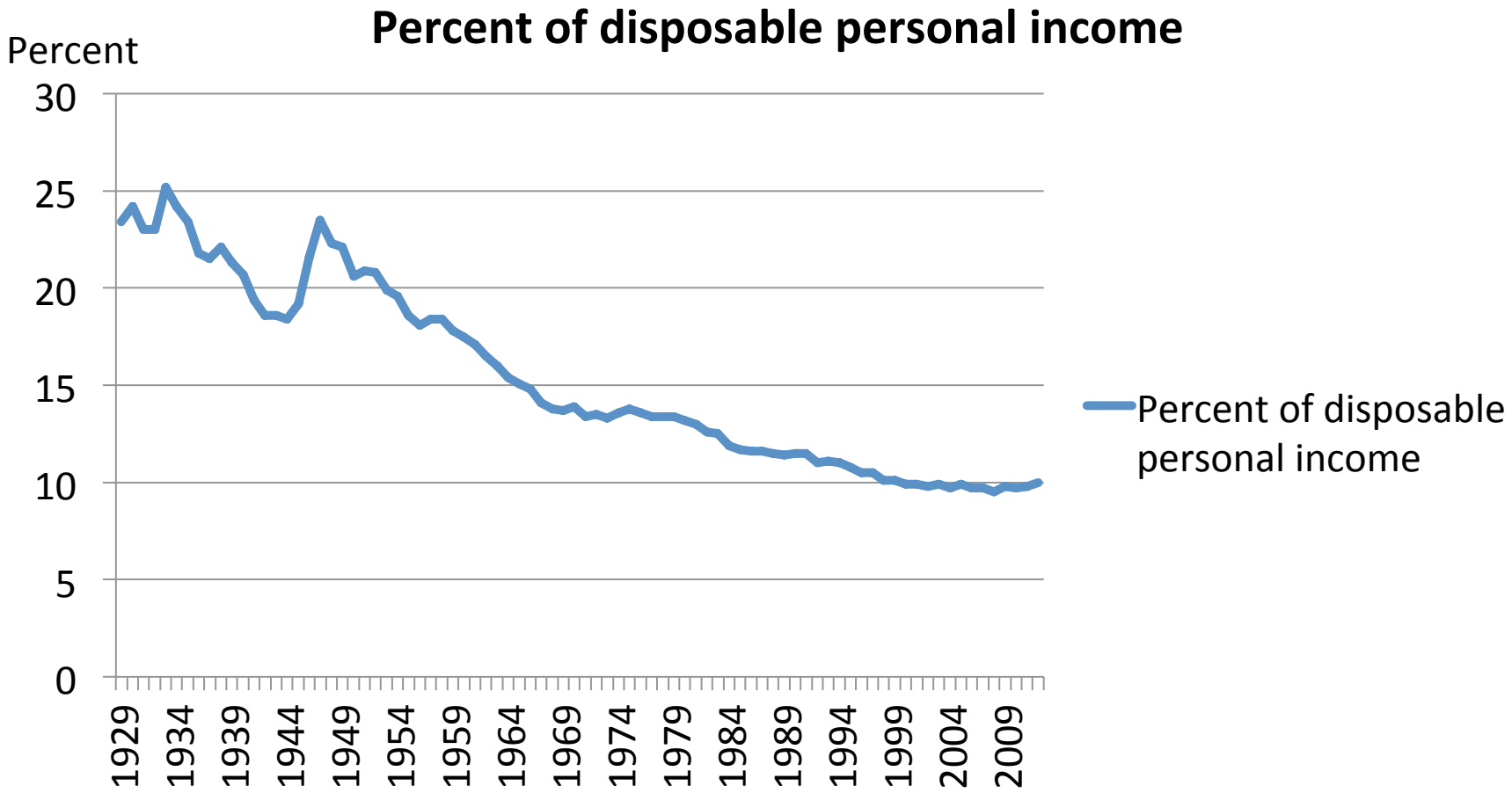
Number survivors at 25 days:
Control 1: 3
Control 2: 1
Liver extract: 11
Aureomycin: 11

Derived from: Jukes TH Advances in Applied Microbiology 1973; 16: 1-30. Data abstracted From Table 1, page 2.

FDA never “approved” antibiotics for growth promotion in livestock

- The Penicillin Amendment of 1945
- Allowed FDA to waive the requirements to ensure the safety and efficacy of penicillin-based drugs if doing so was considered safe.
- Waiver provided FDA the flexibility to approve antibiotics for purposes other than treating infections.
- In 1951 and 1953, respectively, FDA waived requirements for batch certification of antibiotics intended as growth promoting agents and preventive agents in livestock.

Since WWII, Cost of Food in U.S. Has Decreased



USDA Economic Research Service. Food Expenditures. Table 7, Column H.
http://www.ers.usda.gov/data-products/food-expenditures.aspx#.VAnM6P2jShM

United Kingdom

- 1960's: British Enteric Reference Lab (ERL) noted an increase in resistant *Salmonella typhimurium* in calves, appearing soon after farmers adopted intensive farming methods (separating calves from dams).
- Many animals got infected, developed infectious diarrhea, and died.
- Sick animals were treated with antibiotics and healthy animals were given antibiotics to prevent infections.
- Outbreaks in humans developed. One outbreak sickened almost 60 people who consumed raw milk of dairy cows infected with the organism.

Swann Report 1969

Meredith Michael Swann, PhD (Baron Swann) 1920-1990

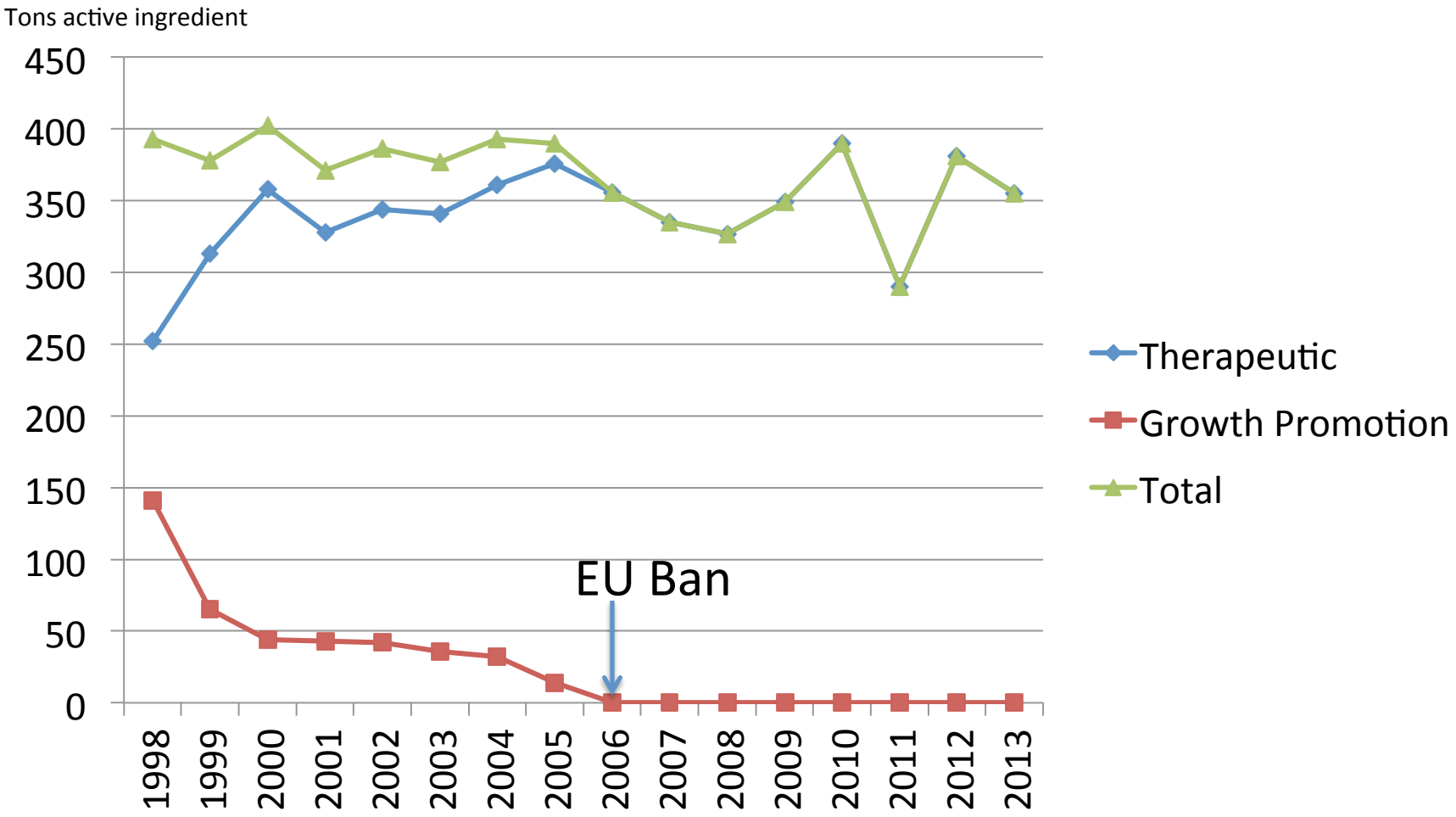
Recommendations

- Divided antibiotics into three categories:
  - Feed antibiotics—growth promotion
  - Therapeutic antibiotics—treat illnesses
  - Prophylactic antibiotics—prevent illness
- Recommended banning feed antibiotics that have important human health uses.
- Feed antibiotics should be available without a prescription to pigs, poultry, and calves up to 3 months of age.
- Veterinarians should be able to prescribe any antibiotic for sick animals.
- Alternative methods of growth promotion should be investigated and developed.
- A committee to oversee antibiotic use in humans and livestock recommended.

Response to Swann Recommendations

- Farming and pharmaceutical industries voiced strong opposition.
- Recommendations based on scanty evidence.
- Outbreaks were due to poor animal husbandry practices rather than use of antibiotics.
- 1970: Parliament banned 2 tetracyclines and penicillin as feed additives.
- Rest of Swann recommendations were either implemented half-heartedly or ignored.

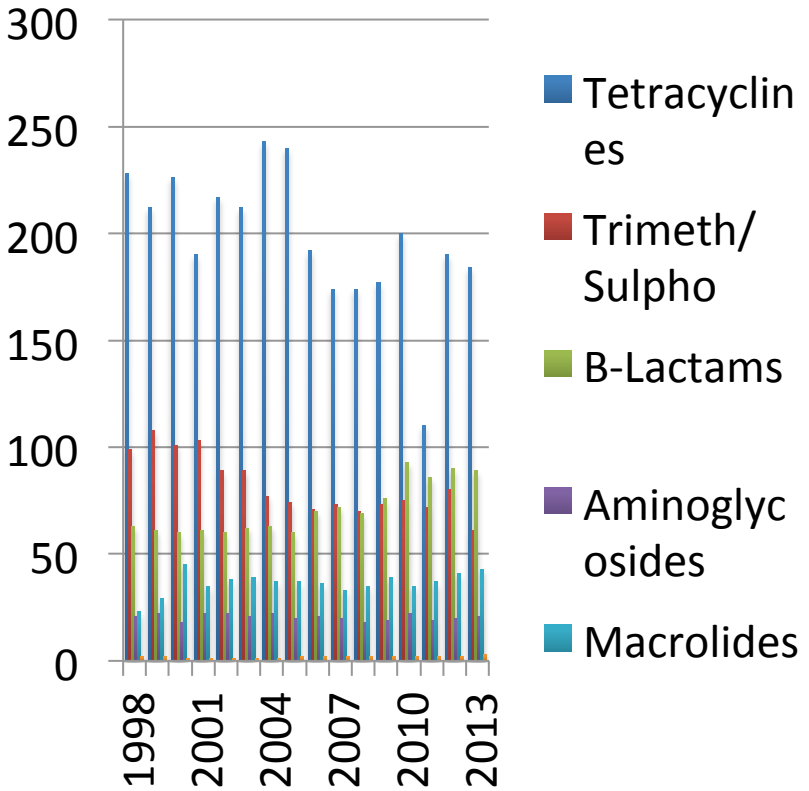
UK Antibiotic Sales Data for Food Animals, 1998–2013



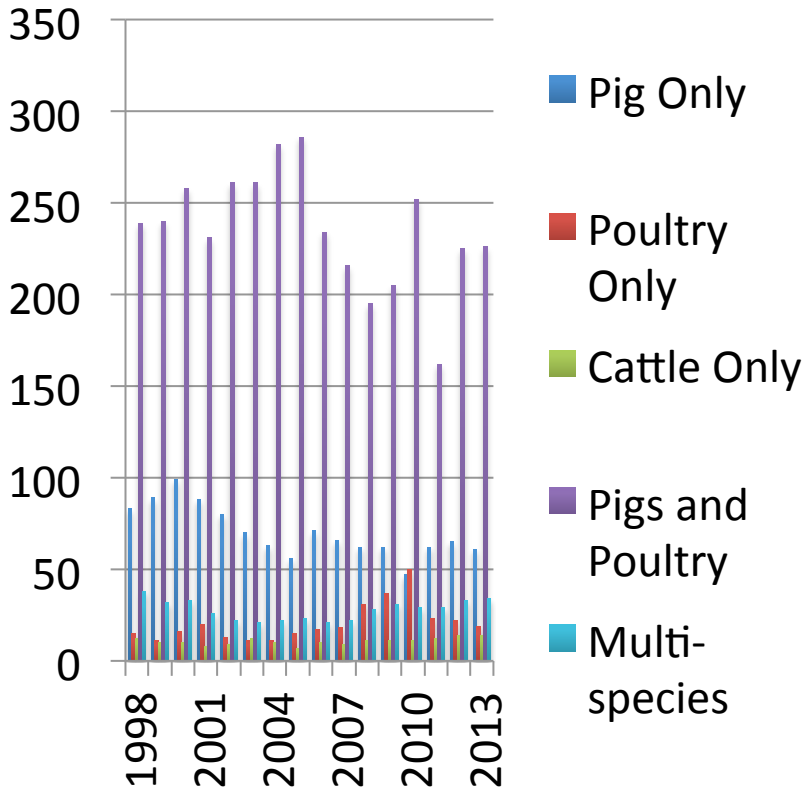
Source: Veterinary Medicines Directorate, "Sales of Antimicrobial Products Authorized for Use as Veterinary Medicines in the UK," 2003 Report p. 13; 2006 Report, p. 14; "UK Veterinary Antibiotic Resistance and Sales Surveillance," 2013 Report, p. 30, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/382991/VARSS.pdf.

Antibiotic Sales by Drug Class and Animal Species, U.K. 1998-2013

Tetracyclines Highest Use



Pigs and Poultry Use Most



Source: Veterinary Medicines Directorate, "Sales of Antimicrobial Products Authorized for Use as Veterinary Medicines in the UK," 2003 Report, p. 18, 24; 2006 Report, p. 19, 24. "UK Veterinary Antibiotic Resistance and Sales Surveillance" 2013 Report, p. 26,31. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/382991/VARSS.pdf.

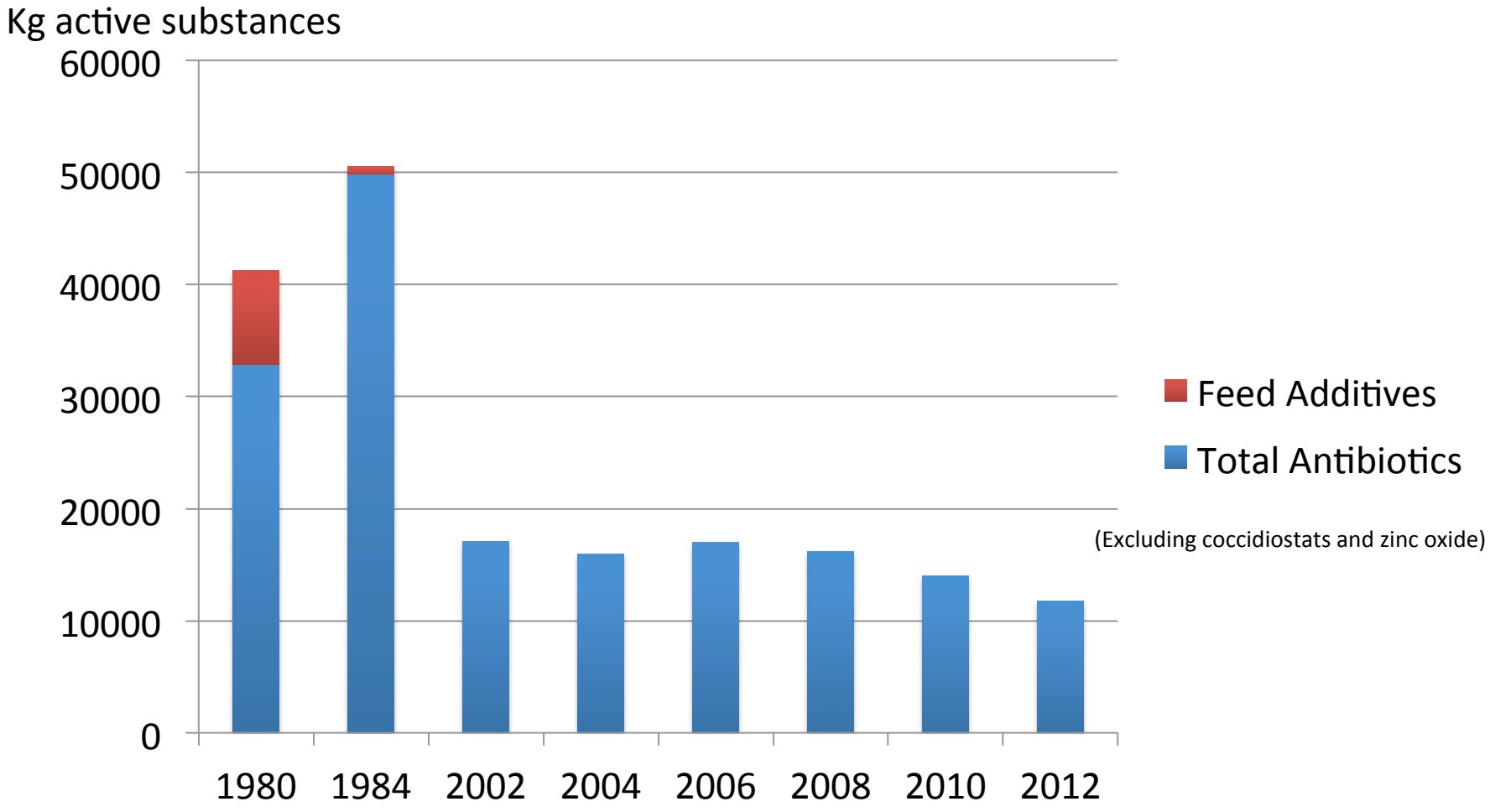
Sweden

- Swedes highly concerned about the environment after Rachel Carson's book *Silent Spring* published in 1962.
- In 1977, in response to Swann Report, banned some antibiotics for growth promotion that were also used in clinical medicine.
- In 1981, series of newspaper articles in *Dagens Nyheter* (Daily News)reported that more than 30 tons of antibiotics used in animal feed for growth promotion each year. Public was outraged.

Swedish Farmers Pushed for Ban

- Federation of Swedish Farmers decided that a ban of antibiotic growth promoting agents would regain consumer confidence.
- Farmers wanted Swedish Parliament to pass a mandatory ban and wanted compensation from government to cover expenses for adjusting livestock production methods.
- They got the ban, but not the compensation.
- Feedingstuffs Act 1986.
- In 1988, Parliament passed strict animal welfare laws, maximum weaning age for pigs, space requirements for animals, etc.
- Sweden wanted to have the cleanest agriculture in the world and worked hard to make livestock *Salmonella* free.

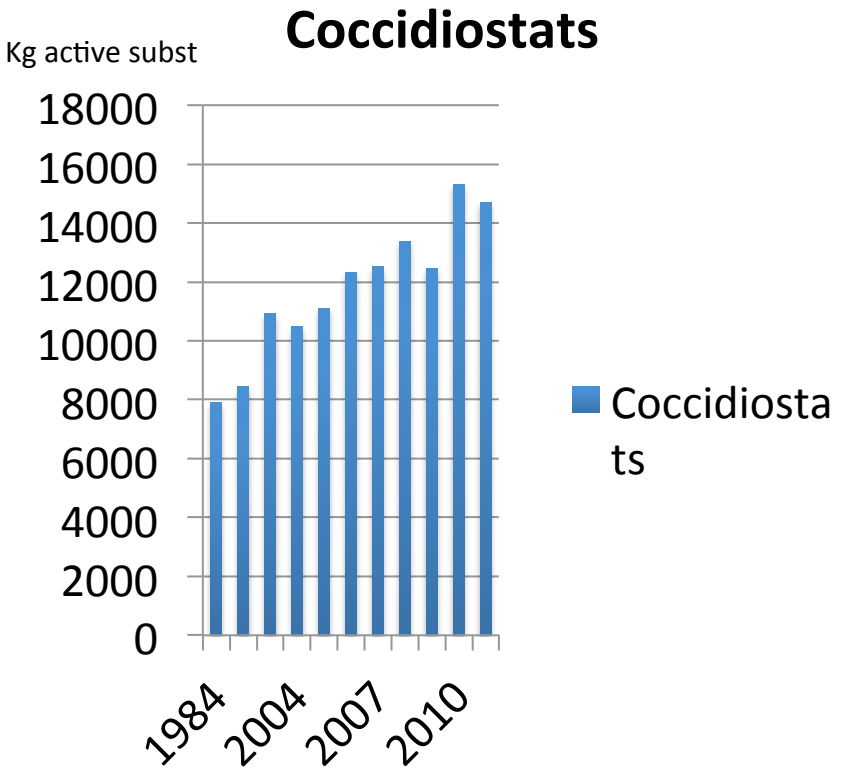
Overall Sales of Antimicrobial Drugs in Livestock, Sweden 1980-84, 2002-2012



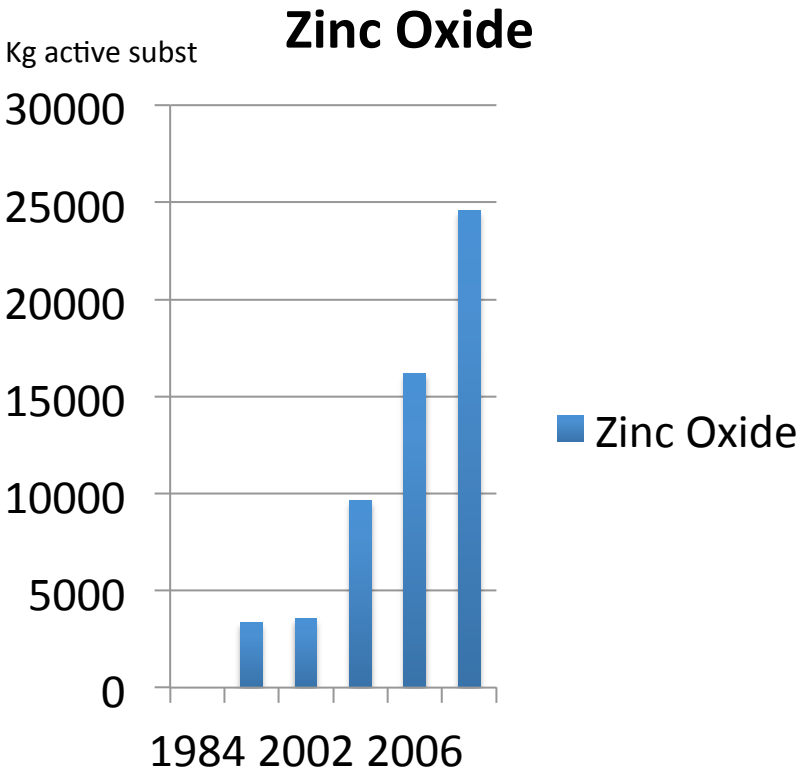
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2000 and SWEDRES/SVARM 2012, page 38-39.

Sales of Substitutes Increased

Sales of Ionophores Increased



Sales of Zinc Oxide Increased

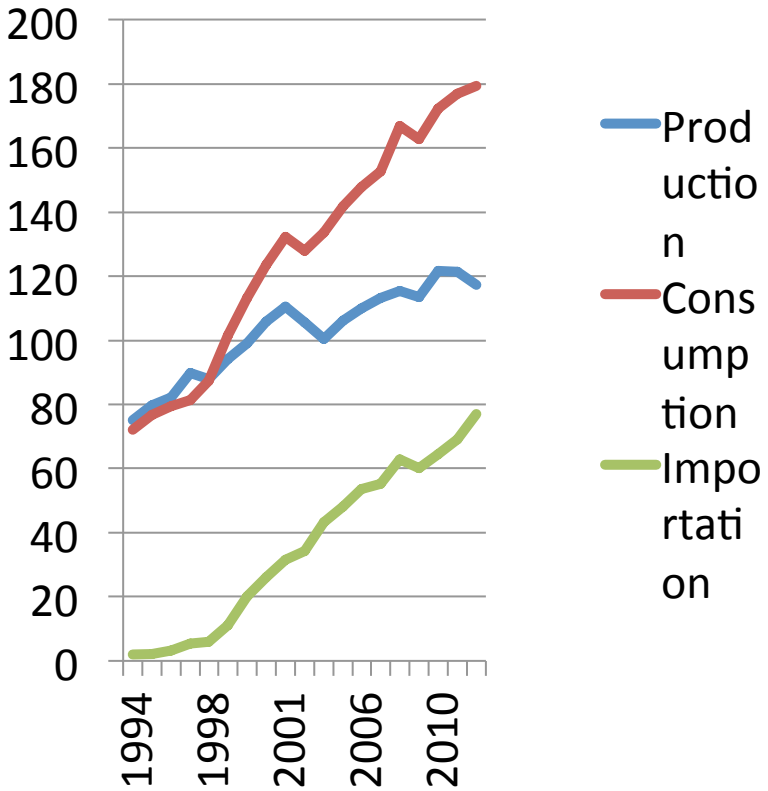


SWEDRES/SVARM 2012, page 39
Data from Swedish Feed Control Board of Agriculture

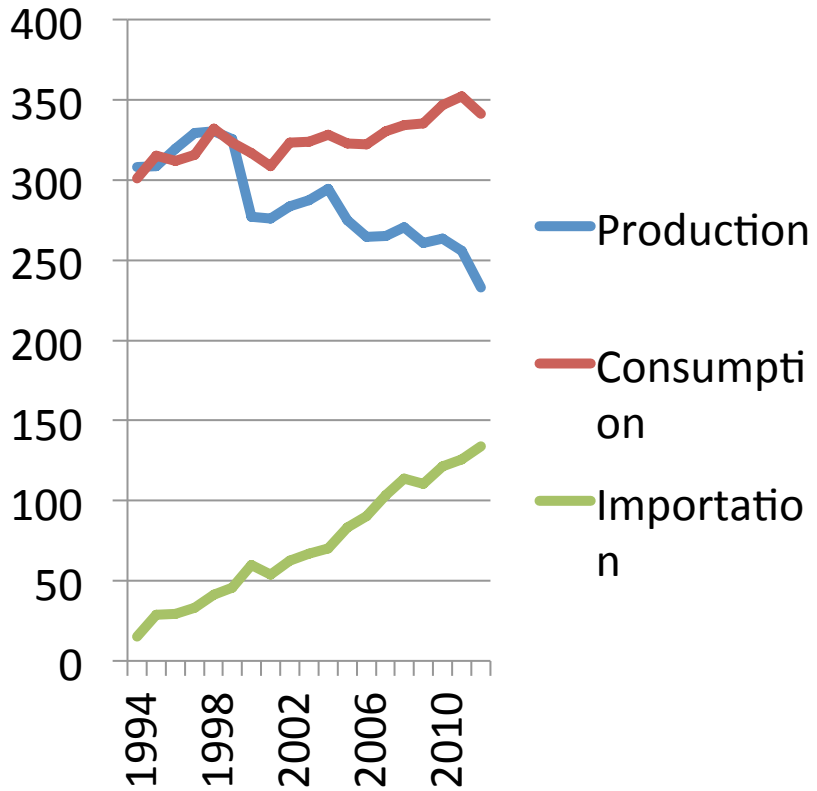
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2009

Sweden joined the EU in 1995, unable to meet domestic consumer demand

Broiler Production, Consumption, Importation



Pork Production, Consumption, Importation



Department of Trade and Markets, Swedish Board of Agriculture

The Rise of Vancomycin-Resistant *Enterococcus faecium* (VRE)

- In 1988, first case reports of VRE reported in seriously ill patients in Paris (acute leukemia) and London (End Stage Kidney Failure).
- Three months before the London VRE cases, a new policy was implemented: administer vancomycin and ceftazidime to all chronically ill (i.e. end stage kidney failure) patients with fever and undiagnosed infections.
- A few years later, VRE was isolated from food animals in England and Germany.
- Avoparcin, a growth promoting agent in livestock, chemically related to vancomycin, was implicated as the probable source of VRE in hospitals.

Relationship between Avoparcin and Vancomycin; Vancomycin is effective against both *E. faecium* and *E. faecalis*

Growth Promoting Antibiotic in Livestock	Related Antibiotic in Human Medicine	Antibiotic Class
Avoparcin	Vancomycin	Glycopeptide
Antibiotic	*Enterococcus faecium*	*Enterococcus faecalis*
Ampicillin/Gentamicin of Ampicillin/Cephtriaxone	+ increasing resistance	+
Vancomycin	+	+

Vancomycin used to treat Gram positive bacteria.

*New Antibiotics:
Quinupristin-Dalfopristin, approved by FDA Sept. 1999, only treats *E. faecium*
Linezolid, approved by FDA April 2000, only treats *E. faecium*

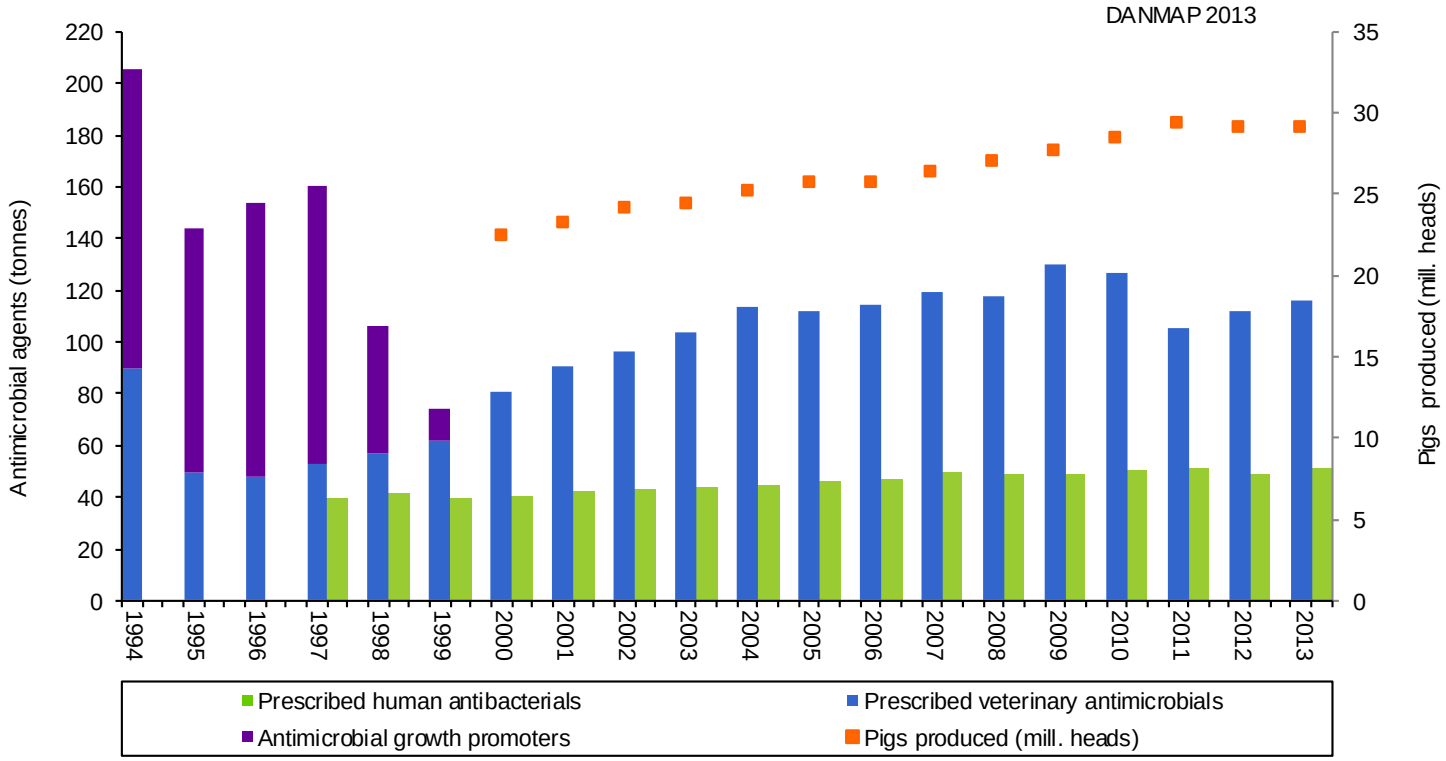
Denmark

- Danish scientists concerned about emergence of VRE and general use of antibiotics in livestock.
- Denmark relied heavily on avoparcin and other growth promoting antibiotics.
- In January 1995, VRE identified in fecal samples from healthy chickens and pigs in Denmark.
- Danish farmers concluded that they had to change their practices and stop using antibiotics as growth promoting agents.

Danish Growth Promoter Ban

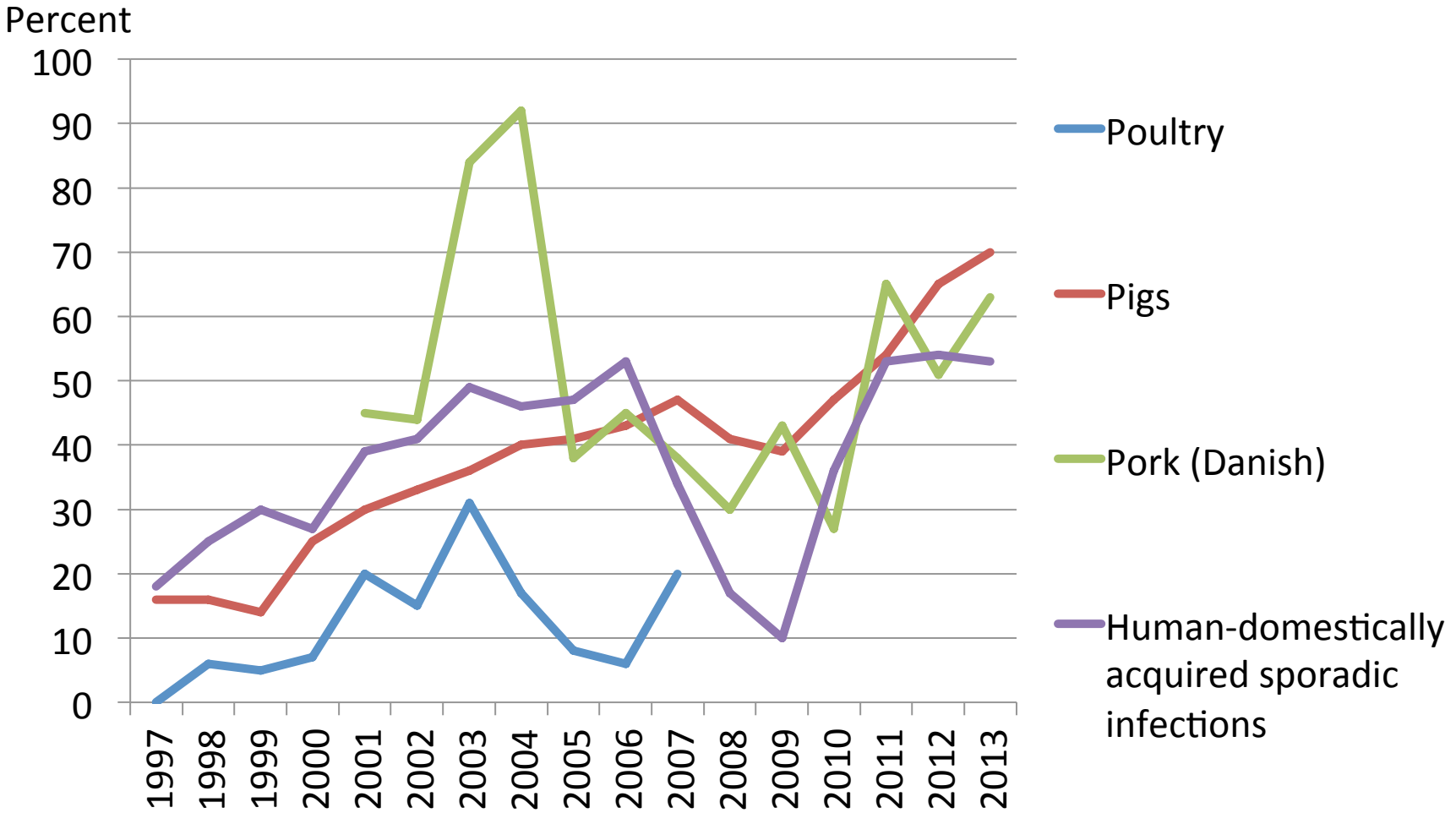
- Farmers voluntarily stopped using avoparcin in May 1995.
- In 1997, the EU banned avoparcin.
- 1998, Denmark banned virginiamycin, another growth promoting antibiotic, related to quinupristin/dalfopristin, an antibiotic used to treat VRE.
- 1999, Danish farmers stopped using *all* antibiotic growth promoting agents in response to consumer concerns

Figure 4.1. Prescribed antimicrobial agents for humans, and for animals compared with the number of pigs produced, Denmark



Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996–2000). Data from 2001–2013 originate from VetStat

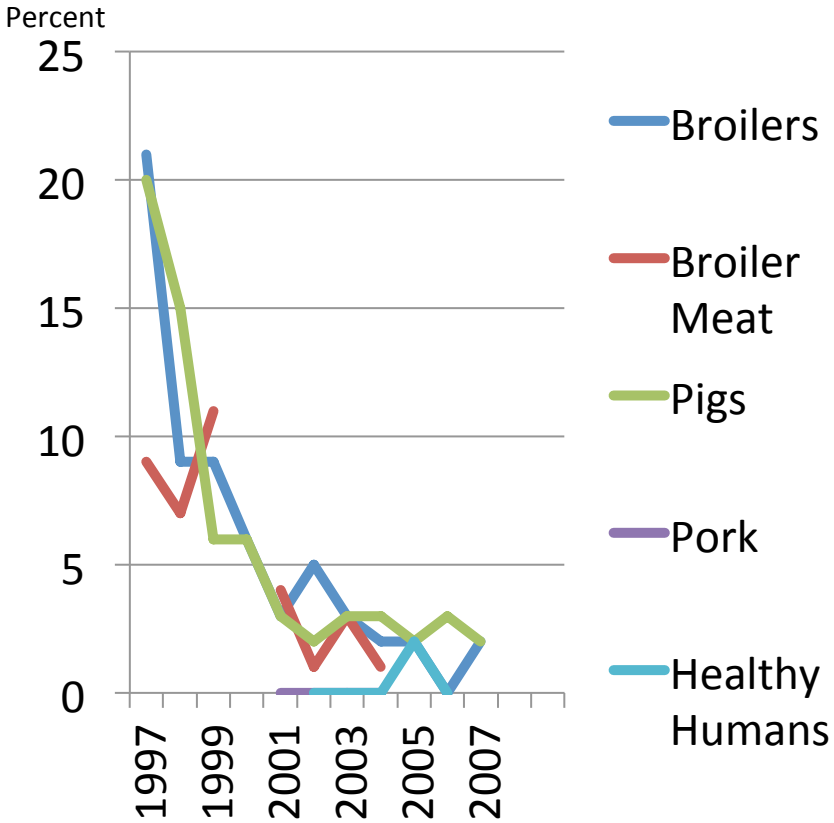
Salmonella typhimurium Tetracycline resistance (%), Denmark, 1997-2013



DANMAP 1997-2013

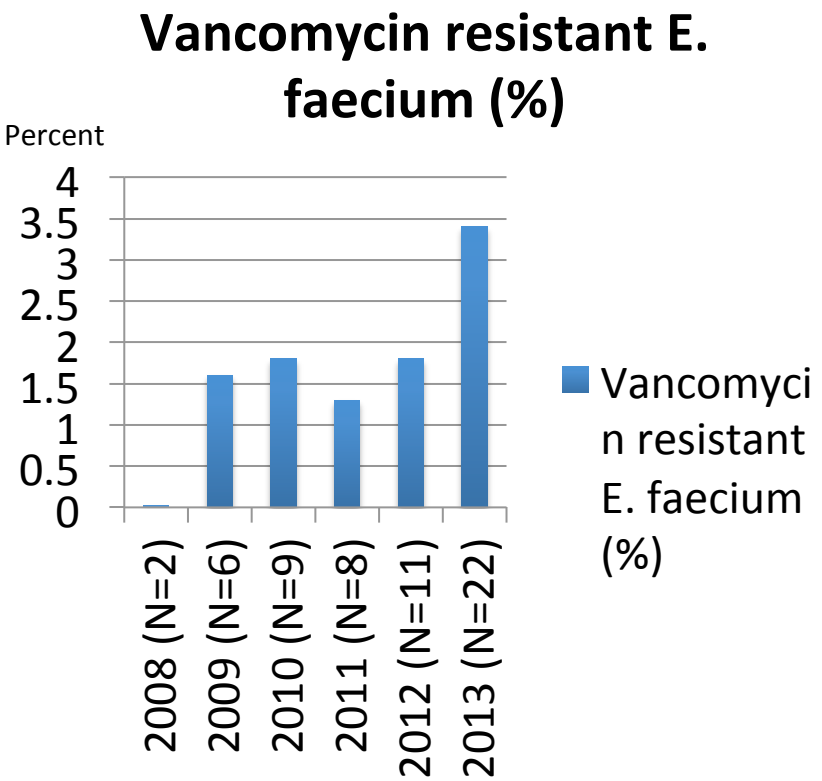
Denmark: Ban Decreases VRE in Farm Animals! But not in hospitals

VRE declined on farms



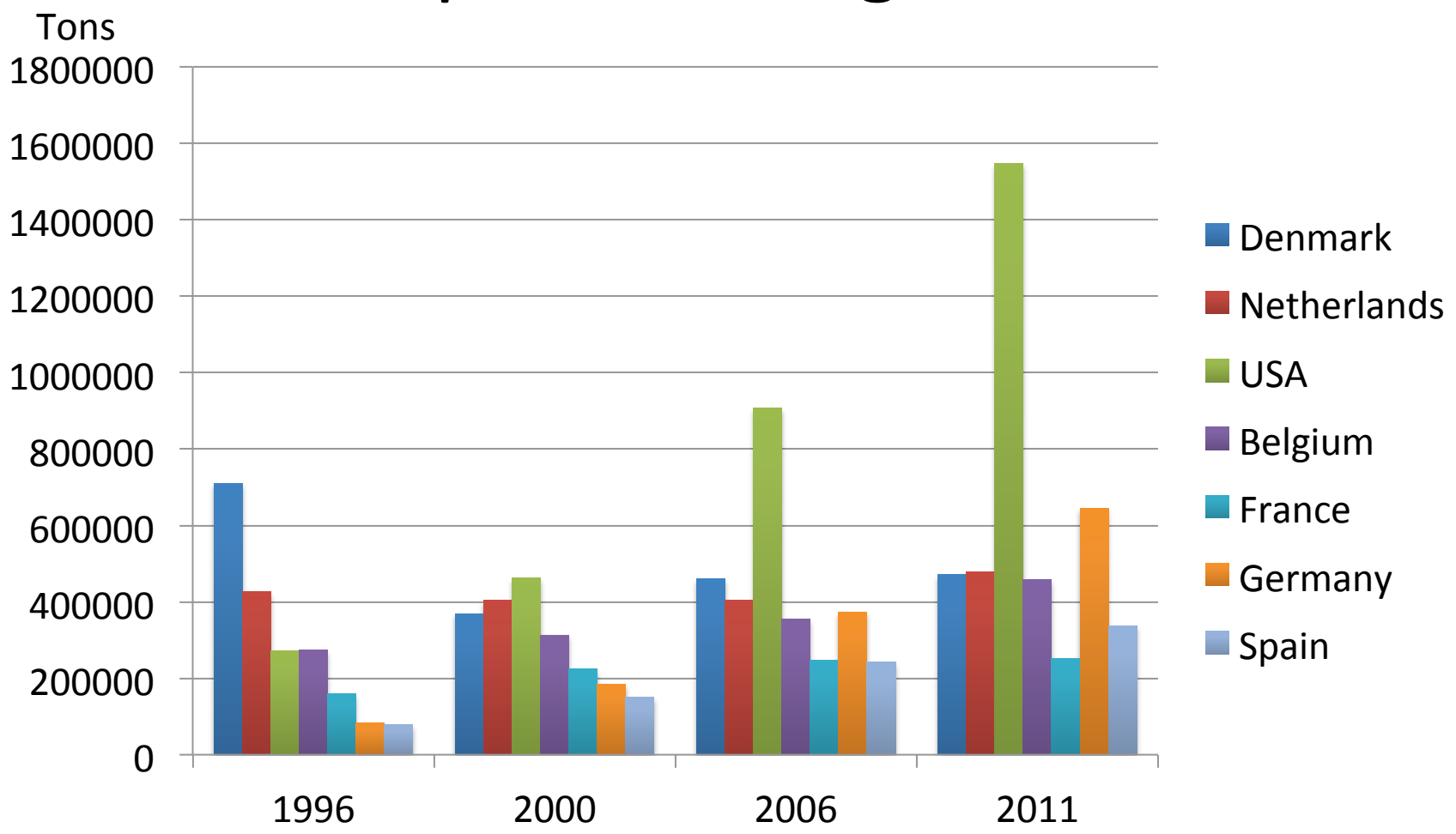
DANMAP 1997 to 2008

VRE in hospitals increased



DANMAP 2008, page 84, DANMAP 2009, page 84, DANMAP 2010, page 97, DANMAP 2011, page 110, DANMAP 2012, page 95, DANMAP 2013, page 85.

Denmark No Longer World's Top Exporter of Pig Meat



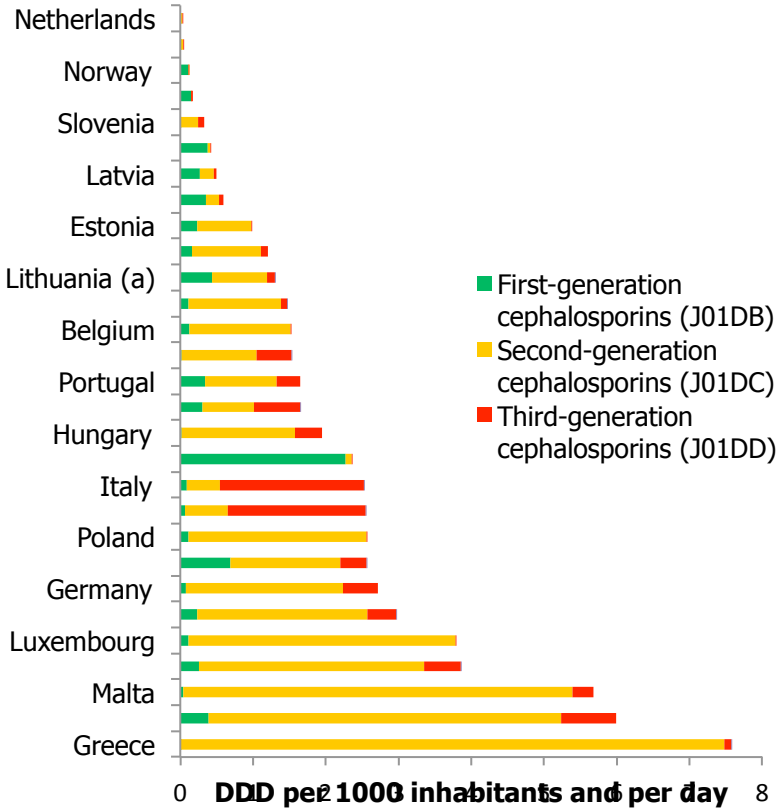
FAOSTAT: Exports. Countries by commodity http://faostat.fao.org/site/342/default.aspx

European Union

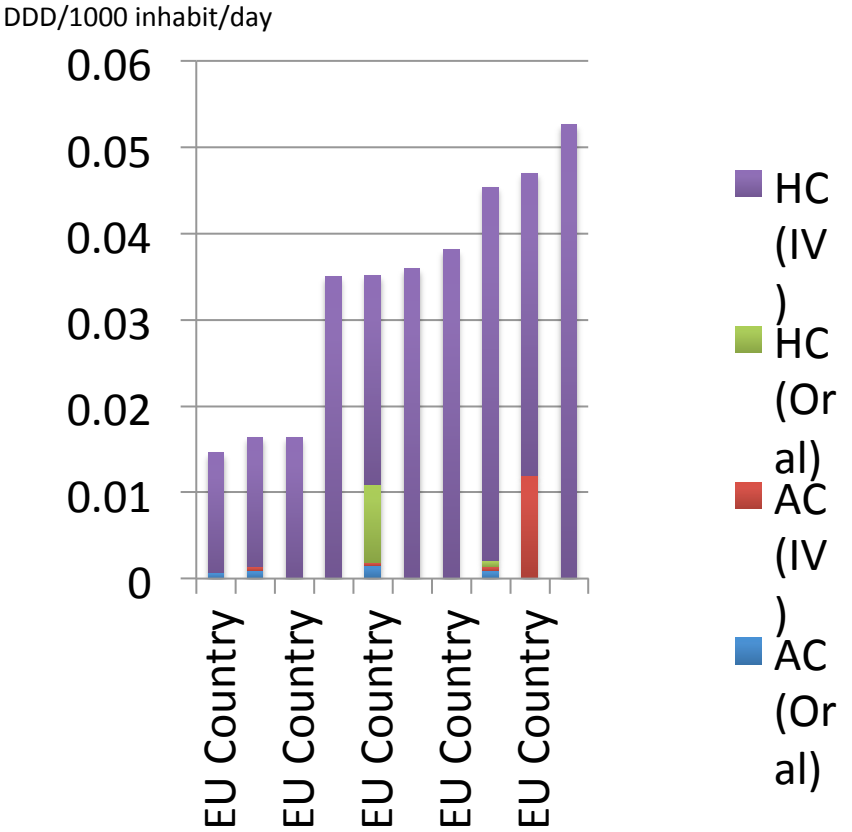
- 2003, European Parliament passed regulations prohibiting all antibiotics as growth promoters.
- Ban took effect January 1, 2006.
- European Union established a number of surveillance systems to assess antibiotic use and resistance.
- Reporting was voluntary for enterococcus in livestock, not possible to assess VRE rates in livestock before or after ban.

EU countries vary widely in human antibiotic use

Cephalosporin Use 2011



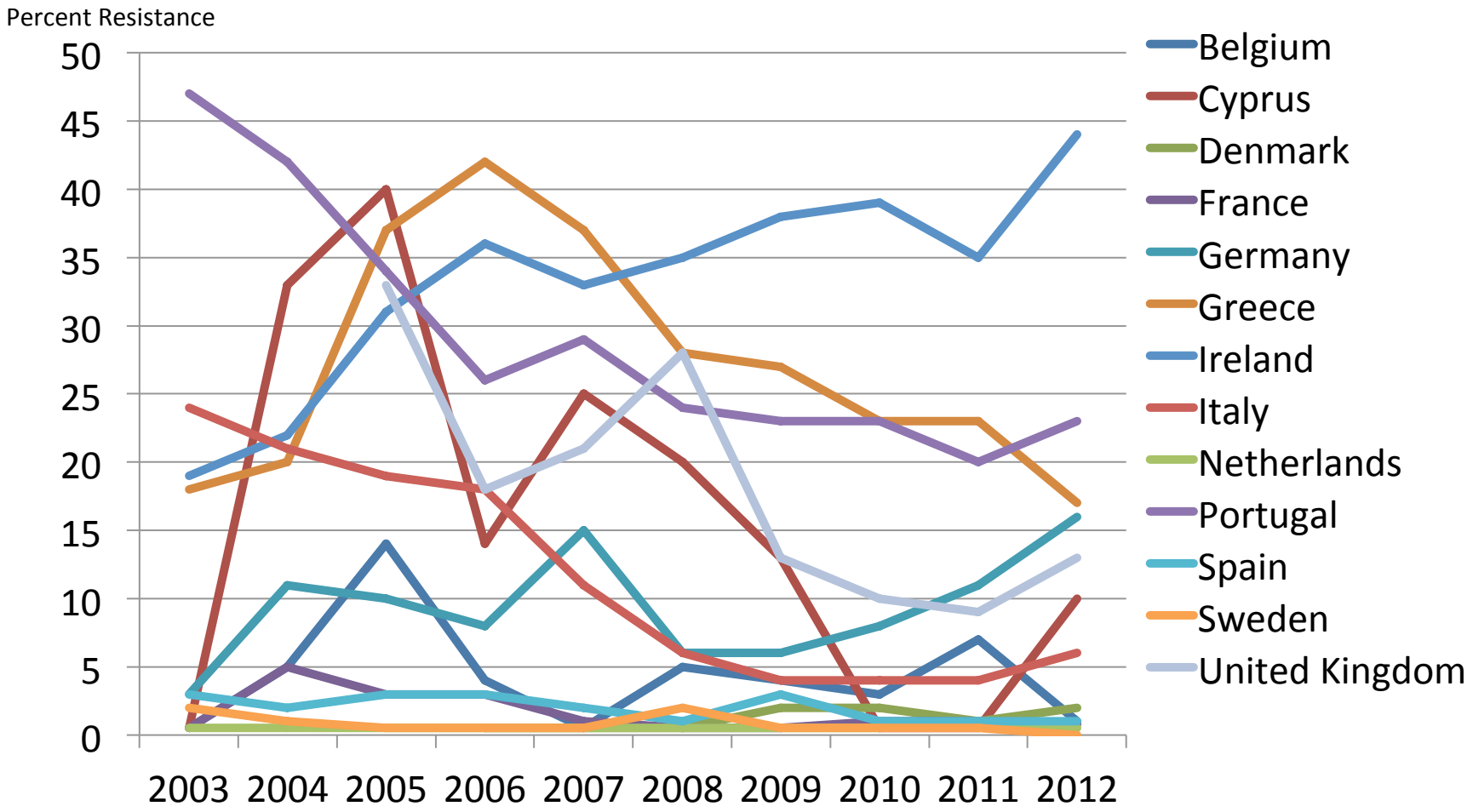
Vancomycin Use 2011



ECDC Surveillance Report 2011, Page 24, Table 3.12.

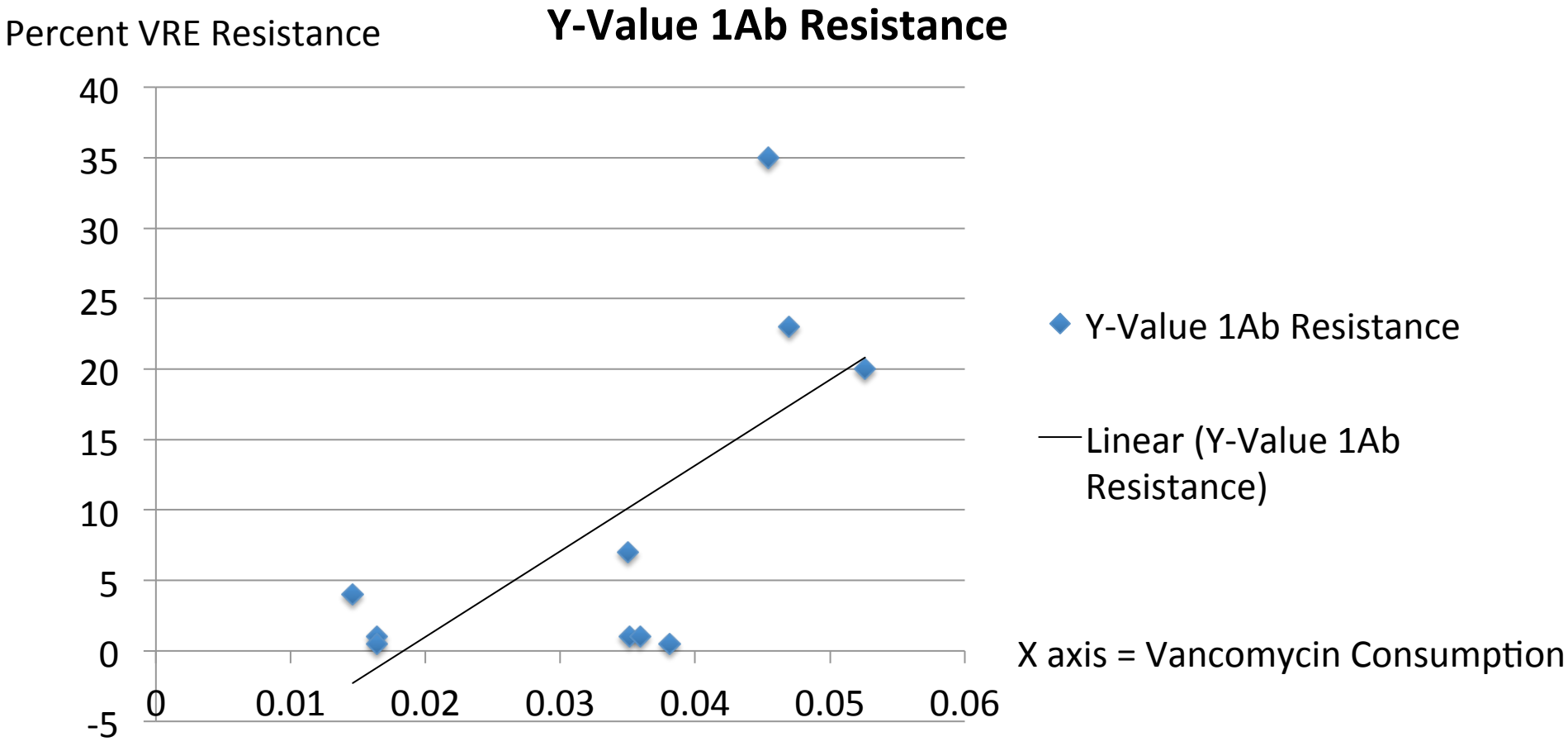
Courtesy of ECDC TESSy Data Access Team, Surveillance of Antimicrobial Consumption in Europe.
Names of countries removed at request of ECDC

No consistent trend in VRE isolates from hospitalized humans after 1997 EU avoparcin ban



Data derived from Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-NET), 2012. Country summary sheets, Pgs 83-202.

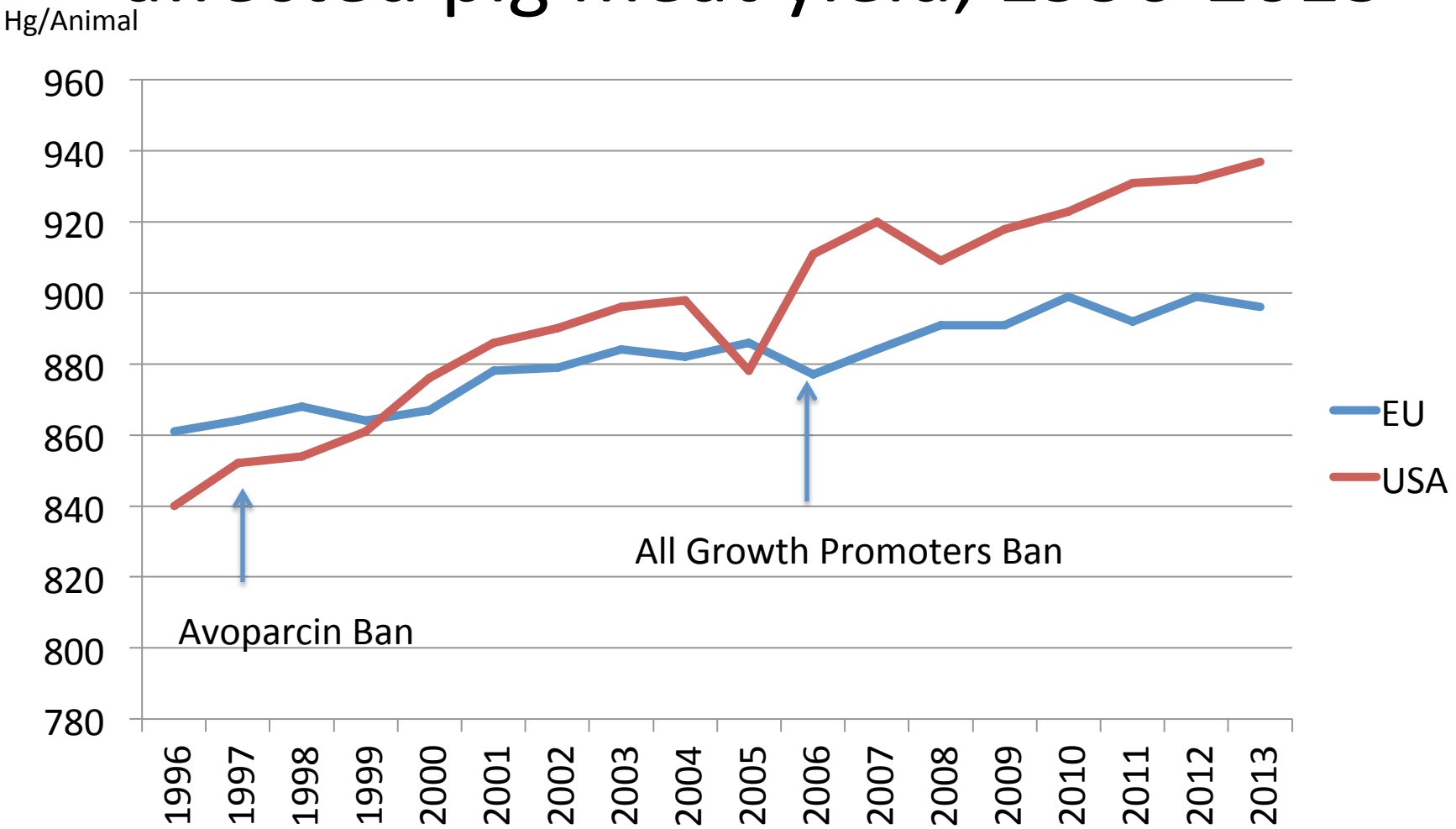
Human vancomycin use and VRE in hospitals are highly correlated



Countries: Belgium, Cyprus, Denmark, France, Greece, Ireland, Italy, Netherlands, Portugal, Sweden.

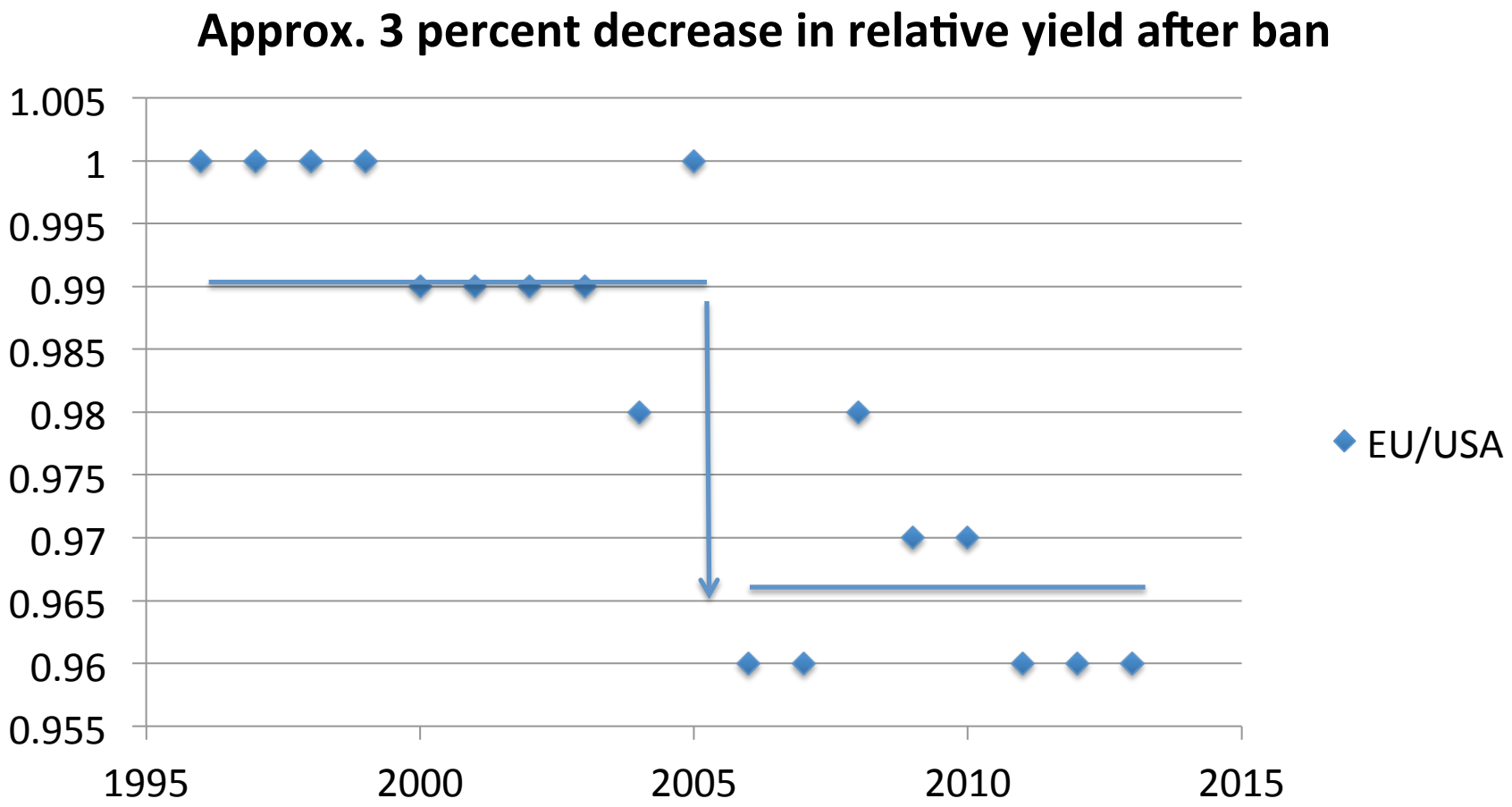
R = .673

Evidence that 2006 ban adversely affected pig meat yield, 1996-2013



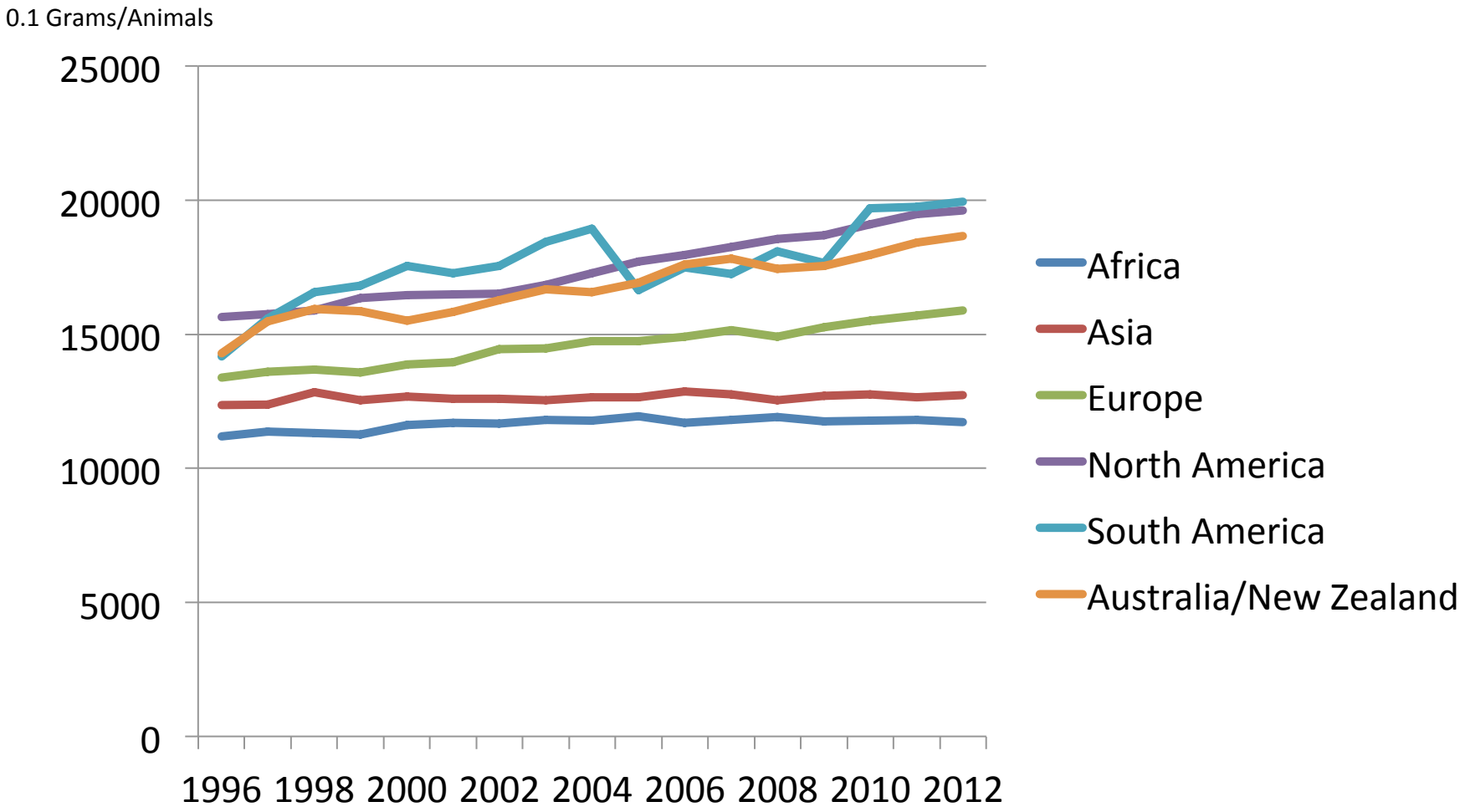
U.N. Food and Agriculture Organization. FAOSTAT. Production. Livestock Primary. http://faostat3.fao.org/download/Q/QL/E
(Hg = heclogram (100 grams))

Relative Pig Meat Yield (EU/USA)



Decrease in Yield Cost EU Approx. $1.1 Billion Per Year (in 2012 USD)

No effect on chicken production; EU did not ban coccidiostats



Food and Agriculture Organization FAOSTAT http://faostat3.fao.org/download/Q/QL/E

United States

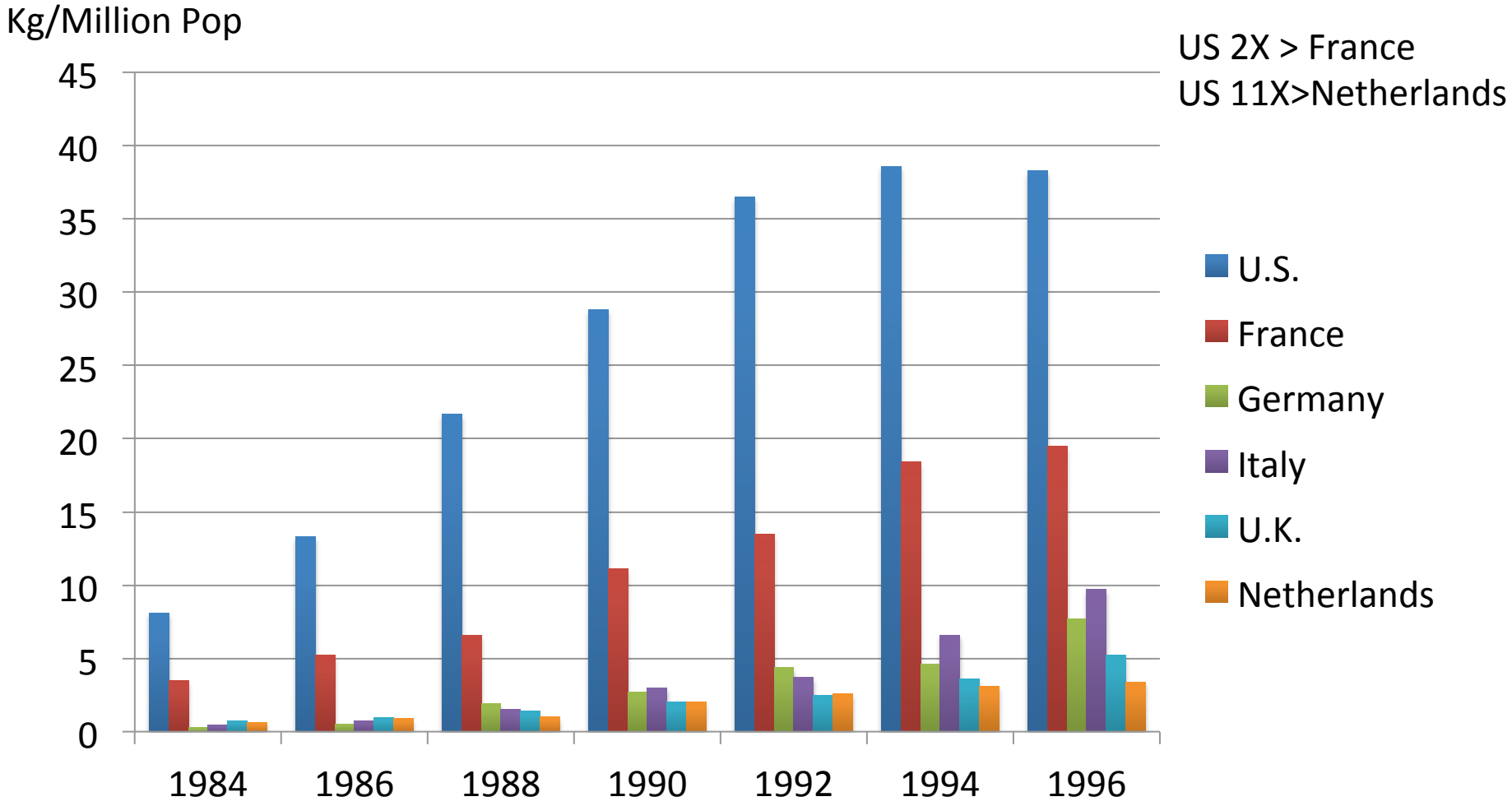
- US never approved avoparcin, so epidemiology of VRE has been different compared to Europe.
- Congress has spent decades debating the risks of growth promoting antibiotics.
- Consistently concluded that more data was needed, but never appropriated resources to get more data.
- Bureaucratic leaders at CDC, FDA, USDA scrounged together funds for NARMS and NAHMS.

VRE in U.S.

- VRE in US emerged in 1990's in hospitals.
- Preceded spread in European hospitals by about a decade even though first few cases reported in Europe.
- CDC estimates that 77% of US healthcare-associated infections due to *Enterococcus faecium* are resistant to vancomycin.*
- CDC estimates approximately 10,000 VRE infections and 650 deaths per year.*
- Healthcare costs specifically for VRE not available.
- CDC estimates that >2 million people fall ill with resistant infections, 23,000 die, healthcare costs between $20 to $35 billion per year.*

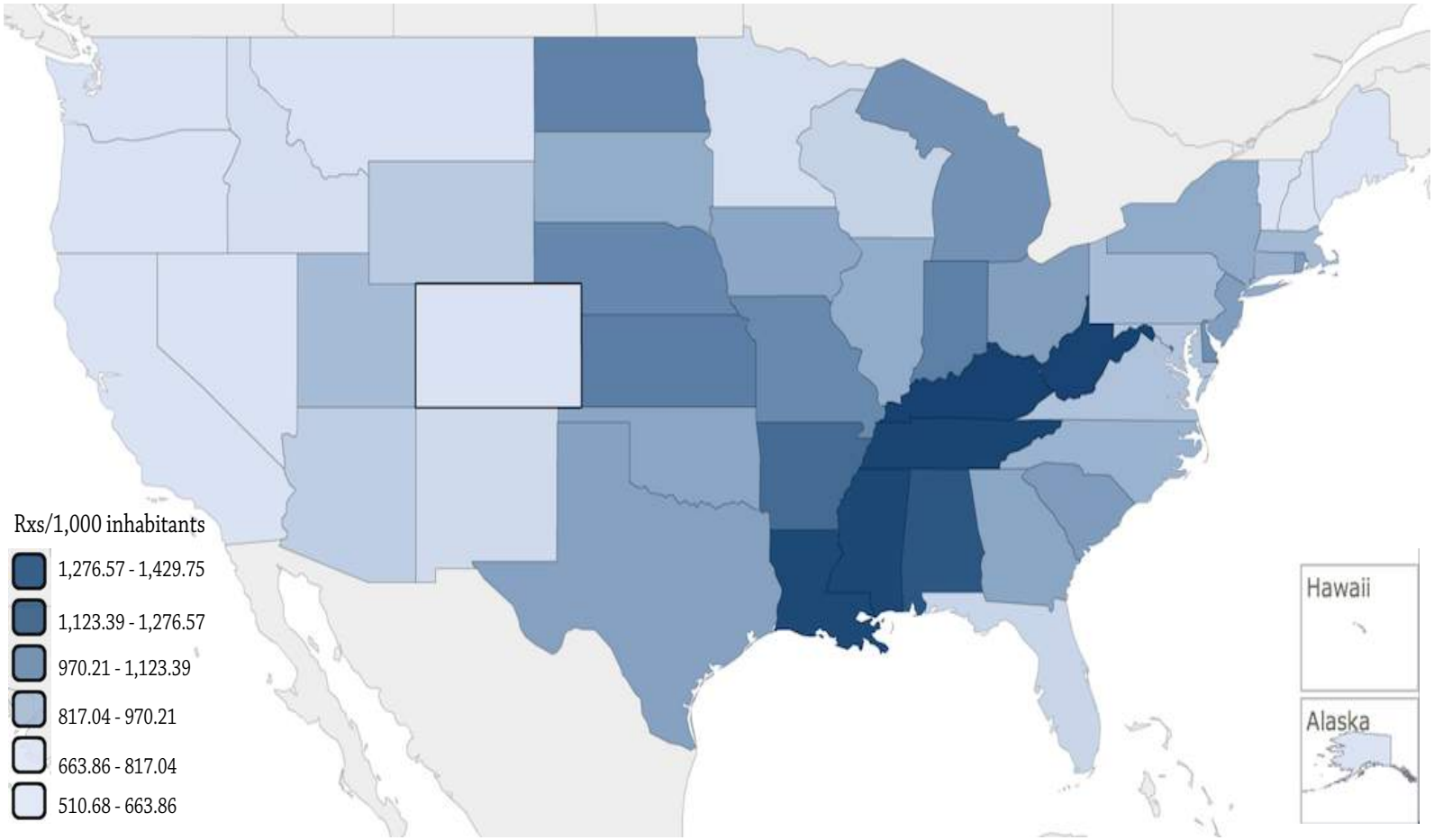
*CDC. Antibiotic Resistance Threats in the United States 2013.
http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

Americans Used Much More Vancomycin than the Europeans: Human vancomycin use (in kg) per capita per year



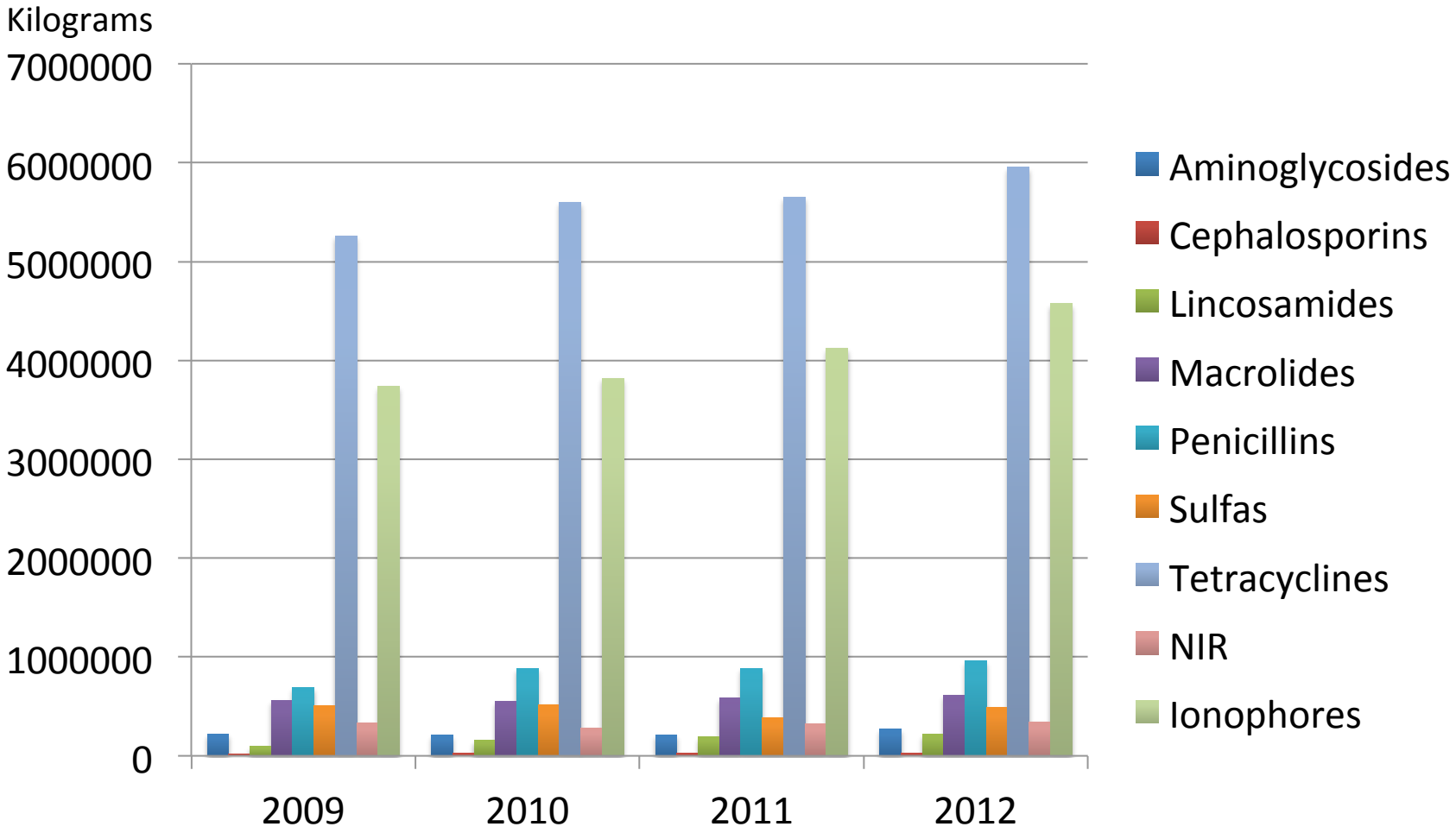
Kirst HA, Thompson DG, Nicas TI. Historical Yearly Usage of Vancomycin. Antimicrobial Agents and Chemotherapy 1998; 42: 1303-1304.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC105816/

Outpatient antibiotic consumption, by state in the US in 2010



The Center for Disease Dynamics, Economics & Policy, “Outpatient Antibiotic Use”. Available online at: ***http://cddep.org/node/4933***

Food and Non-Food Animals Receive Primarily Tetracyclines and Ionophores (Coccidiostats) in U.S.



FDA Summary Reports on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. Page 40, Table 10.
NIR (Not Independently Reported)
http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm

National Antibiotic Resistance Monitoring System (NARMS): *Enterococcus faecium*

Antibiotic	Chickens*			Chicken Meat**			Pork Chops		
	2003 (2216)	2006 (1500)	%Δ	2002 (134)	2011 (186)	%Δ	2002 (93)	2011 (37)	%Δ
Vancomycin	0	0	0	0	0	0	0	0	0
Linezolid	0	0	0	0	0	0	0	0	0
Quinupristin/ dalfopristin	36.9	65.8	+28.9	55.4^	32.1^	-23.3	24.7^	13.5^	-11.2

NARMS does not collect *Enterococcus faecium* data on humans!

Unspecified Enterococcus in Chickens; ***Enterococcus faecium* and *Enterococcus faecalis* in Chicken Meat and Pork Chops
^ Enterococcus faecium resistance
USDA NARMS:
http://www.ars.usda.gov/SP2UserFiles/Place/66120508/NARMS/NARMS2011/NARMS%20USDA%202011%20Report.pdf
Page 16, 52, Table 4D
FDA NARMS Report 2011 Pages 50 and 51, Table 22.1 and Table 22.2
http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pd
( ) =Total number of isolates tested.

National Animal Health Monitoring System (NAHMS): Resistant Enterococcus in Pigs

Antibiotic	2006 (857)*	%	2012 (563)*	%	Change
Vancomycin	0	0	0	0	0
Linezolid	0	0	0	0	0

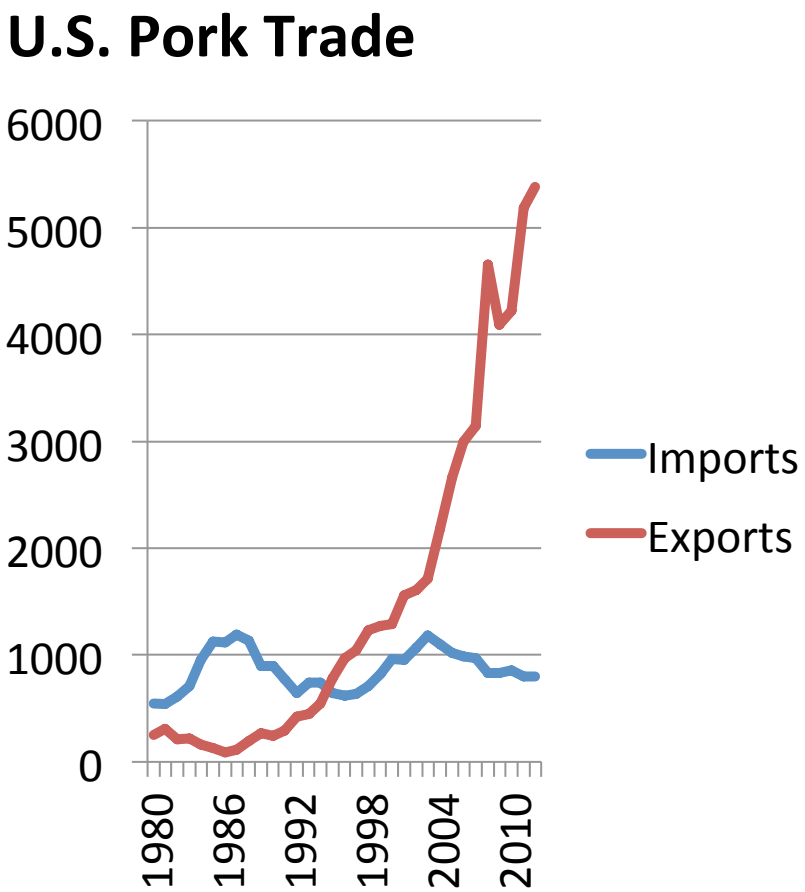
*( )= total number isolates tested.
USDA APHIS Commensal Enterococcus on U.S. Swine Sites: Prevalence and Antimicrobial Drug Susceptibility. April 2009.
Enterococcus species included: *E. hirae (29.6%), E. faecalis (27.4%), E. species not identified (16%), E. faecium (7.9%), E. mundtii (7.7%), E. casseliflavus (3%)* and others.
http://www.aphis.usda.gov/animal_health/nahms/swine/downloads/swine2006/Swine2006_is_entero.pdf
Eric J. Bush. Veterinary Epidemiologist. Animal and Plant Health Inspection Service, USDA. Personal communication. January 20, 2015.
Susceptibility against quinupristin/dalfopristin was not done.

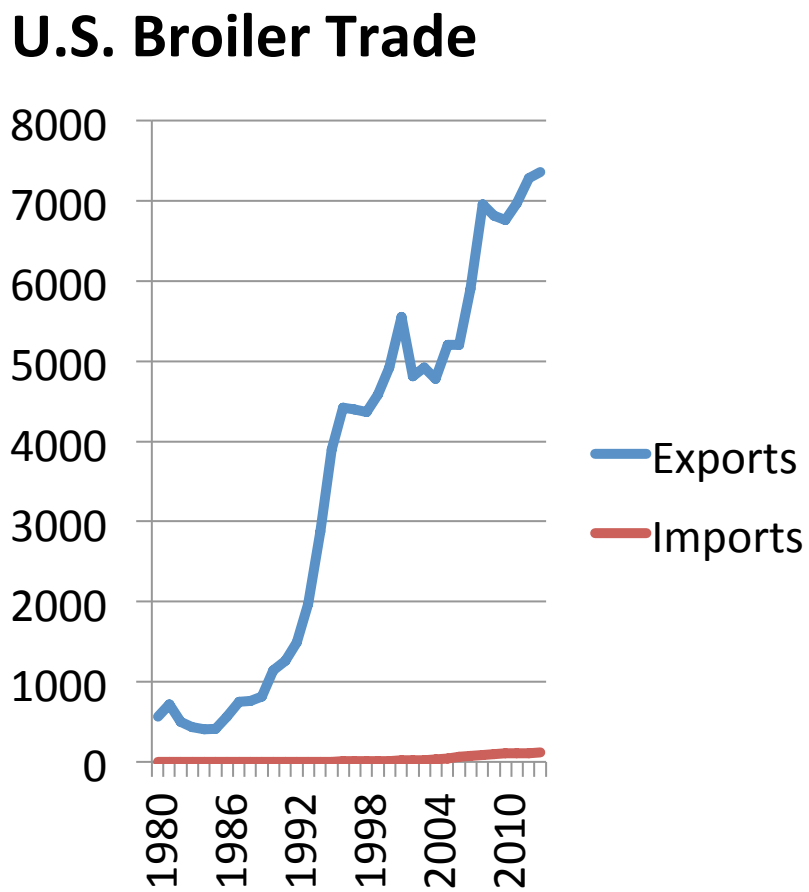
NARMS: Percent Resistance in *non-typhoidal Salmonella*

Antibiotic	Chickens 1997 (214)	2011 (491)	%Δ	Chicken Meat 2002 (60)	2011 (158)	%Δ	Swine 1997 (111)	2011 (90)	%Δ	Pork Chops 2002 (10)	2011 (28)	%Δ	Humans 2002 (1998)	2011 (2344)	%Δ
Ceftriaxone	0.5	6.3	+5.8	10	33.5	+23.5	0	2.2	+2.2	20	7.1	-12.9	4.4	2.5	-1.9
Ciprofloxacin	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0.2	+0.1
Tetracyclines	20.6	40.9	+20.3	33.3	65.8	+32.5	52.3	41.1	-11.2	70	39.3	-30.7	14.9	10.5	-4.4
Trimethoprim/ Sulfamethoxazole	0.5	0.2	-0.3	0	1.3	+1.3	1.8	0	-1.8	20	0	-20	1.4	1.2	-0.2

USDA NARMS:
http://www.ars.usda.gov/SP2UserFiles/Place/66120508/NARMS/percent_resistance/SalmChickenSlaughter.pdf
FDA NARMS Report 2011 Page 23, Table 8
http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf
USDA NARMS
http://www.ars.usda.gov/SP2UserFiles/Place/66120508/NARMS/percent_resistance/SalmSwineSlaughter.pdf
FDA NARMS Report 2011 Page 23, Table 8
http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf
CDC NARMS Annual Report 2011 Page 31, Table 8.
http://www.cdc.gov/narms/pdf/2011-annual-report-narms-508c.pdf
( ) = Total number isolates tested.

U.S. Exports of Pork and Broiler Chickens Have Skyrocketed

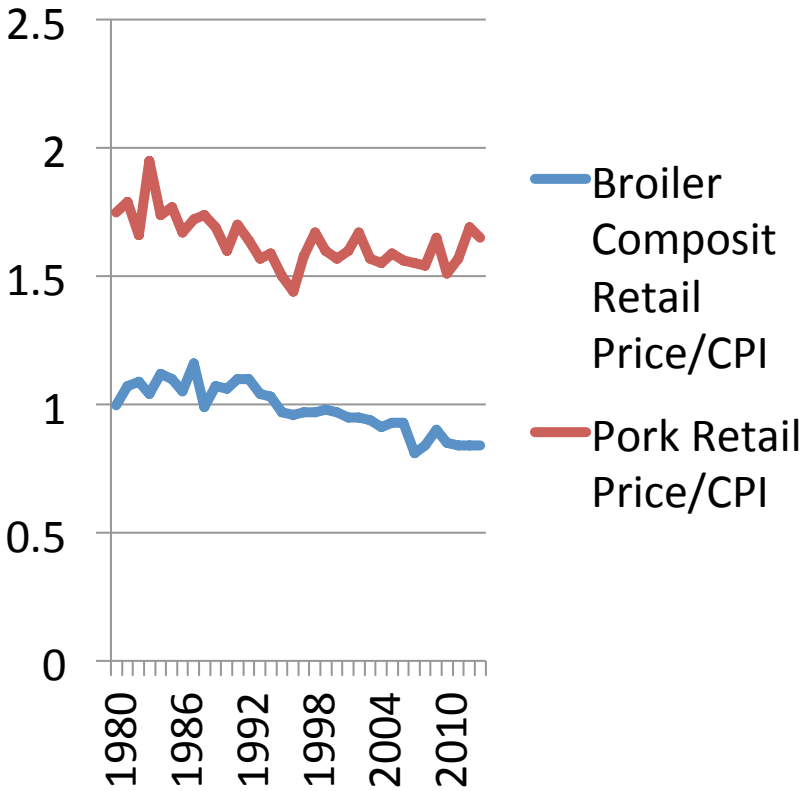




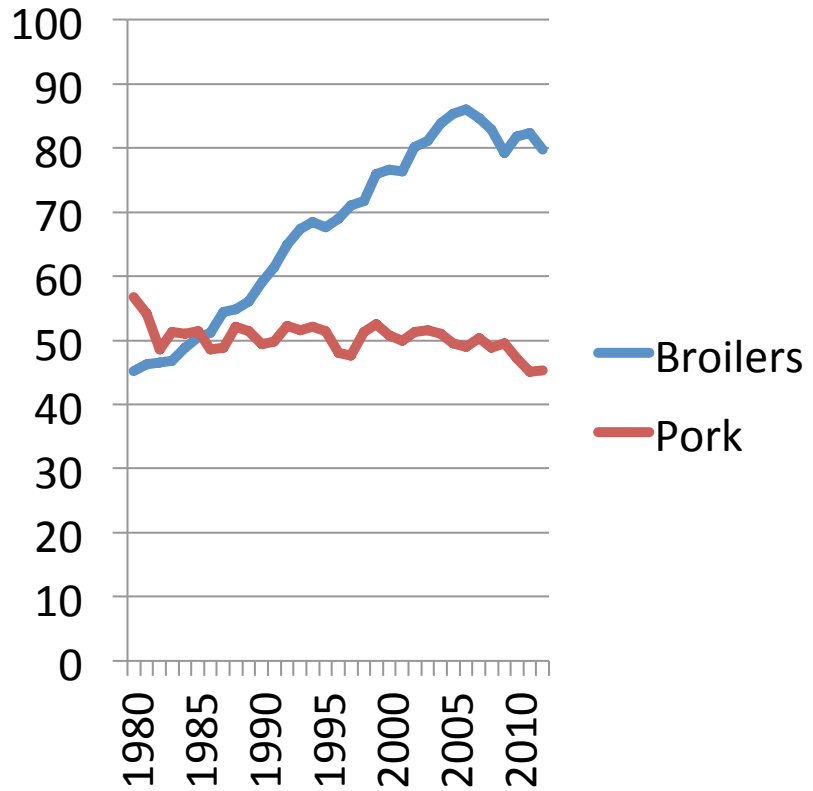
USDA Economic Research Service Food Availability (Per Capita) Data System. Red meat (beef, veal, pork, lamb, and mutton)
http://www.ers.usda.gov/data-products/food-availability-%28per-capita%29-data-system.aspx

Americans eat a lot of chicken

Retail Prices/CPI: Chicken is cheaper than pork



Per Capita Consumption



USDA Economic Research Service. Meat Price Spreads. Historical monthly price spread data for beef, pork, broilers. Retail prices for beef, pork. Poultry cuts, eggs, and dairy products. Pork values and spreads.
http://www.ers.usda.gov/data-products/meat-price-spreads.aspx
U.S. Dept. of Labor, Bureau of Labor Statistics Consumer Price Index http://www.bls.gov/cpi/
Poultry includes chicken, turkey, duck, quail.

USDA Economic Research Service. Food Availability (Per Capita) Data System. Poultry (chicken and turkey). Red Meat (beef, pork, lamb, and mutton). Retail meat pounds per U.S. population per year.
http://www.ers.usda.gov/data-products/food-availability-%28per-capita%29-data-system.aspx

Comparing the EU and USA

EU

- Banned avoparcin after rise of VRE in food animals.
- Banned all antibiotic growth promoting agents.
- Evidence that total ban adversely affected pig meat production.
- No evidence that avoparcin ban decreased VRE in hospitalized humans.

USA

- Never approved avoparcin.
- Very high vancomycin use in hospitals
- VRE appeared in hospitalized patients about a decade before widespread in Europe.
- No evidence that VRE came from US livestock.
- Implemented voluntary measures to stop using growth promoting antibiotics.

VRE genomic data reveals surprising findings

- One or two VRE clones caused initial outbreaks, proliferating into multiple clones, and becoming endemic in hospitals. VRE CC17
- Hospital associated VRE appears to be genetically distinct from VRE in livestock and from healthy people in the community.
- Genetic analysis suggests that VRE precursor came from an animal, just not the livestock that everyone assumed…

Willems R, van Schaik W. Transition of *Enterococcus faecium* from commensal organism to nosocomial pathogen. Future Microbiology 2009; 4: 1125-1135.

VRE precursors (AREF CC17) genetically related to VRE CC17 in hospitals have been isolated in dogs

Two Danish studies

1. First Danish study analyzed fecal specimens from 127 healthy dogs and found 20 *E. faecium* isolates resistant to ampicillin. One isolate was related to VRE CC17. Only 14 dogs had been treated with antibiotics within 6 months of the study.

2. Second Danish/UK study found ampicillin resistant *E. faecium* in 61/208 dogs. Only 1 person out of 18 tested positive—a 10 year old boy. 1 in every 4 dogs tested had AREF CC17, precursor to VRE CC17.

1. Damborg P, Sorensen AH, Guardabassi L. Monitoring of antimicrobial resistance in healthy dogs:
first report of canine ampicillin-resistant *Enterococcus faecium* clonal complex 17. 2008; 132: 190-196.
2. Damborg P, Top J, Hendrickx AP et al. Dogs are a reservoir of ampicillin-resistant *Enterococcus faecium* lineages associated with human infections.
Applied and Environmental Microbiology 2009; 75: 2360-2365.

Conclusions

- Denmark's ban of avoparcin decreased VRE in pigs and poultry.
- No evidence that EU ban in 2006 decreased VRE in hospitals.
- Evidence that EU ban adversely affected pig meat yield in Europe compared to the US.
- Antibiotic use varies widely between states and countries showing large variations in how medicine is practiced.
- Surveillance must include microbial genomes.
- Antibiotic resistance in pets is potentially an important hidden source of resistance in humans.
- Antibiotic resistance surveillance should include pets.

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http://www.onehealthinitiative.com