One Health and the Politics of Antibiotic Resistance
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One Health and the Politics of Antibiotic Resistance

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Teleclass broadcast sponsored by Virox Technologies Inc.

CME Disclosure

Dr. Laura Kahn is a research scholar with the Program on Science and Global Security, Woodrow Wilson School of Public and International Affairs, Princeton University.

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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.

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

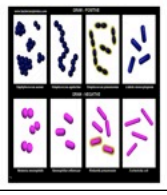
Zoonotic Bacteria

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

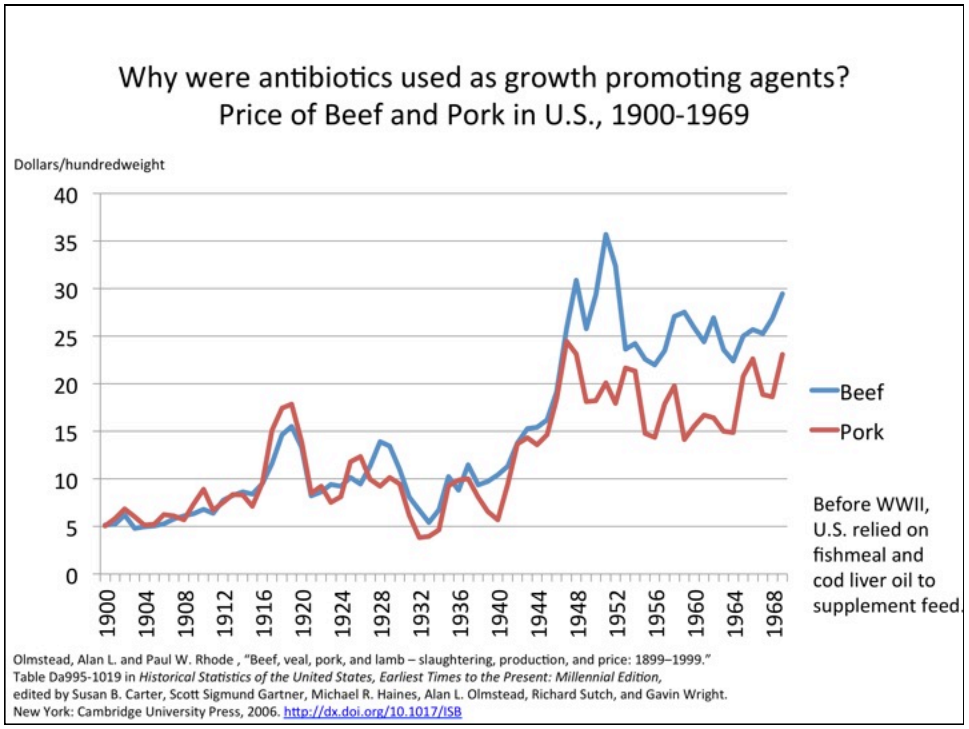
Indicator Bacteria

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



Gram positive: Stain blue
Enterococcus

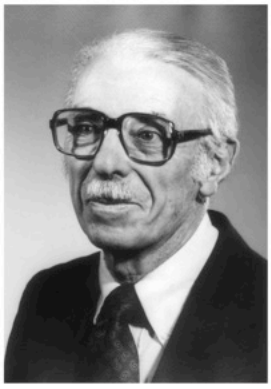


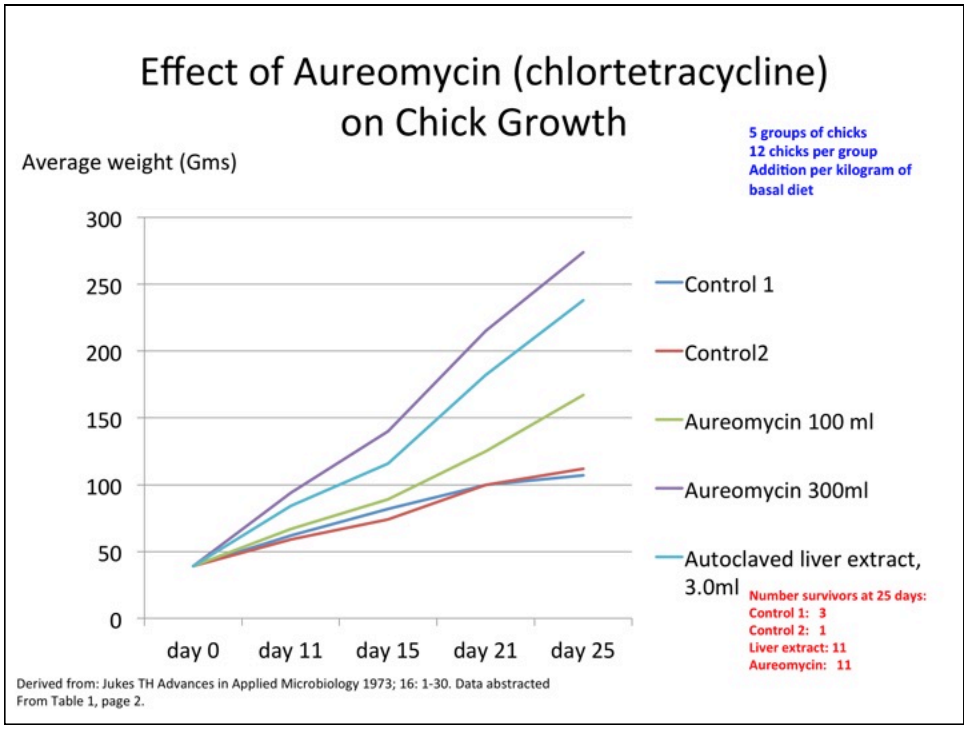
Accidental Discovery of Antibiotics as Growth Promoting Agents in 1940's

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

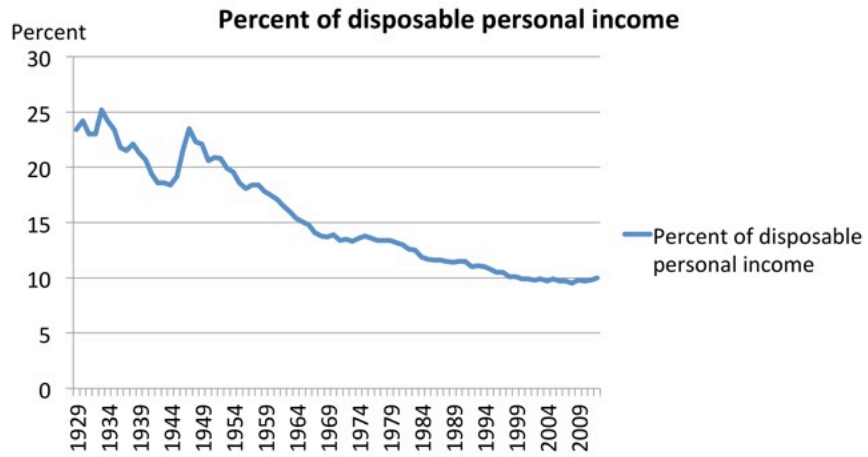




FDA never "approved" antibiotics for growth promotion in livestock

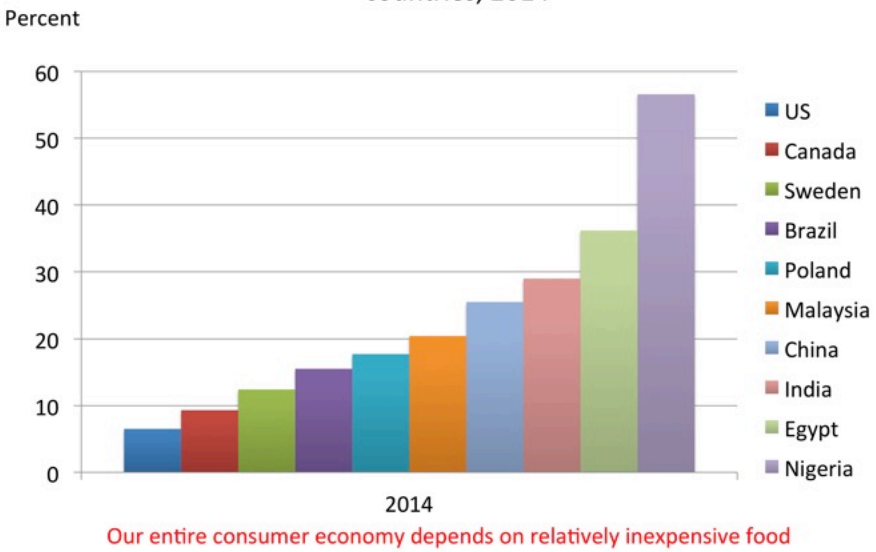
- The Penicillin Amendment of 1945
- Allowed FDA to waive the requirements to ensure the safety and efficacy of penicillin-based drugs if doing so was considered safe.
- Waiver provided FDA the flexibility to approve antibiotics for purposes other than treating infections.
- In 1951 and 1953, respectively, 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

USDA: Percent of consumer expenditures spent on food, alcoholic beverages, and tobacco that were consumed at home by selected countries, 2014



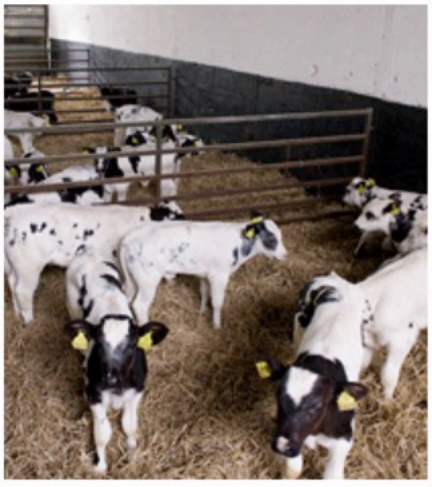
Our entire consumer economy depends on relatively inexpensive food

http://www.ers.usda.gov/data-products/food-expenditures.aspx

Can we have our pork chops and antibiotics too?

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

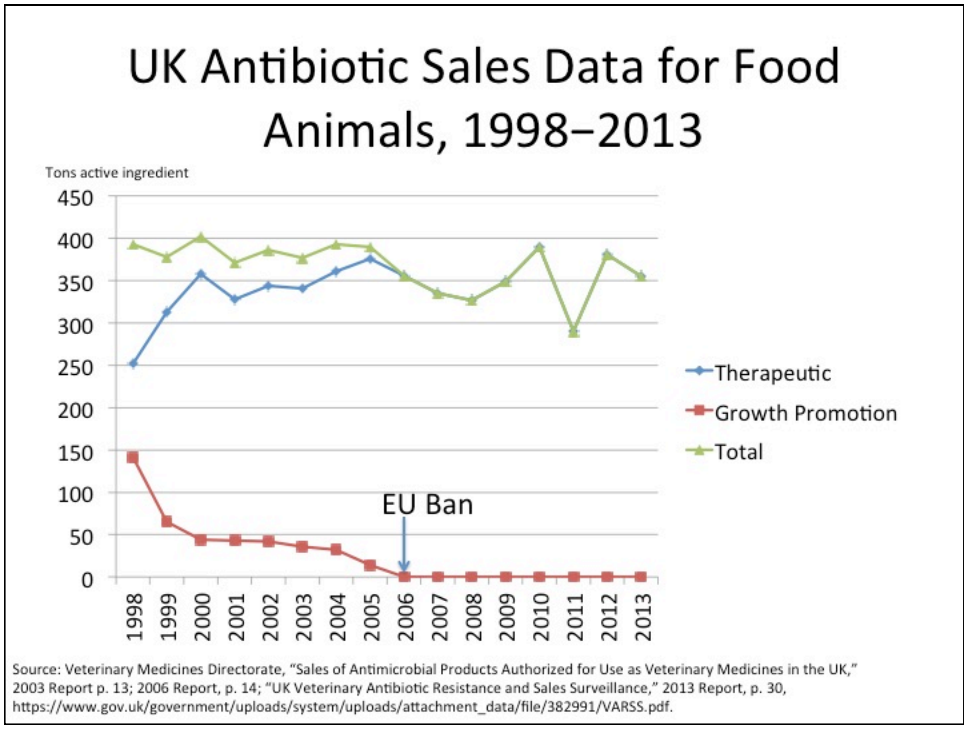
Meredith Michael Swann, PhD (Baron Swann) 1920-1990

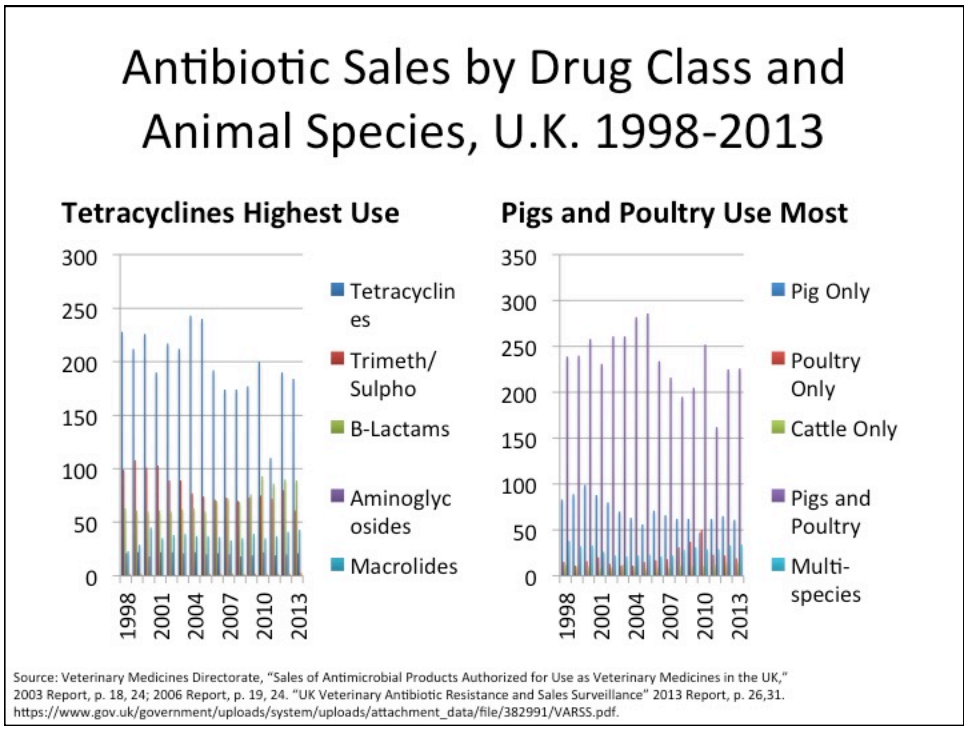
Recommendations

- 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
Tons active ingredient
450
400
350
300
250
200
150
100
50
0
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
EU Ban
Therapeutic
Growth Promotion
Total
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.

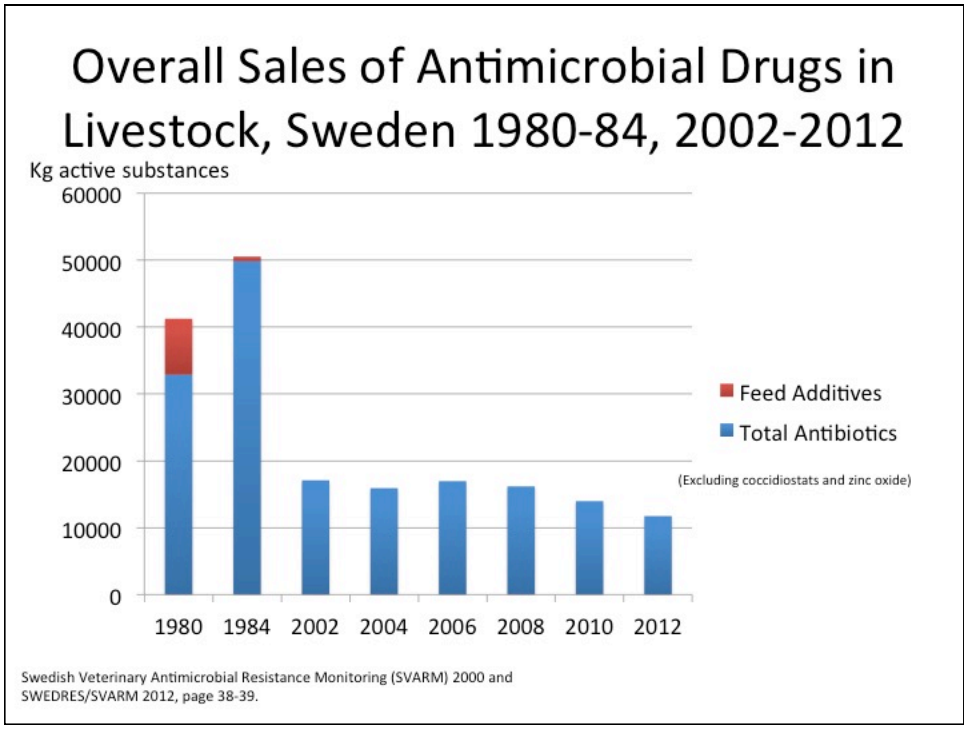

Antibiotic Sales by Drug Class and Animal Species, U.K. 1998-2013
Tetracyclines Highest Use
300
250
200
150
100
50
0
1998
2001
2004
2007
2010
2013
Tetracyclines
Trimeth/ Sulpho
B-Lactams
Aminoglycosides
Macrolides
Pigs and Poultry Use Most
350
300
250
200
150
100
50
0
1998
2001
2004
2007
2010
2013
Pig Only
Poultry Only
Cattle Only
Pigs and Poultry
Multi-species
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.

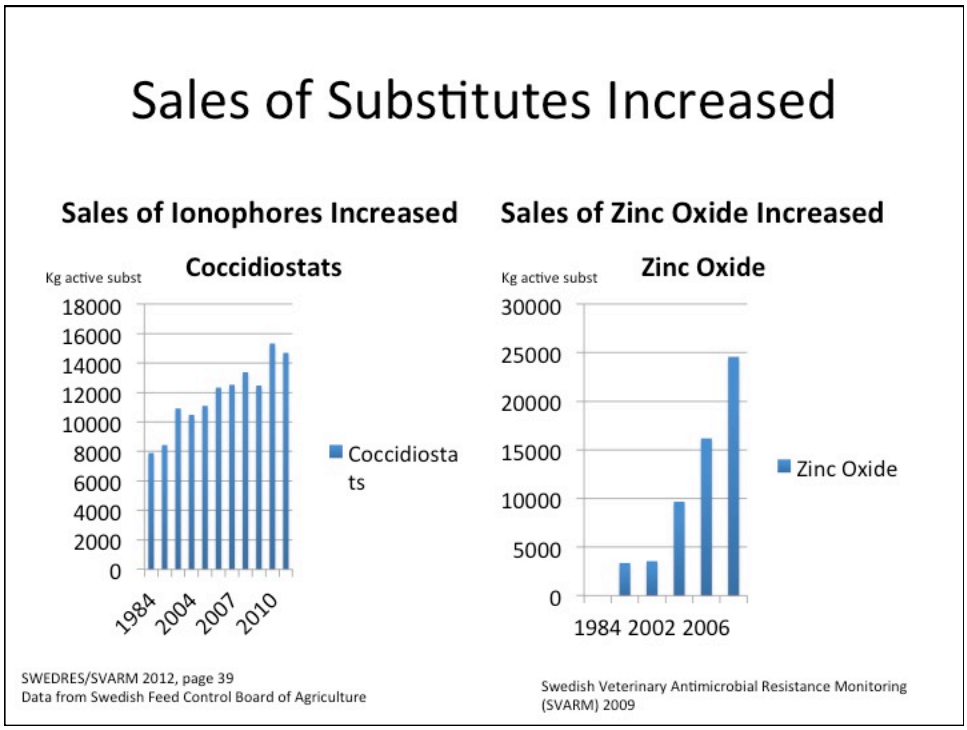
Sweden

- 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.

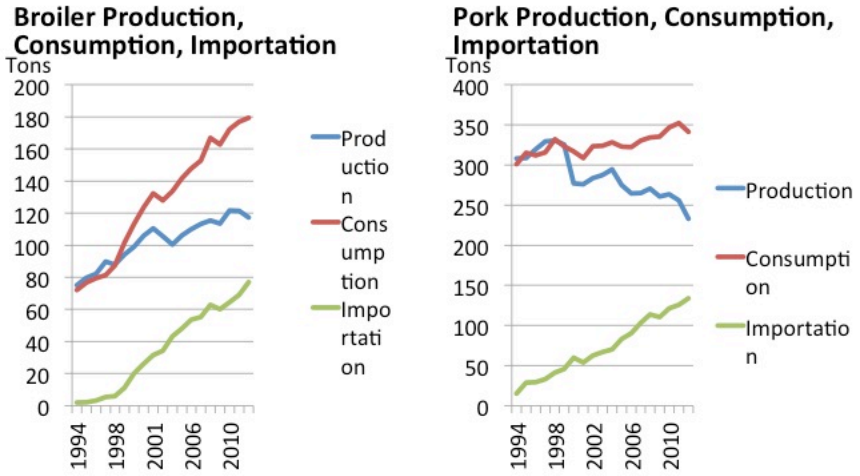
Swedish Farmers Pushed for Ban

- 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
Kg active substances
60000
50000
40000
30000
20000
10000
0
1980
1984
2002
2004
2006
2008
2010
2012
Feed Additives
Total Antibiotics
(Excluding coccidiostats and zinc oxide)
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2000 and SWEDRES/SVARM 2012, page 38-39.


Sales of Substitutes Increased
Sales of Ionophores Increased
Coccidiostats
Kg active subst
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
1984
2004
2007
2010
Coccidiosta ts
SWEDRES/SVARM 2012, page 39
Data from Swedish Feed Control Board of Agriculture
Sales of Zinc Oxide Increased
Zinc Oxide
Kg active subst
30000
25000
20000
15000
10000
5000
0
1984 2002 2006
Zinc Oxide
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2009

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



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 and used in Europe since the early 1970's, 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*

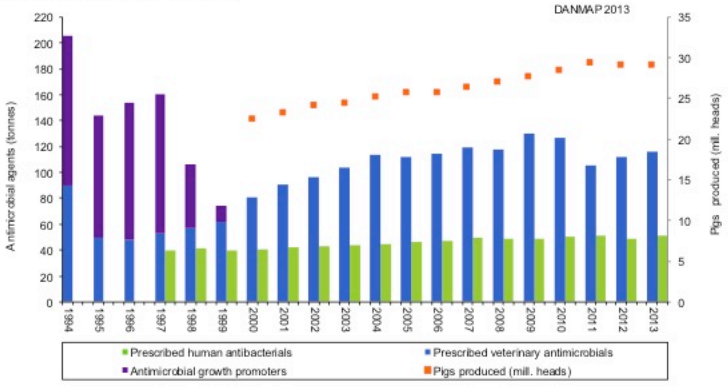
Denmark

- 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.

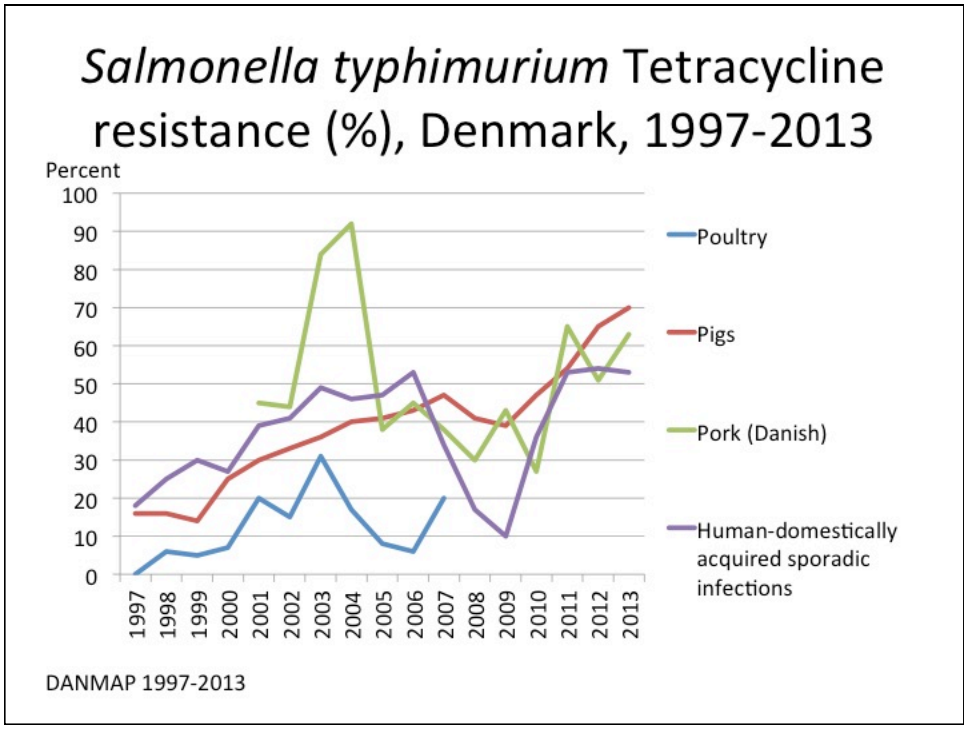
Danish Growth Promoter Ban

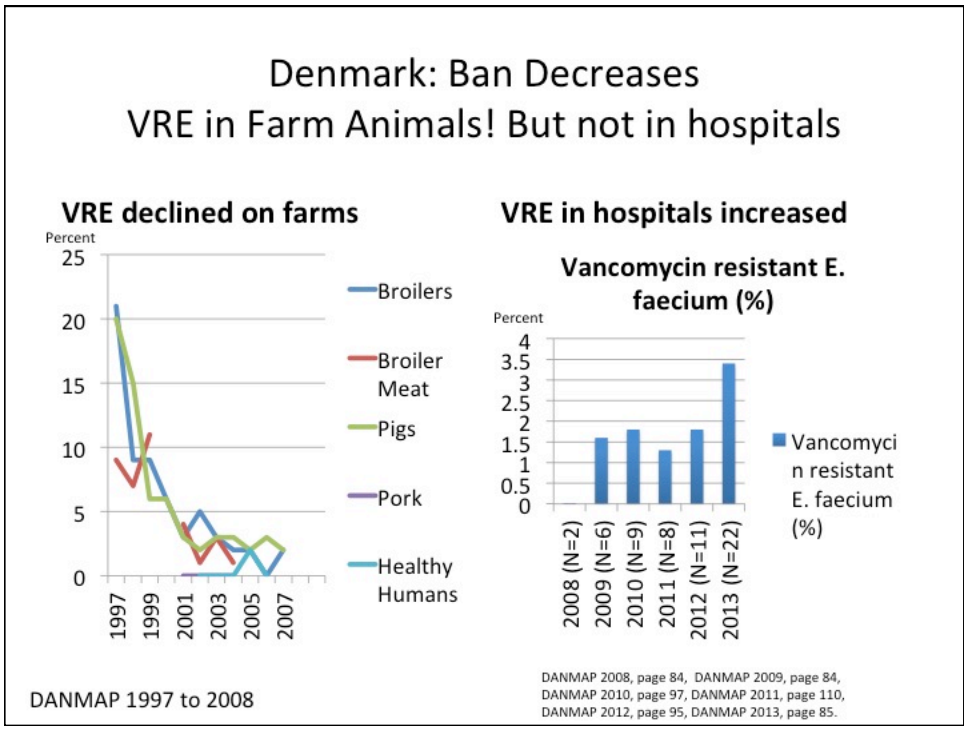
- Farmers voluntarily stopped using avoparcin in May 1995.
- In 1997, the EU banned avoparcin.
- 1998, Denmark banned virginiamycin, another growth promoting antibiotic, related to quinupristin/dalfopristin, an antibiotic used to treat VRE.
- 1999, Danish farmers stopped using *all* antibiotic growth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

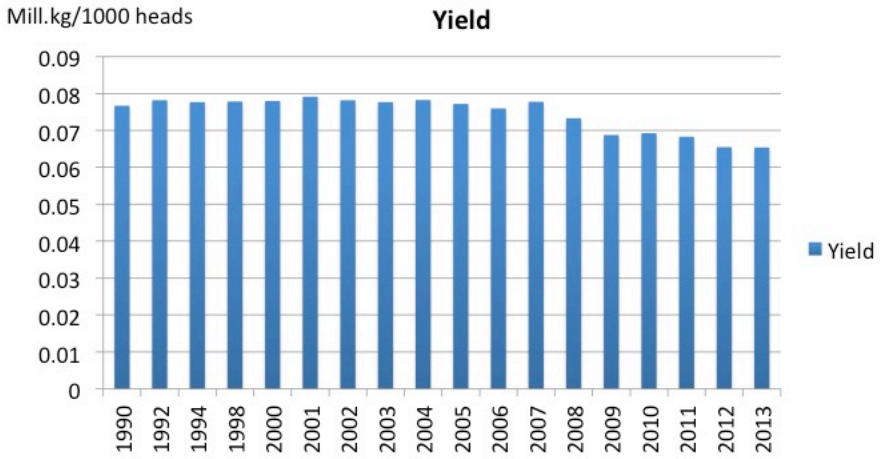


Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate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


Salmonella typhimurium Tetracycline resistance (%), Denmark, 1997-2013
Percent
100
90
80
70
60
50
40
30
20
10
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Poultry
Pigs
Pork (Danish)
Human-domestically acquired sporadic infections
DANMAP 1997-2013

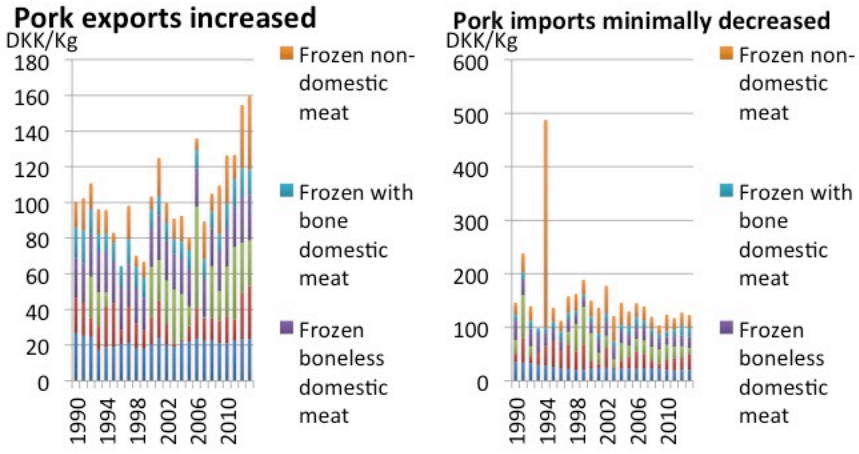

Denmark: Ban Decreases
VRE in Farm Animals! But not in hospitals
VRE declined on farms
Percent
25
20
15
10
5
0
1997
1999
2001
2003
2005
2007
Broilers
Broiler Meat
Pigs
Pork
Healthy Humans
DANMAP 1997 to 2008
VRE in hospitals increased
Vancomycin resistant E. faecium (%)
Percent
4
3.5
3
2.5
2
1.5
1
0.5
0
2008 (N=2)
2009 (N=6)
2010 (N=9)
2011 (N=8)
2012 (N=11)
2013 (N=22)
Vancomycin resistant E. faecium (%)
DANMAP 2008, page 84, DANMAP 2009, page 84,
DANMAP 2010, page 97, DANMAP 2011, page 110,
DANMAP 2012, page 95, DANMAP 2013, page 85.

Pig meat yield (mill.kg/1000 heads), Denmark, 1990-2013



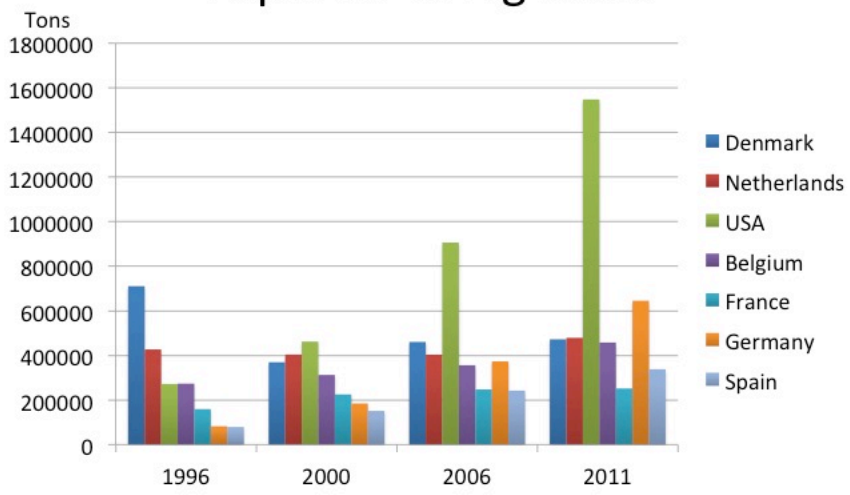
DANMAP 2013, Page 21, Table 3.1

Danish pork exports and imports do not appear adversely affected by ban



Statistics Denmark; does not include processed swine meat.
DKK = Danish Krone

Denmark No Longer World's Top Exporter of Pig Meat

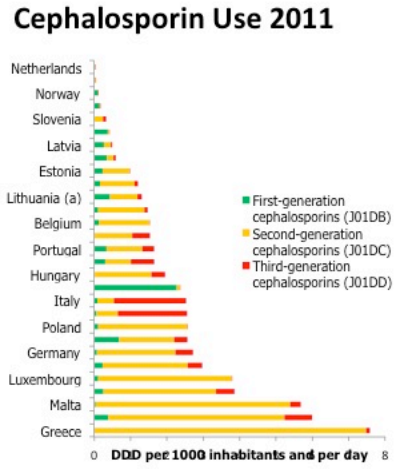


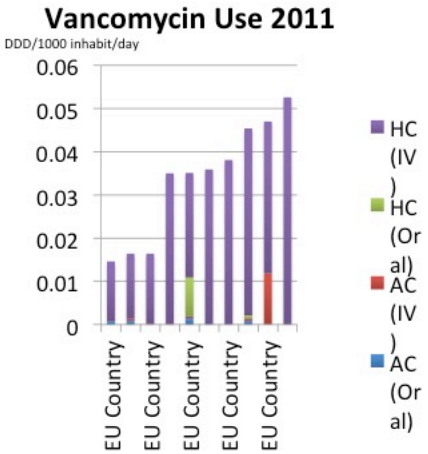
FAOSTAT: Exports. Countries by commodity http://faostat.fao.org/site/342/default.aspx

European Union

- 2003, European Parliament passed regulations prohibiting all antibiotics as growth promoters.
- Used Precautionary Principle to set policy.
- 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

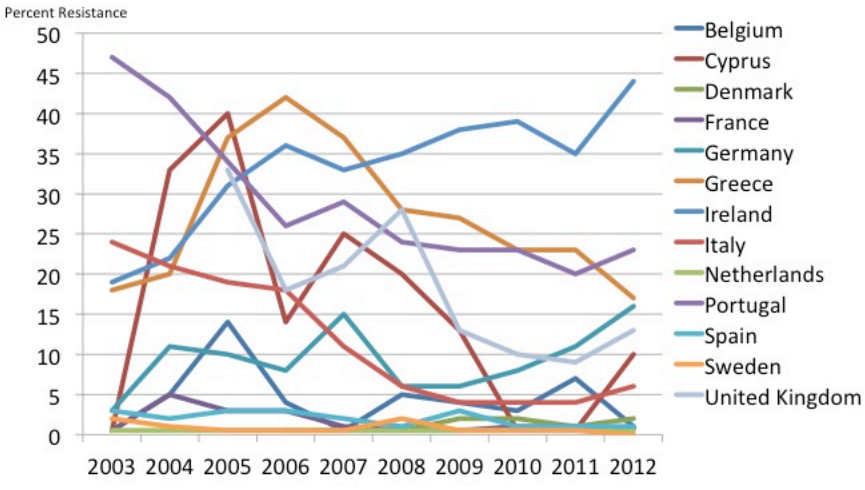




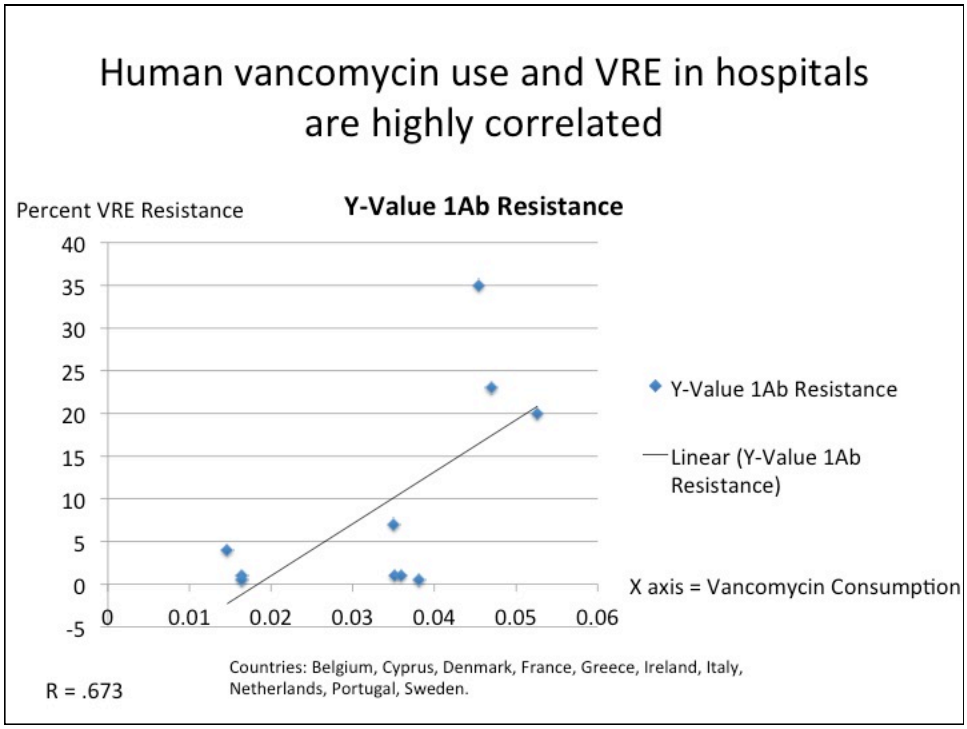
ECDC Surveillance Report 2011, Page 24, Table 3.12.

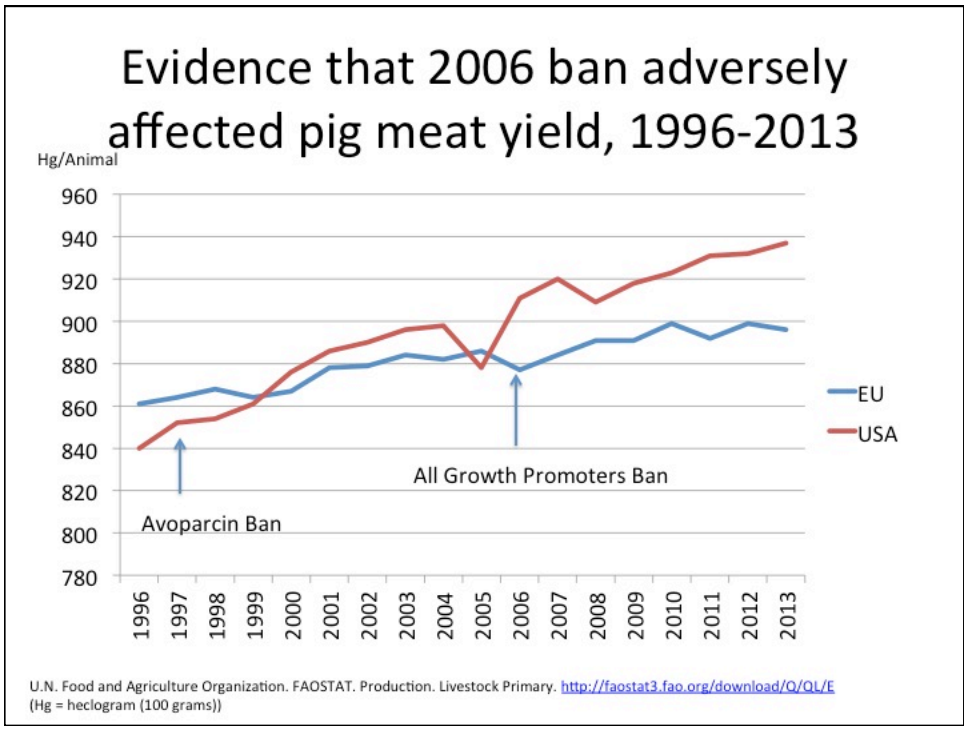
Courtesy of ECDC TESSy Data Access Team, Surveillance of Antimicrobial Consumption in Europe.
Names of countries removed at request of ECDC

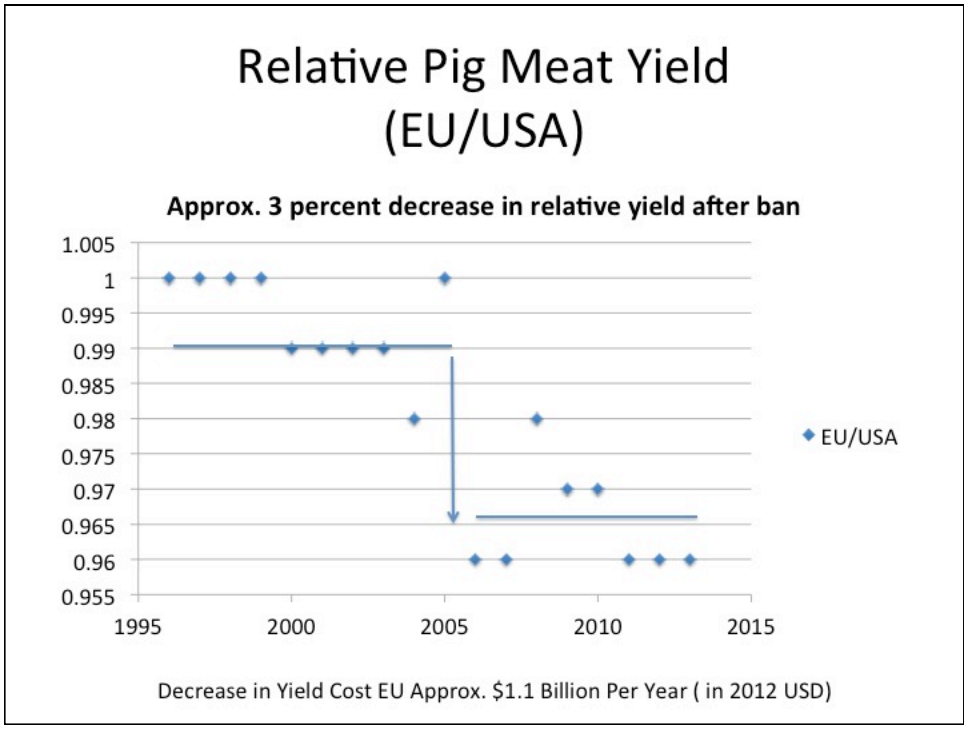
No consistent trend in VRE isolates from hospitalized humans after 1997 EU avoparcin ban

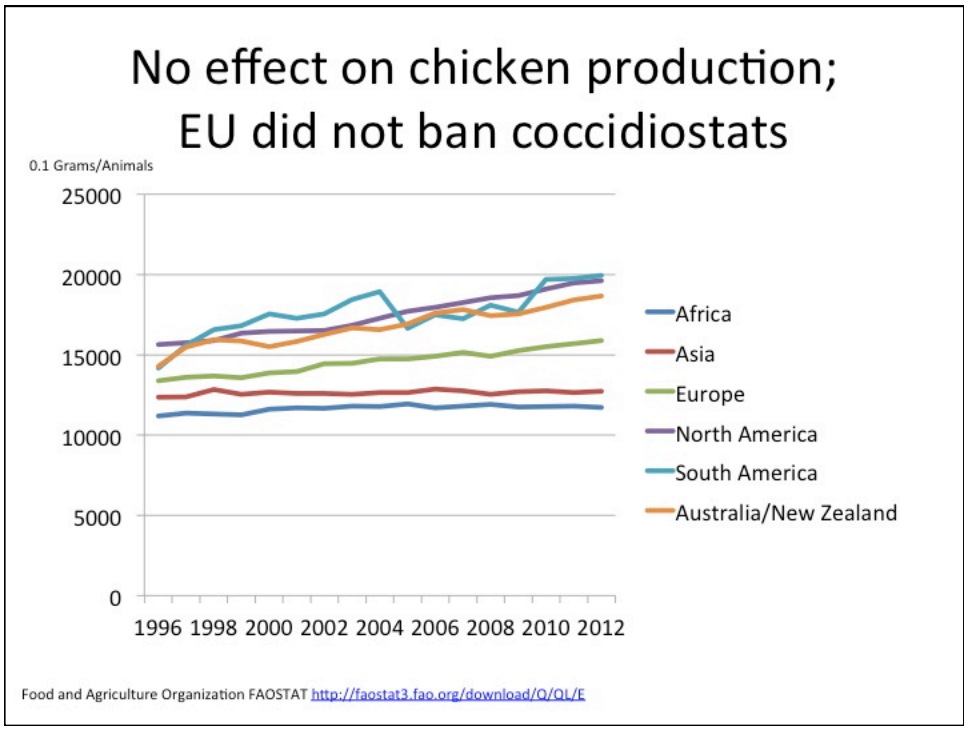


Data derived from Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-NET), 2012. Country summary sheets, Pgs 83-202.


Human vancomycin use and VRE in hospitals are highly correlated
Percent VRE Resistance
Y-Value 1Ab Resistance
40
35
30
25
20
15
10
5
0
-5
0
0.01
0.02
0.03
0.04
0.05
0.06
Y-Value 1Ab Resistance
Linear (Y-Value 1Ab Resistance)
X axis = Vancomycin Consumption
R = .673
Countries: Belgium, Cyprus, Denmark, France, Greece, Ireland, Italy, Netherlands, Portugal, Sweden.


Evidence that 2006 ban adversely affected pig meat yield, 1996-2013
Hg/Animal
960
940
920
900
880
860
840
820
800
780
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
EU
USA
All Growth Promoters Ban
Avoparcin Ban
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)
Approx. 3 percent decrease in relative yield after ban
1.005
1
0.995
0.99
0.985
0.98
0.975
0.97
0.965
0.96
0.955
1995
2000
2005
2010
2015
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
0.1 Grams/Animals
25000
20000
15000
10000
5000
0
1996 1998 2000 2002 2004 2006 2008 2010 2012
Africa
Asia
Europe
North America
South America
Australia/New Zealand
Food and Agriculture Organization FAOSTAT http://faostat3.fao.org/download/Q/QL/E

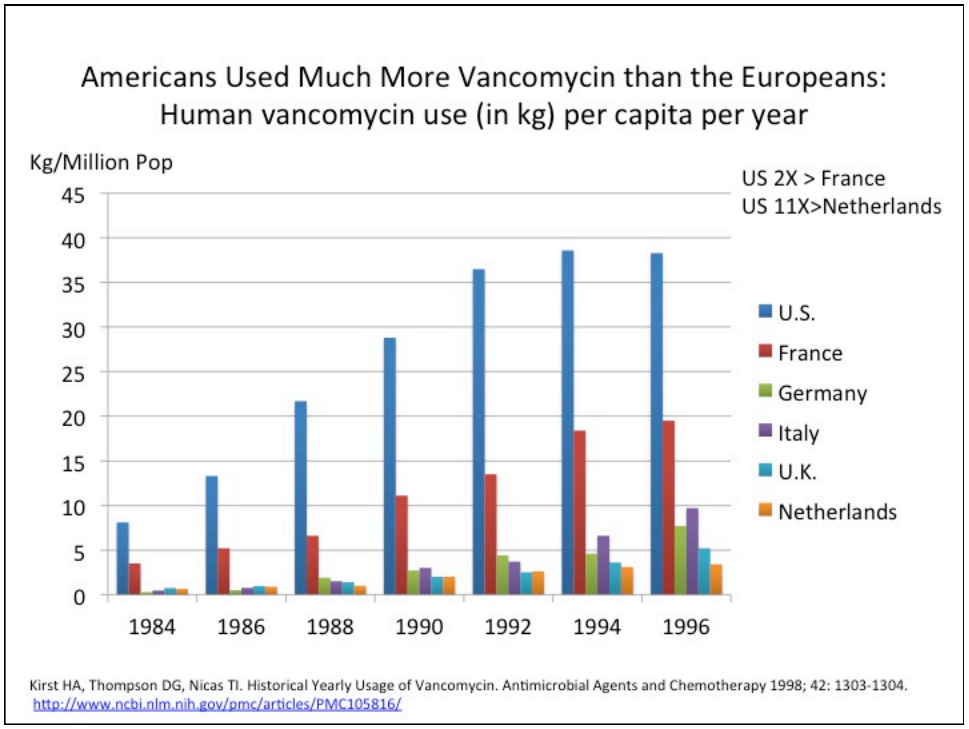
United States

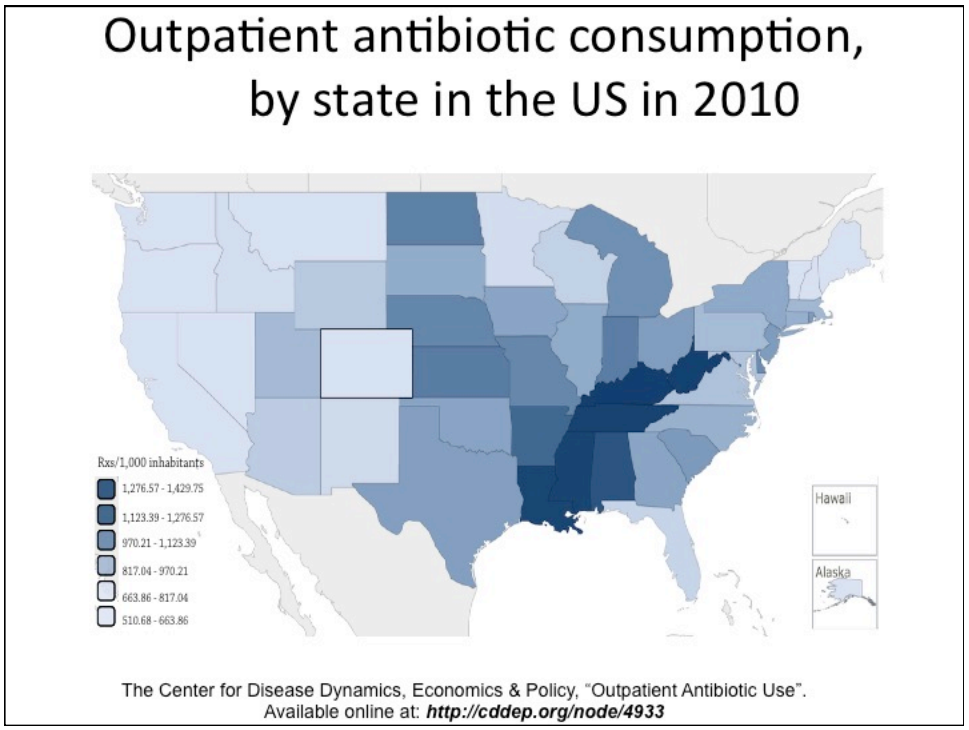
- US never approved avoparcin because of concerns about its carcinogenicity, so epidemiology of VRE has been different compared to Europe.
- Congress has spent decades debating the risks of growth promoting antibiotics.
- Consistently concluded that more data was needed, but never appropriated resources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

VRE in U.S.

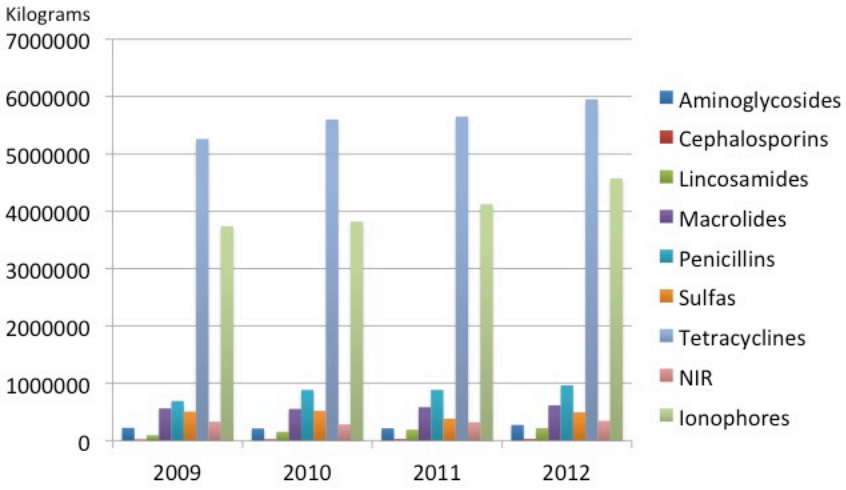
- VRE in US emerged in 1990's in hospitals.
- Preceded spread in European hospitals by about a decade even though first few cases reported in Europe.
- CDC estimates that 77% of US healthcare-associated infections due to *Enterococcus faecium* are resistant to vancomycin.*
- CDC estimates approximately 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
Kg/Million Pop
45
40
35
30
25
20
15
10
5
0
1984
1986
1988
1990
1992
1994
1996
US 2X > France
US 11X>Netherlands
U.S.
France
Germany
Italy
U.K.
Netherlands
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
Rxs/1,000 inhabitants
1,276.57 - 1,429.75
1,123.39 - 1,276.57
970.21 - 1,123.39
817.04 - 970.21
663.86 - 817.04
510.68 - 663.86
Hawaii
Alaska
The Center for Disease Dynamics, Economics & Policy, "Outpatient Antibiotic Use".
Available online at: http://cddep.org/node/4933

Food-Producing Animals Primarily Use 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* 2003 (2216)	2006 (1500)	%Δ	Chicken Meat** 2002 (134)	2011 (186)	%Δ	Pork Chops 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.p
( ) =Total number of isolates tested.

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

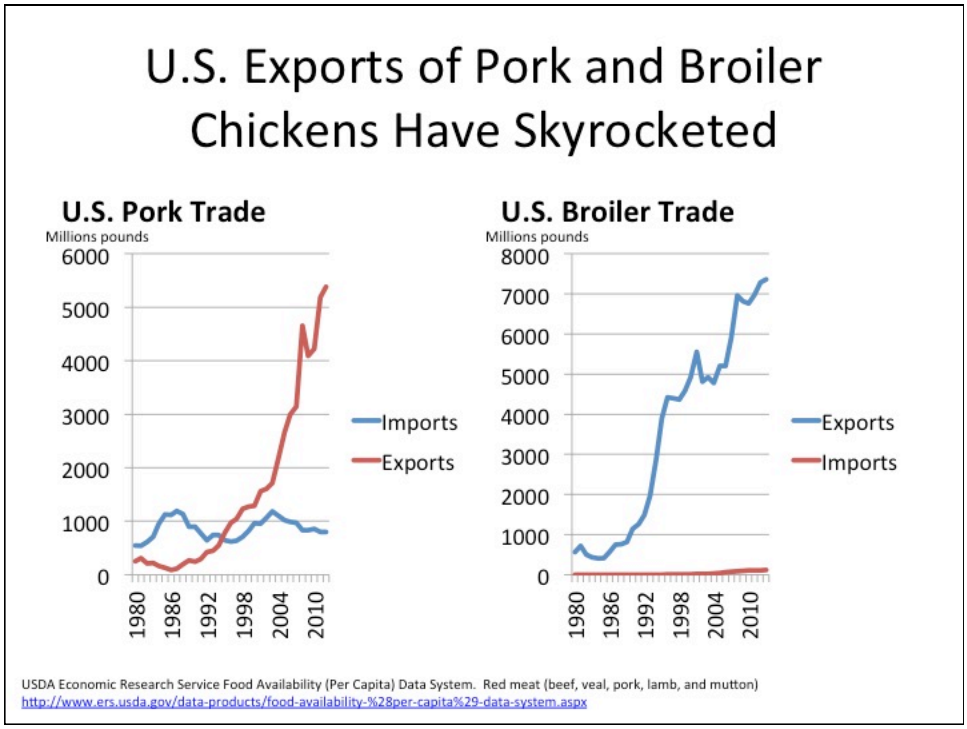
Antibiotic	2006 (857)*	%	2012 (563)*	%	Change
Vancomycin	0	0	0	0	0
Linezolid	0	0	0	0	0

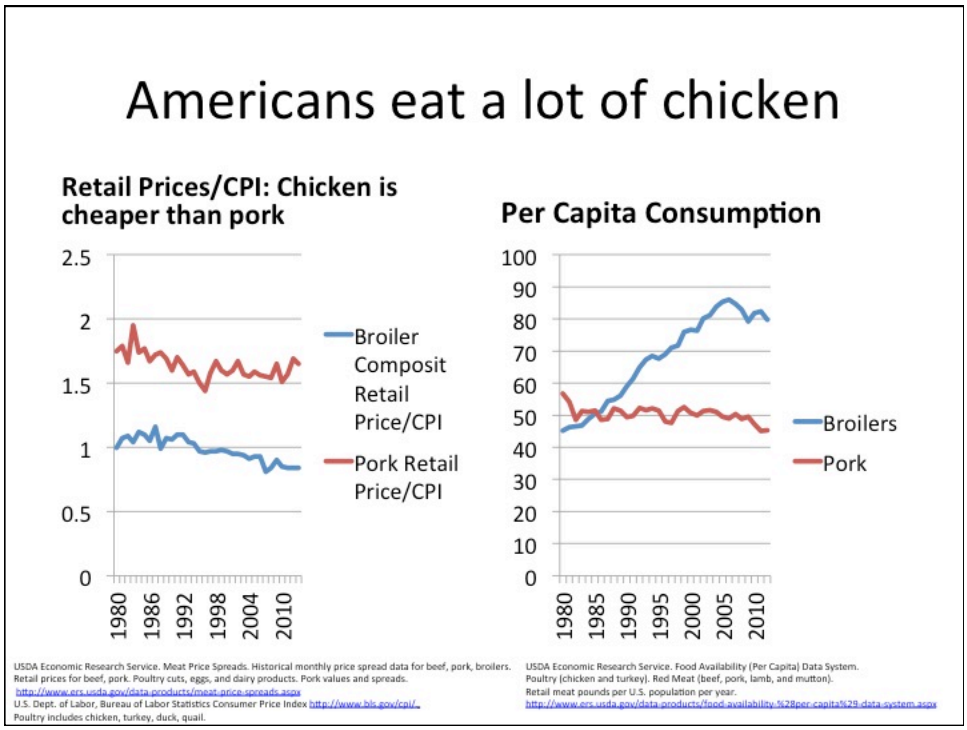
*( )= total number isolates tested.
USDA APHIS Commensal Enterococcus on U.S. Swine Sites: Prevalence and Antimicrobial Drug Susceptibility. April 2009.
Enterococcus species included: *E. hirae (29.6%), E. faecalis (27.4%), E. species not identified (16%), E. faecium (7.9%), E. mundtii (7.7%), E. casseliflavus (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
U.S. Pork Trade
Millions pounds
6000
5000
4000
3000
2000
1000
0
1980
1986
1992
1998
2004
2010
Imports
Exports
U.S. Broiler Trade
Millions pounds
8000
7000
6000
5000
4000
3000
2000
1000
0
1980
1986
1992
1998
2004
2010
Exports
Imports
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
2.5
2
1.5
1
0.5
0
1980
1986
1992
1998
2004
2010
Broiler Composit Retail Price/CPI
Pork Retail Price/CPI
Per Capita Consumption
100
90
80
70
60
50
40
30
20
10
0
1980
1985
1990
1995
2000
2005
2010
Broilers
Pork
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

- Unclear why Europe approved avoparcin in the early 1970's.
- Banned avoparcin after rise of VRE in food animals.
- Almost all VRE *vanA**
- Banned all antibiotic growth promoting agents using Precautionary Principle.
- Evidence that total ban adversely affected pig meat production.
- No evidence that avoparcin ban decreased VRE in hospitalized humans.

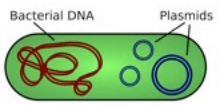
USA

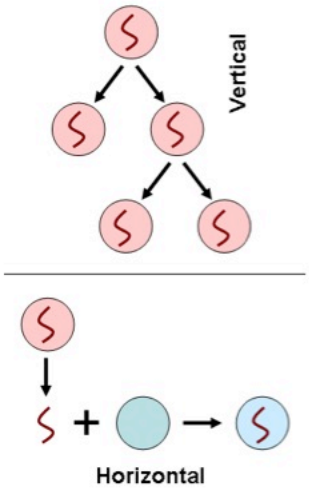
- Never approved avoparcin because of cancer concerns. (Precautionary Principle)
- Very high vancomycin use in hospitals
- VRE appeared in hospitalized patients about a decade before widespread in Europe.
- 70% *vanA* and 25% *vanB**
- No evidence that VRE came from US livestock.
- Needed better data to do proper risk analysis before making any decisions.
- Implemented voluntary measures to stop using growth promoting antibiotics.

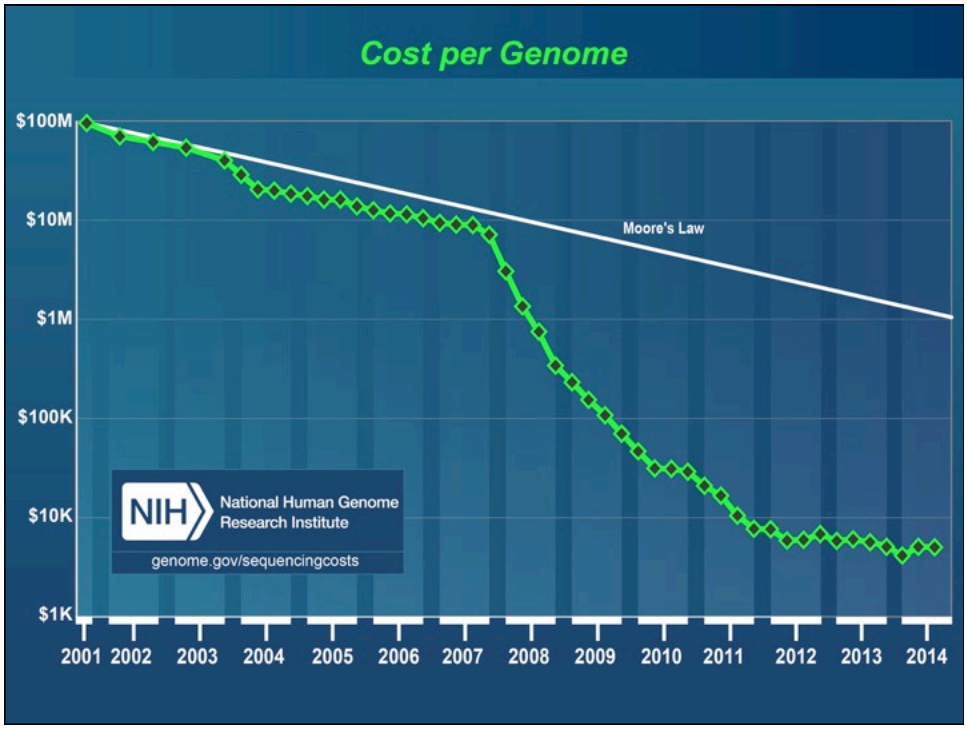
*Acar J, Casewell M, Freeman J, et al. Avoparcin and virginiamycin as animal growth promoters: a plea for science in decision-making. Clinical Microbiology and Infection. Sept. 2000 6(9): 477-482.

Confusing epidemiology of resistant bacteria: horizontal versus vertical gene transmission

- Until 2008, analysis of resistant microbes focused on resistance genes on plasmids.
- Horizontal transmission: exchange of genetic material between microbial contemporaries.
- *vanA*, *vanB*, *vanD* acquired resistance genes spread among VRE.
- Cost of genome sequencing cost $10 million per genome.
- After 2008, cost plummeted.
- Allowed sequencing of microbial genomes.
- Vertical transmission (parent to offspring) of genetic material.
- Genomic data revealed surprising findings.





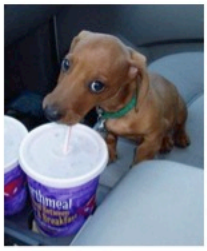


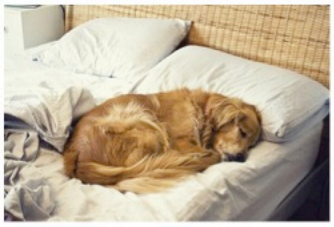
VRE genomic data suggests a surprising culprit

- 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.

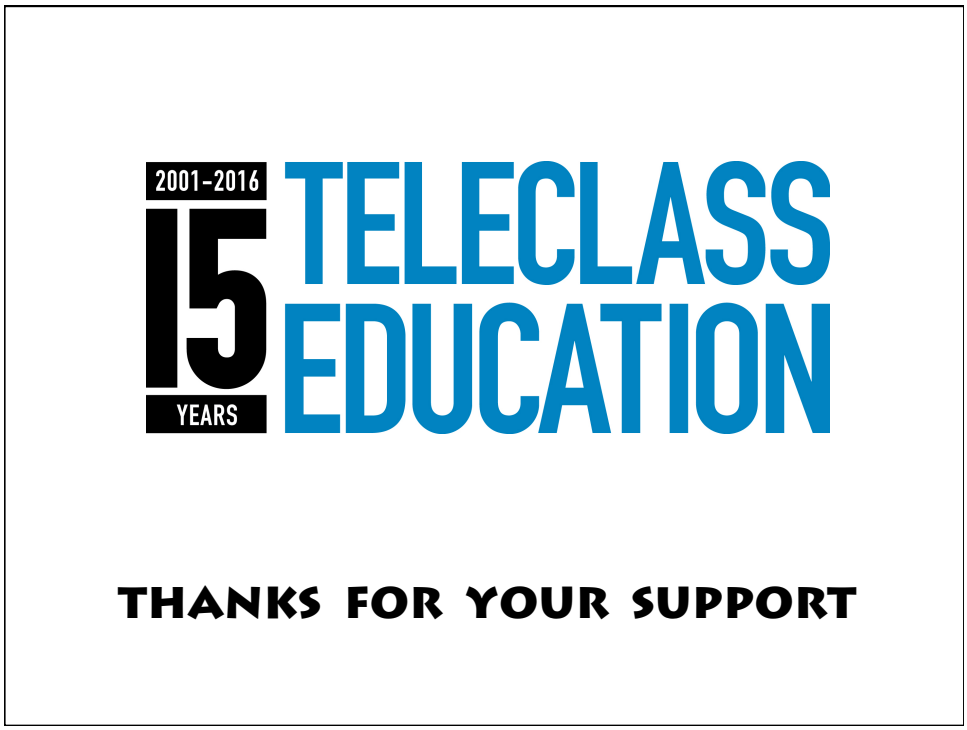
Conclusions

- 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.

- One Health Initiative *pro bono* team:
  - Bruce Kaplan, DVM
  - Tom Monath, MD
  - Jack Woodall, PhD
  - Lisa Conti, DVM, MPH

http://www.onehealthinitiative.com

One Health and the Politics of Antibiotic Resistance
Laura H. Kahn, Princeton University
Broadcast live from the 2016 IPAC-Canada Conference



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