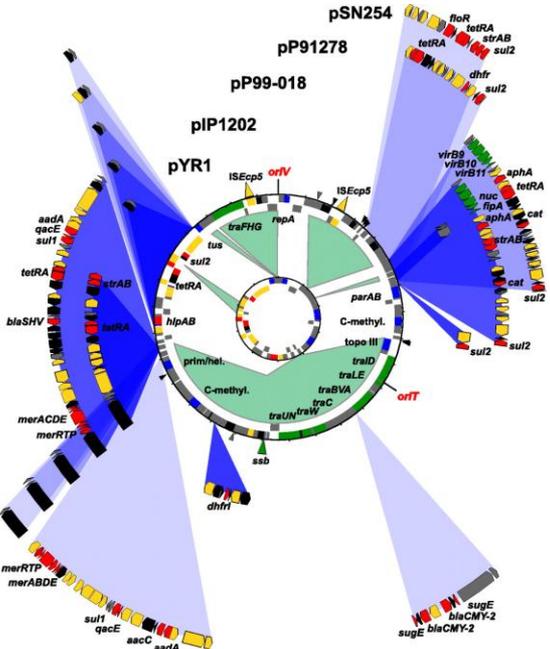
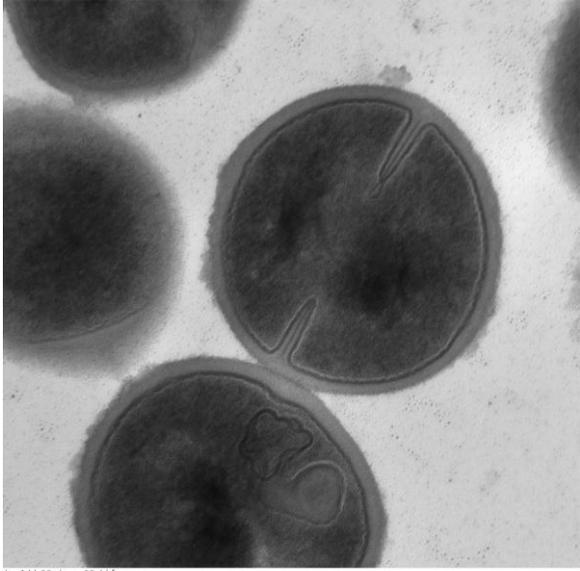


# Bacterial Antibiotic Resistance, Food Animal Production, and Human Health: No Simple Answer at The Interface of Three Complex Systems



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



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Direct Mag: 35000x



John W. Schmidt, Ph. D.  
 United States Department of Agriculture  
 Agricultural Research Service  
 United States Meat Animal Research Center

# Infectious Disease and Antibiotics

- Infectious diseases remain the second-leading cause of death worldwide and third leading cause of death in the US.
- 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.”

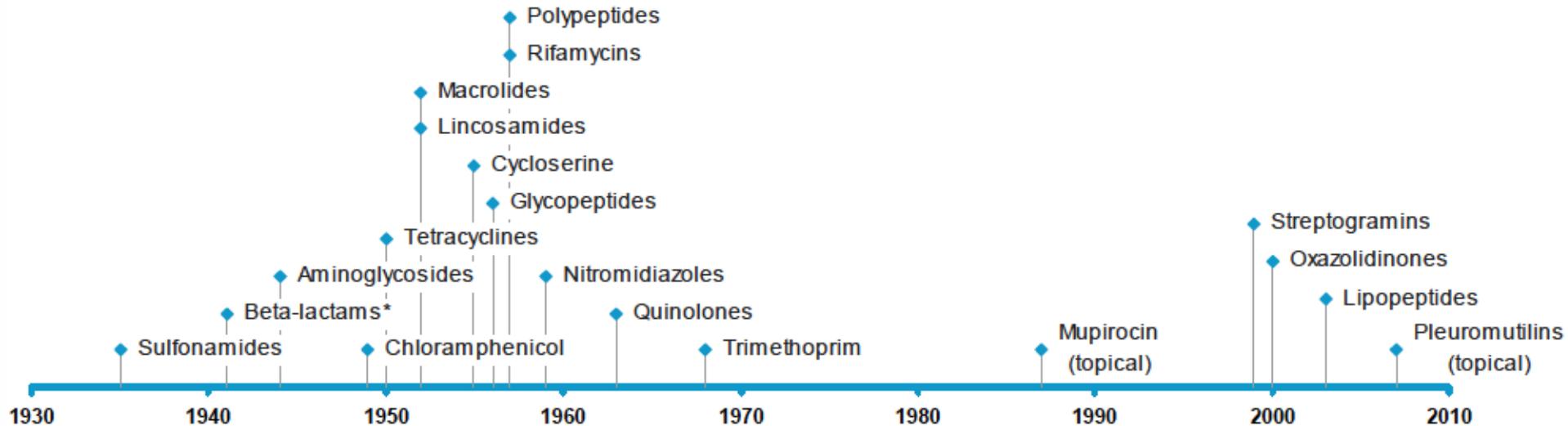
# Overused Introductory Slide at Microbiology Conferences

## *The History of Medicine*

- 2000 B.C. – Here, eat this root.
- 1000 A.D. – That root is heathen. Here, say this prayer.
- 1850 A.D. – That prayer is superstition. Here, drink this potion.
- 1920 A.D. – That potion is snake oil. Here, swallow this pill.
- 1945 A.D. – That pill is ineffective. Here, take this penicillin.
- 1955 A.D. – Oops....bugs mutated. Here, take this tetracycline.
- 1956 - present – 39 more "oops"...Here, take this more powerful antibiotic.
- 2020 A.D.? – The bugs have won! Here, eat this root.

# 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.).

# **No Novel Classes of Antibiotics Forthcoming**

- **Thus, the challenge of antibiotic resistant infections will be met by:**
  - 1. Preserving the effectiveness of existing antibiotics.**
  - 2. Monitoring antibiotic resistance.**
  - 3. Increasing scientific understanding of the processes contributing to the prevalence of antibiotic resistant infections.**

# Bacterial Antibiotic Resistance

- 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<sup>1,2\*</sup>, Christine E. King<sup>3,4\*</sup>, Lindsay Kalan<sup>1,2</sup>, Mariya Morar<sup>1,2</sup>, Wilson W. L. Sung<sup>4</sup>, Carsten Schwarz<sup>3</sup>, Duane Froese<sup>5</sup>, Grant Zazula<sup>6</sup>, Fabrice Calmels<sup>5</sup>, Regis Debruyne<sup>7</sup>, G. Brian Golding<sup>4</sup>, Hendrik N. Poinar<sup>1,3,4</sup> & Gerard D. Wright<sup>1,2</sup>

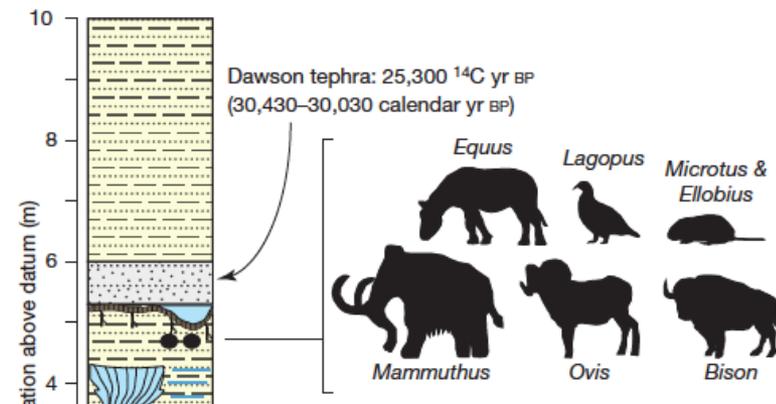
The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes<sup>1,2</sup>. This history has been interpreted to mean that antibiotic 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<sup>3</sup>. 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  $\beta$ -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.

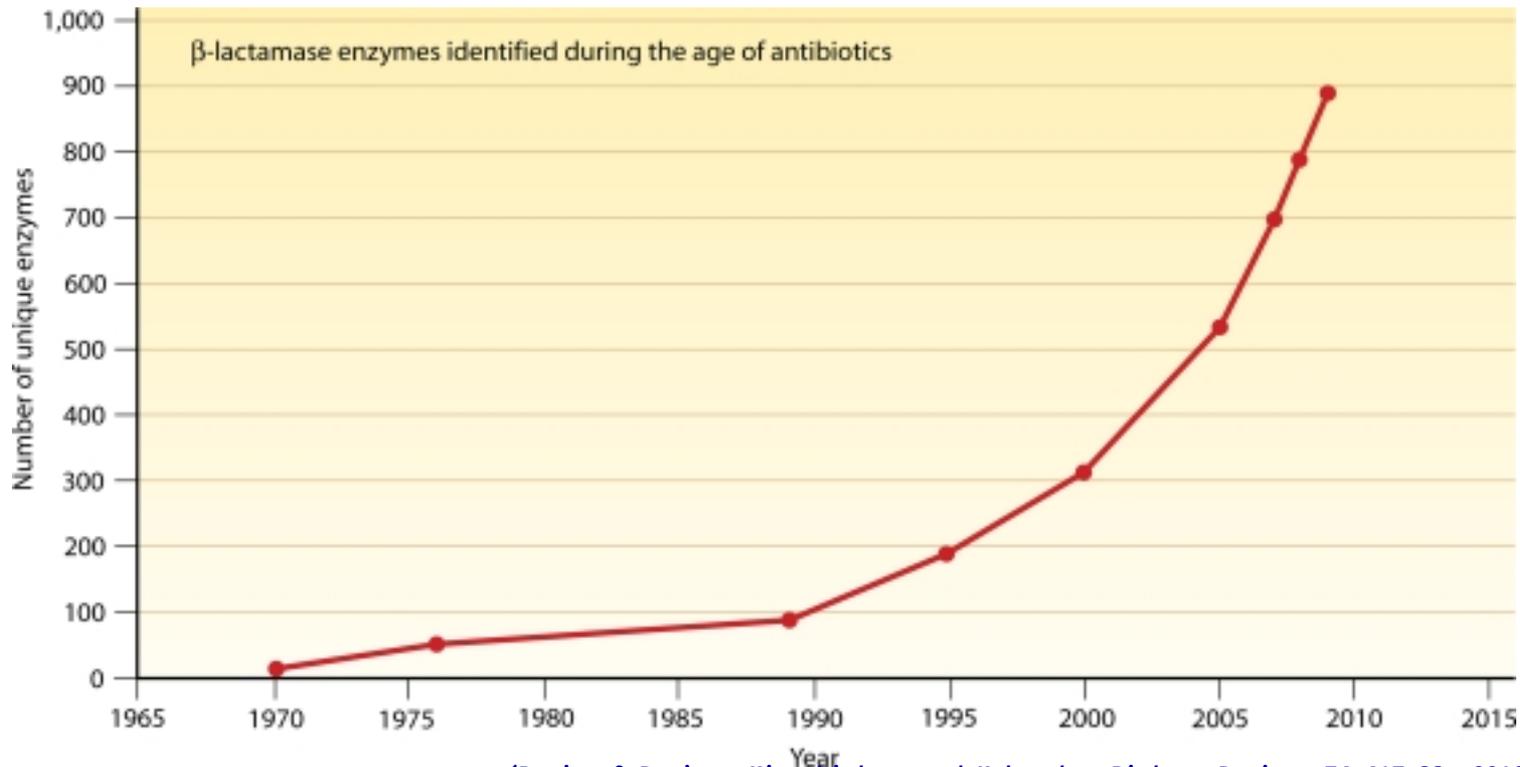
Recent studies of modern environmental and human commensal microbial genomes have a much larger concentration of antibiotic resistance genes than has been previously recognized<sup>4–6</sup>. In addition,

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

After fracturing 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



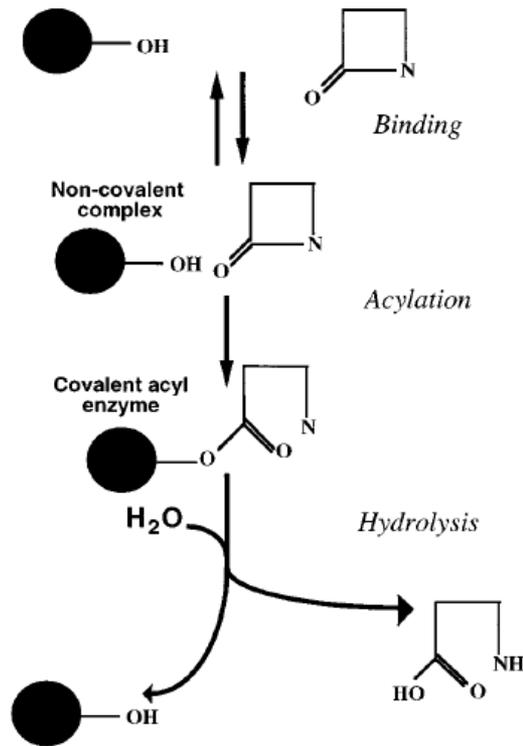
# Antibiotic Resistance is Diverse



- **Greater than 900 β-lactamase enzymes alone.**
- **Bacteria outnumber us by a factor of  $\sim 10^{22}$  and have a 3.5 billion year head start.**

# Antibiotic Resistance Mechanisms (Simplified)

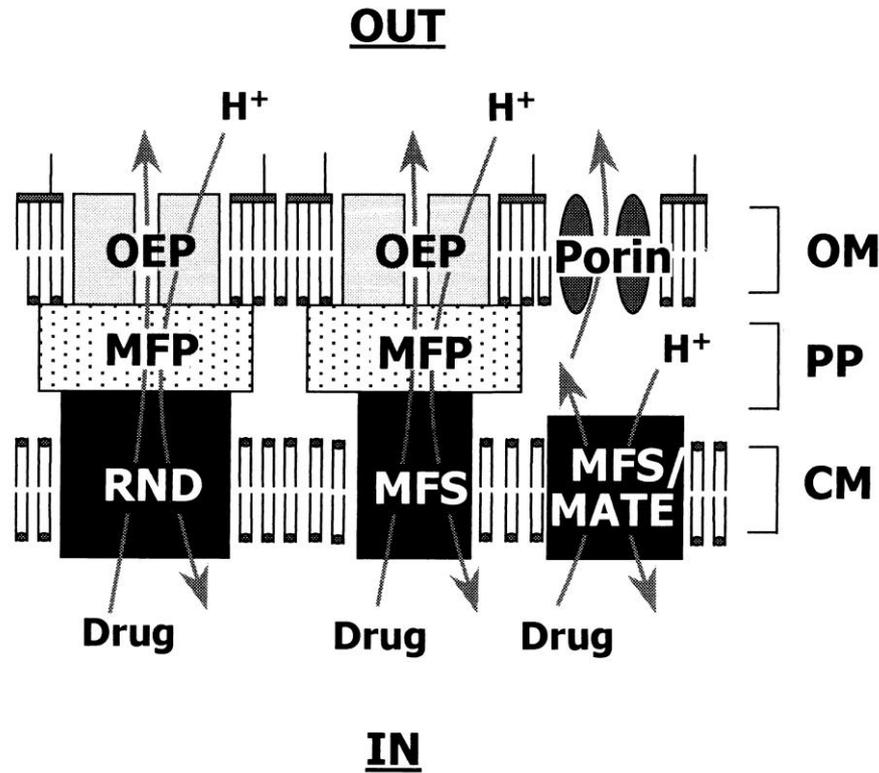
- Antibiotic resistance occurs by four general processes:
  - Inactivation of the antibiotic (e.g.  $\beta$ -lactamase).



(Livermore, *Clinical Microbiology Reviews* 8:557-84, 1995)

# Antibiotic Resistance Mechanisms (Simplified)

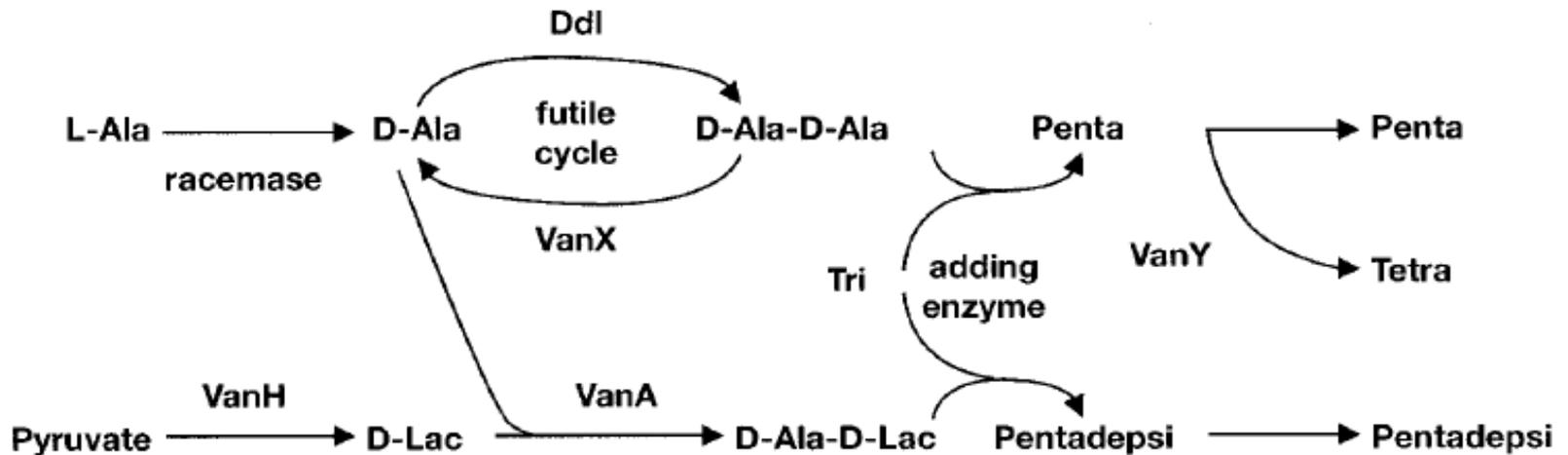
- Antibiotic resistance occurs by four general processes:
  1. Inactivation of the antibiotic ( $\beta$ -lactamase).
  2. Removal of the antibiotic from cell (Efflux pumps).



(Poole, Antimicrob. Agents Chemother.44:2233-41, 2000)

# Antibiotic Resistance Mechanisms (Simplified)

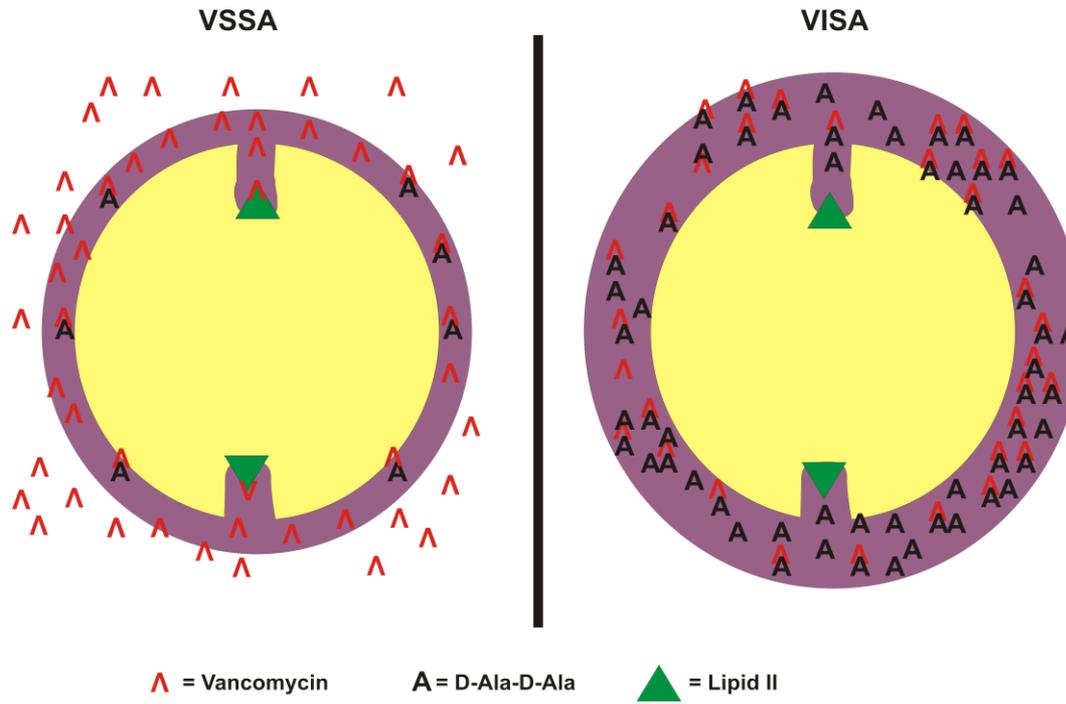
- Antibiotic resistance occurs by four general processes:
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  2. Removal of the antibiotic from cell (Efflux pumps).
  3. Alteration of of the antibiotic target (**VanA vancomycin resistance**).



(Courvalin, *Clinical Infectious Diseases* 42:S25-S34, 2006)

# Antibiotic Resistance Mechanisms (Simplified)

- Antibiotic resistance occurs by four general processes:
  1. Inactivation of the antibiotic ( $\beta$ -lactamase).
  2. Removal of the antibiotic from cell (Efflux pumps).
  3. Alteration of of the antibiotic target (VanA vancomycin resistance).
  4. Increased production of the antibiotic target (VISA vancomycin resistance).



# How Is Resistance Conferred?

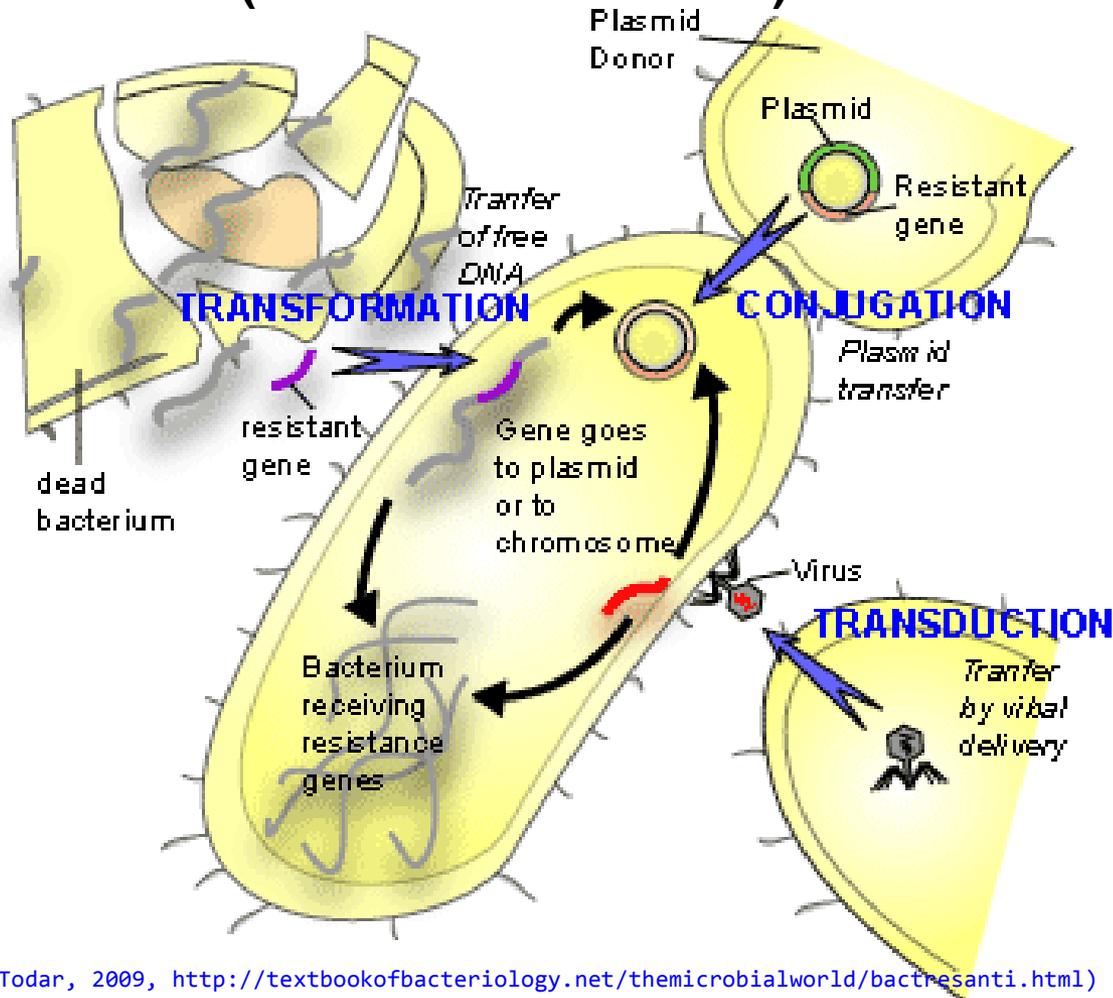
- **Mutation of endogenous genes (or “spontaneous mutation”).**
  - **Single point mutation in *gyrA* confers nalidixic acid resistance.**
  - **Antibiotic resistance in *M. tuberculosis* (TB) occurs exclusively by mutation of endogenous genes.**

*or*

- **Acquisition of exogenous genes encoding resistance, known as Horizontal Gene Transfer (HGT).**

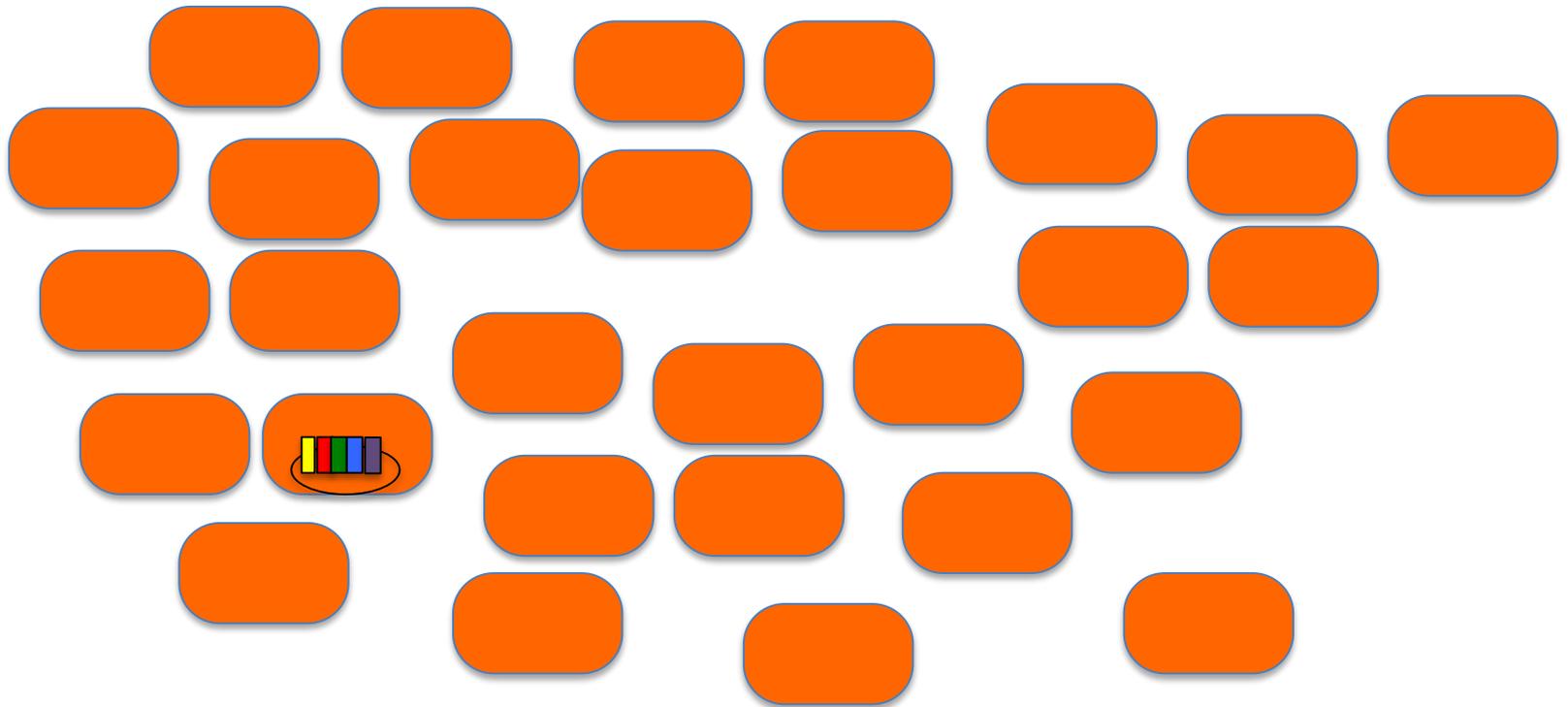
# Horizontal Gene Transfer

- HGT occurs by three general methods.
  - Conjugation (Plasmids, Transposons, Integrons)
  - Transduction (Bacteriophage)
  - Transformation (Free extracellular DNA)



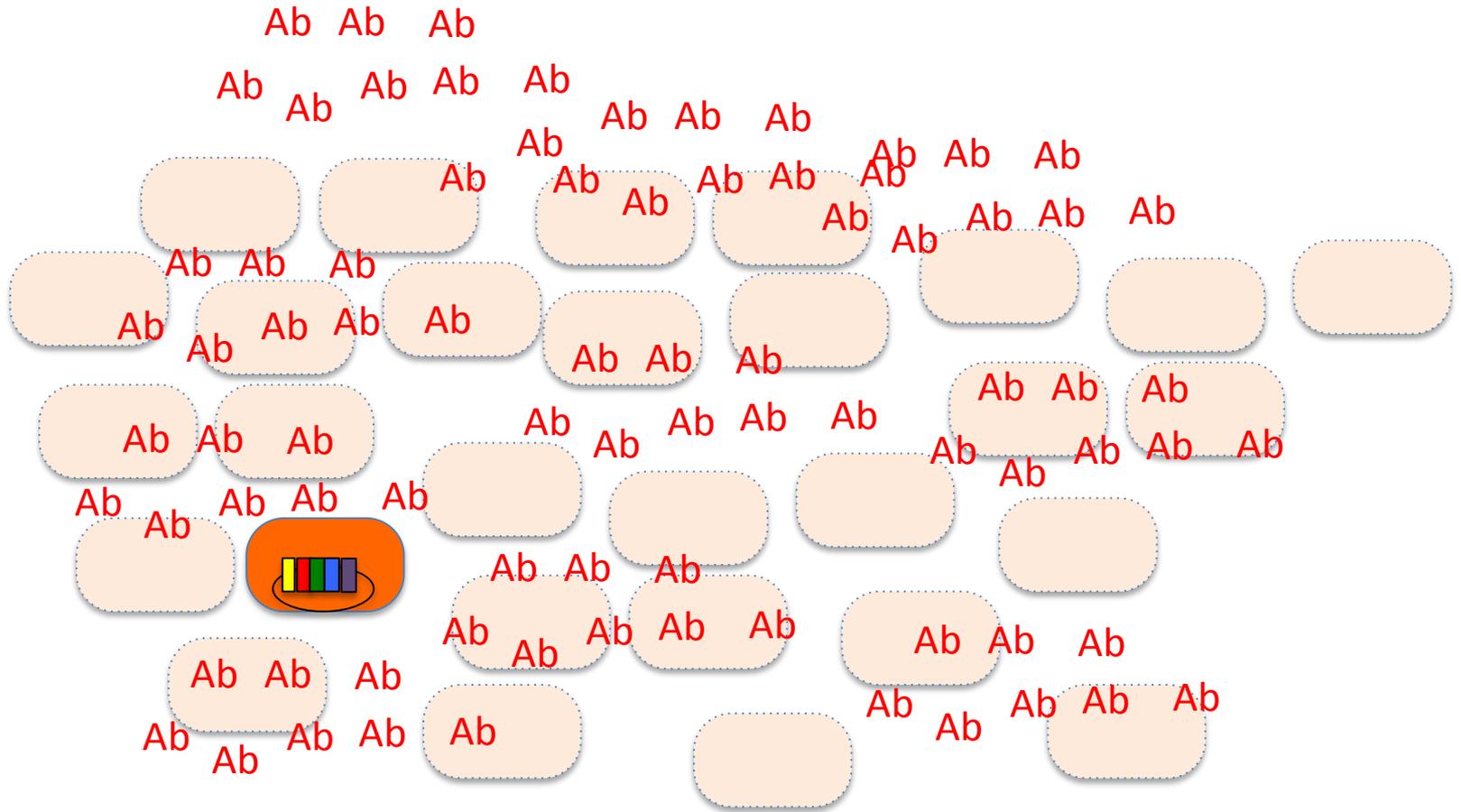
# Antibiotic Use in Animal Agriculture

- Concerns that antibiotic use in animal agriculture adversely impacts human health date to at least to the 1969 release of the *Swann Report*.
- Concerns related to the “selection” of resistant bacteria that occurs when antibiotics are used.



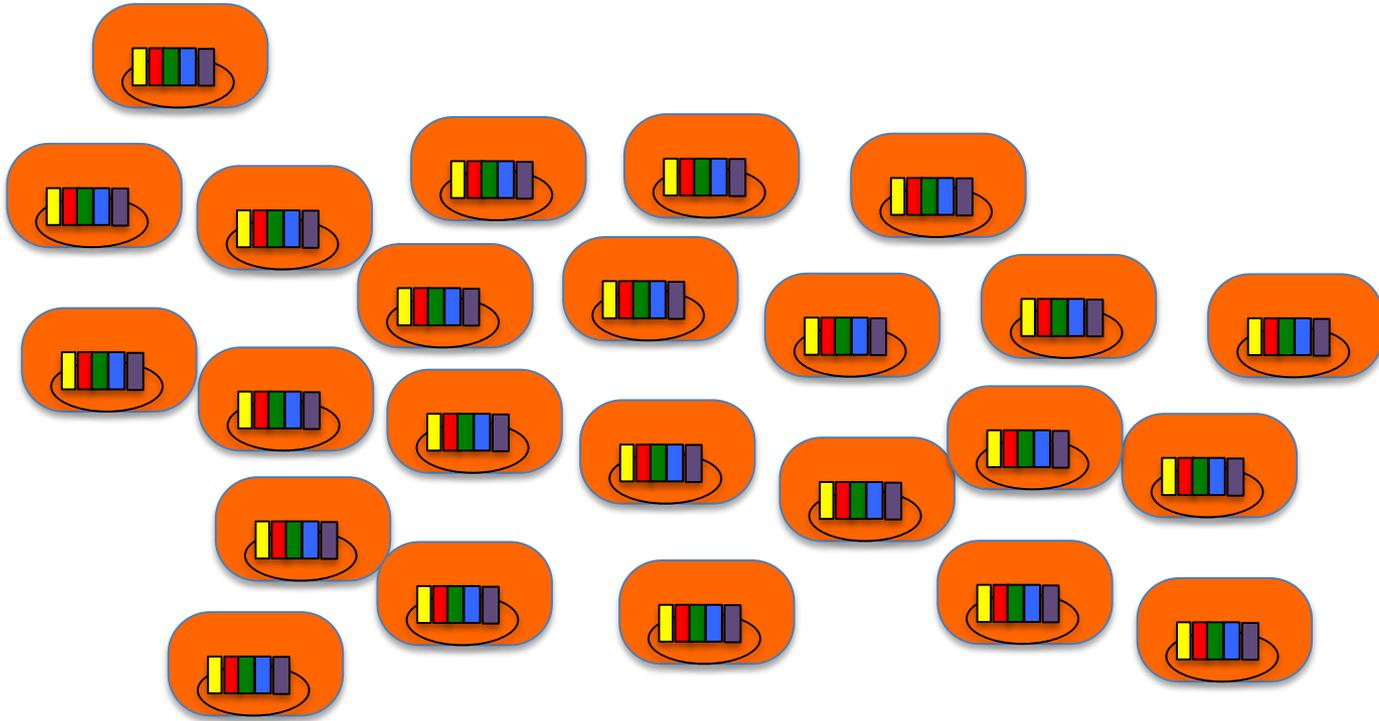
# Antibiotic "Selection"

- When bacteria are exposed to an antibiotic the susceptible population dies.



# Antibiotic “Selection”

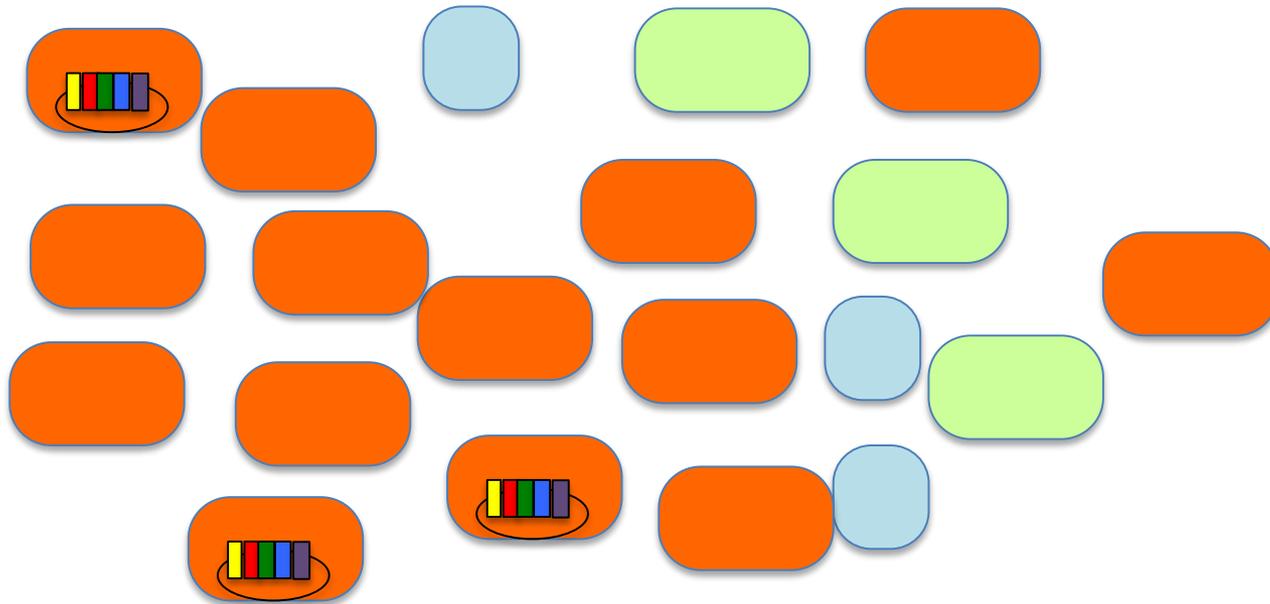
- Resistant bacteria may multiply to fill the space vacated by susceptible bacteria.



- This model is oversimplified.

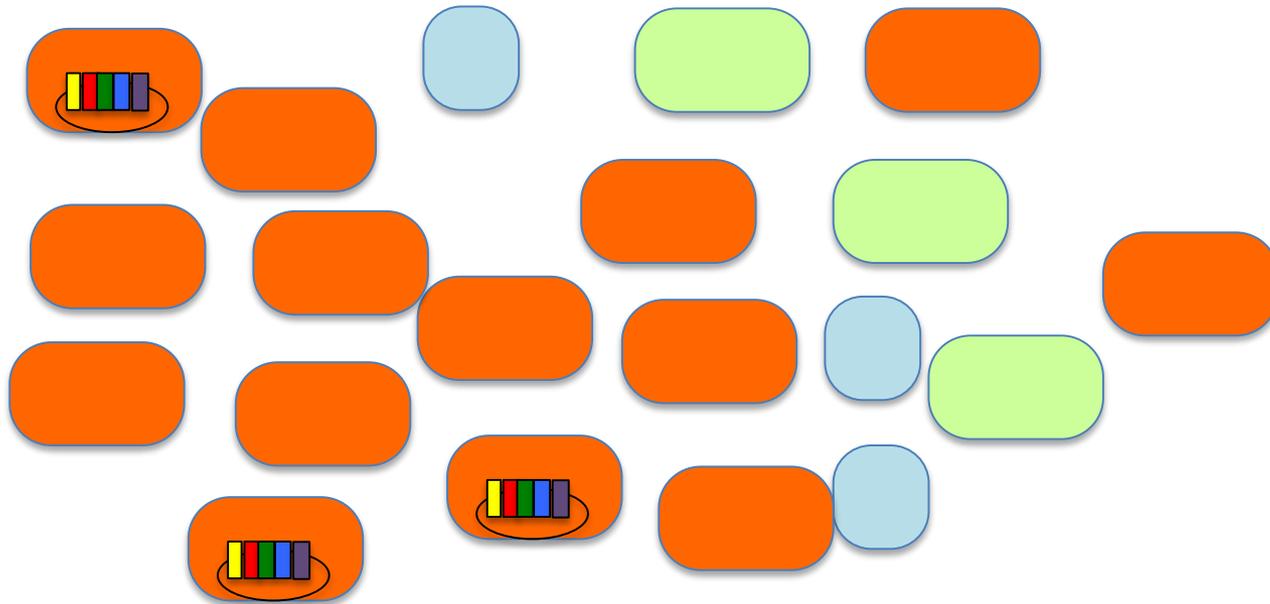
# Antibiotic “Selection”

- In the environment, the niche does not exist in a vacuum; other susceptible bacteria arrive following cessation of treatment.



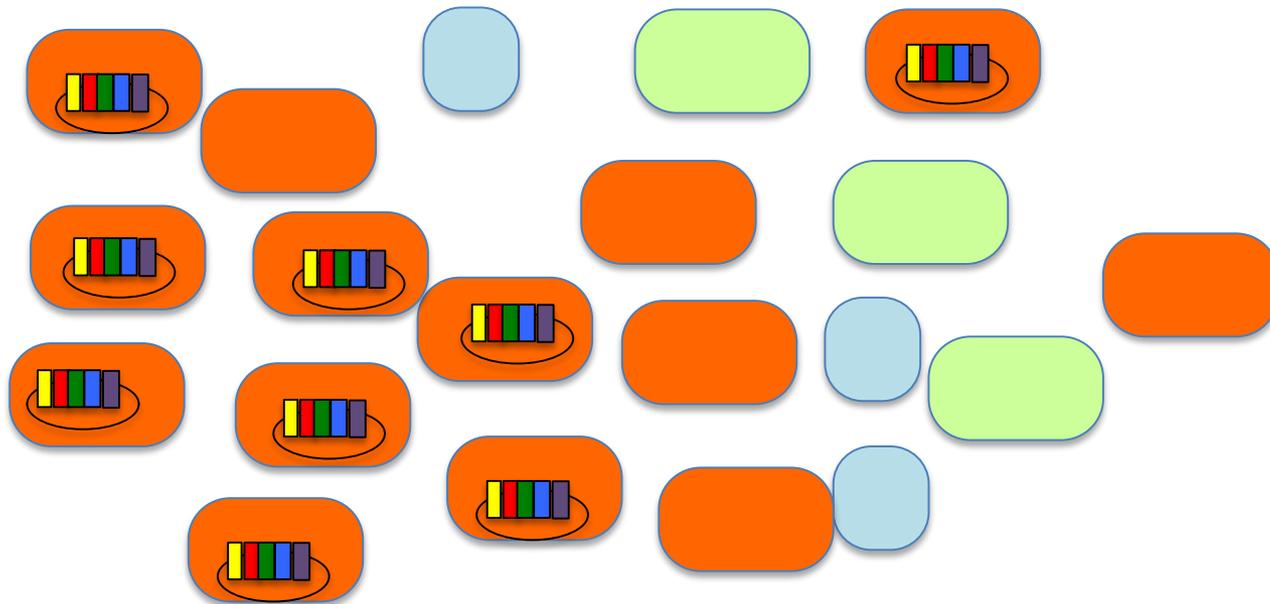
# Routes By Which Ag. Antibiotic Use Impacts Human Health

- “Direct” impact occurs when antibiotic use selects for an antibiotic resistant zoonotic pathogen.



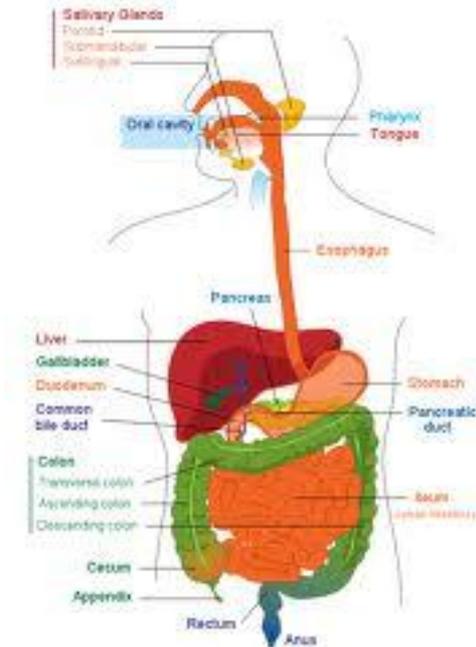
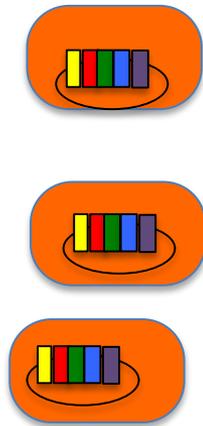
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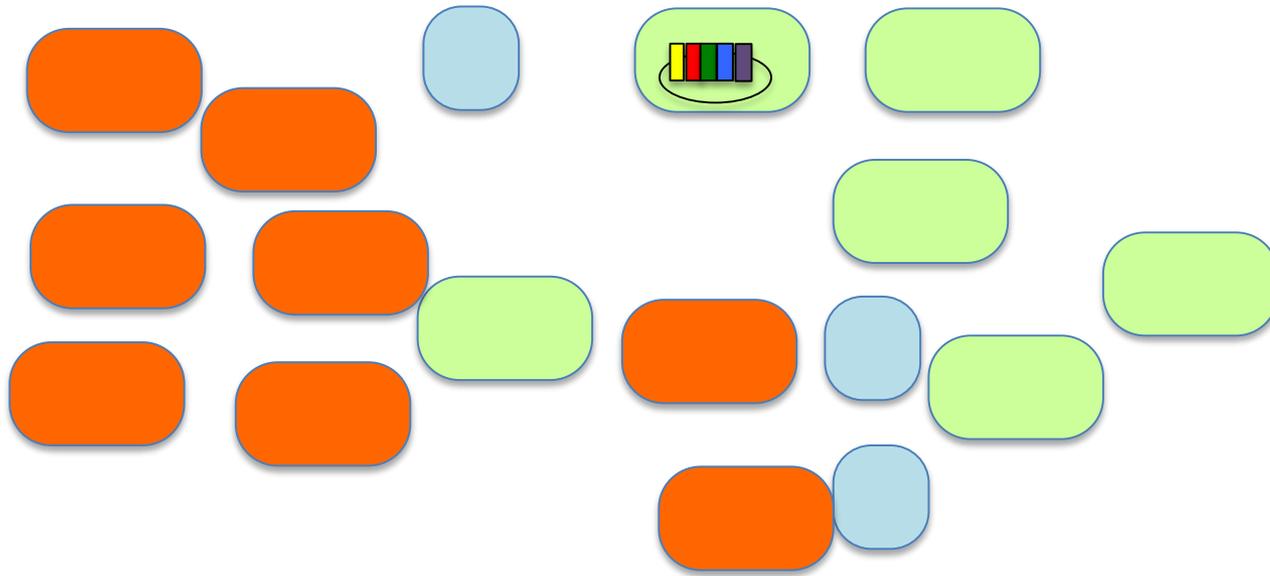
# Routes By Which Ag. Antibiotic Use Impacts Human Health

- “Direct” impact occurs when antibiotic use selects for an antibiotic resistant zoonotic pathogen that contaminates food, is consumed, and results in human illness complicated by antibiotic resistance.



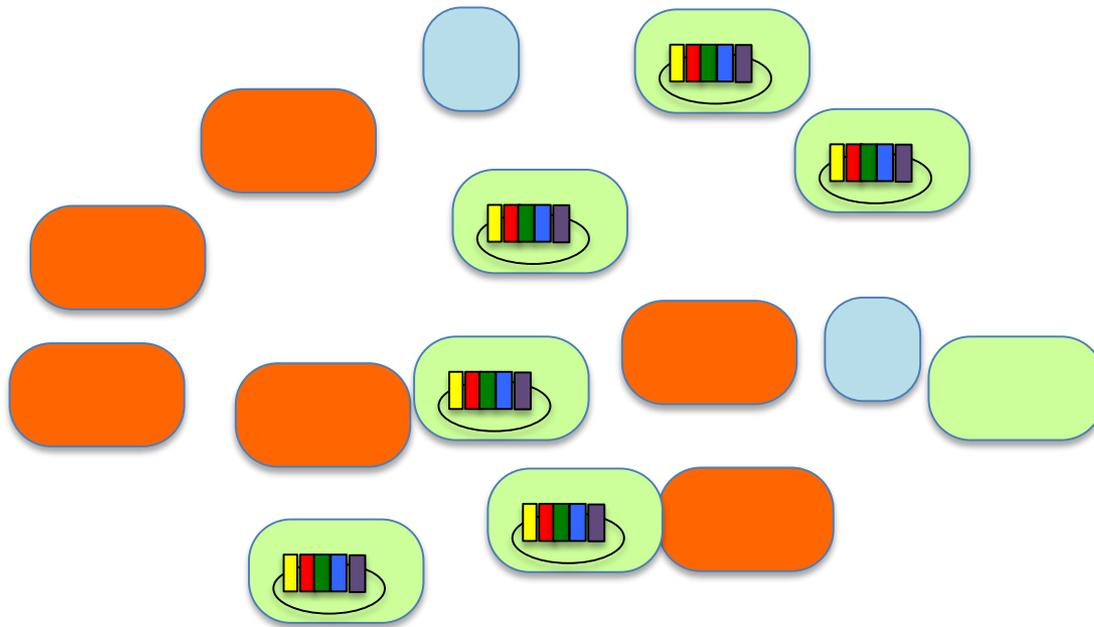
# Routes By Which Ag. Antibiotic Use Impacts Human Health

- “Indirect” impact occurs when antibiotic use selects for an antibiotic resistant commensal.



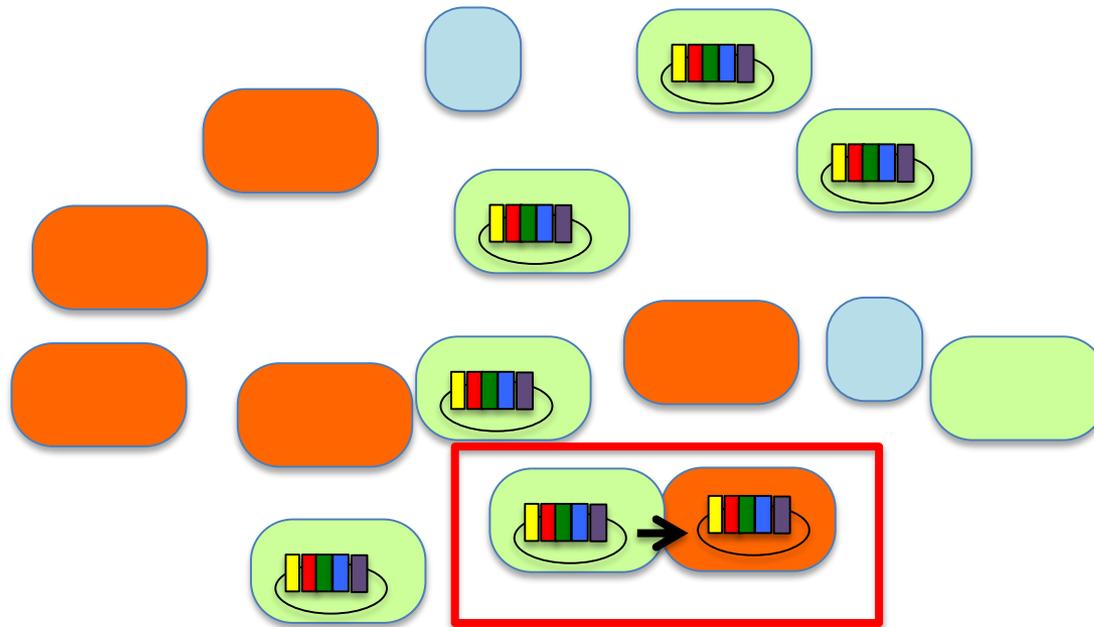
# Routes By Which Ag. Antibiotic Use Impacts Human Health

- “Indirect” impact occurs when antibiotic use selects for an antibiotic resistant commensal.



# Routes By Which Ag. Antibiotic Use Impacts Human Health

- “Indirect” impact occurs when antibiotic use selects for an antibiotic resistant commensal, then either in the production environment or in the human GI system **the antibiotic resistance is transferred to a pathogen** which latter causes illness complicated by resistance.



# Routes By Which Ag. Antibiotic Use Impacts 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<sup>1\*</sup> and Sasidhar Malladi<sup>2</sup>

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<sup>1</sup>, Michael B. Vaughn<sup>2</sup>, Derald Holtkamp<sup>1</sup>, James Dickson<sup>3</sup>, and Lorin Warnick<sup>4</sup>



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Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

 ScienceDirect

Preventive Veterinary Medicine 79 (2007) 186–203

[www.elsevier.com/locate/prevetmed](http://www.elsevier.com/locate/prevetmed)

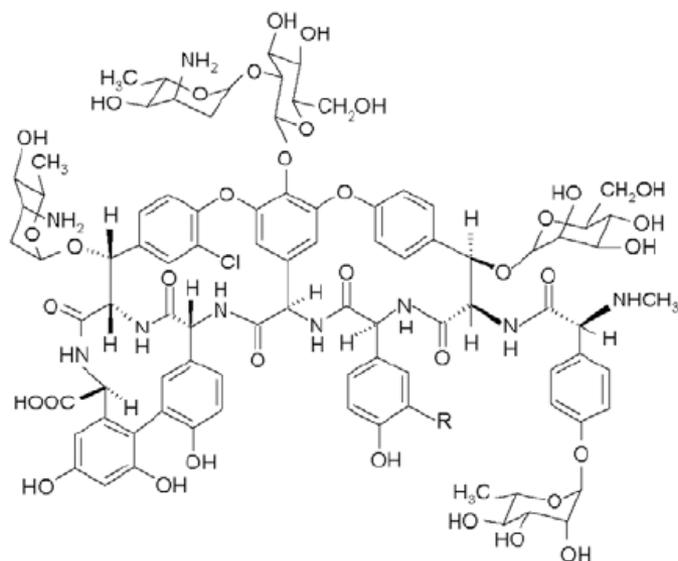
PREVENTIVE  
VETERINARY  
MEDICINE

## Modeling the relationship between food animal health and human foodborne illness

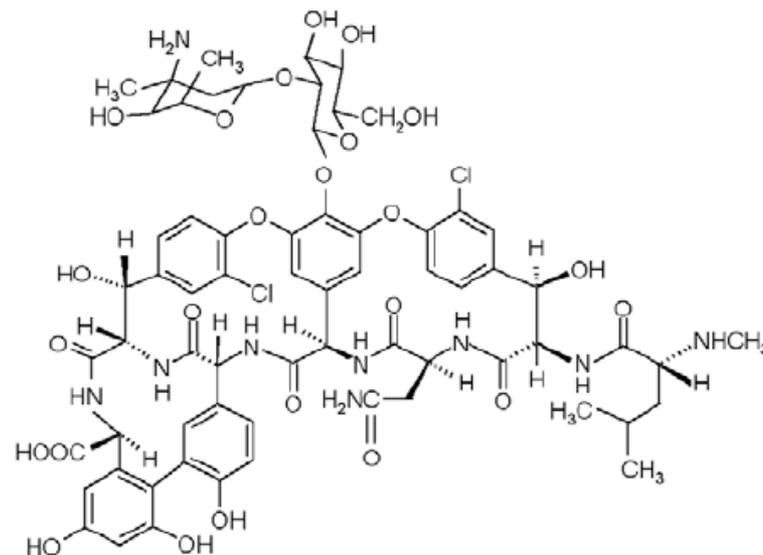
Randall S. Singer<sup>a,b,\*</sup>, Louis A. Cox Jr.<sup>c</sup>, James S. Dickson<sup>d</sup>,  
H. Scott Hurd<sup>e</sup>, Ian Phillips<sup>f</sup>, Gay Y. Miller<sup>g</sup>

# Denmark, EU, Avoparcin, and VRE

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



$\alpha$  - Avoparcin      R=H  
 $\beta$  - Avoparcin      R=Cl



Vancomycin

# Denmark, EU, Avoparcin, and VRE

- **Avoparcin and vancomycin are glycopeptide antibiotics with similar structures and methods of action.**
- **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 levels Denmark banned its use in 1995 and the EU banned its use in 1997.**
- **Following the bans levels of VRE dropped in food animals, meat, and human commensal flora.**

# The “Precautionary Principle”

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

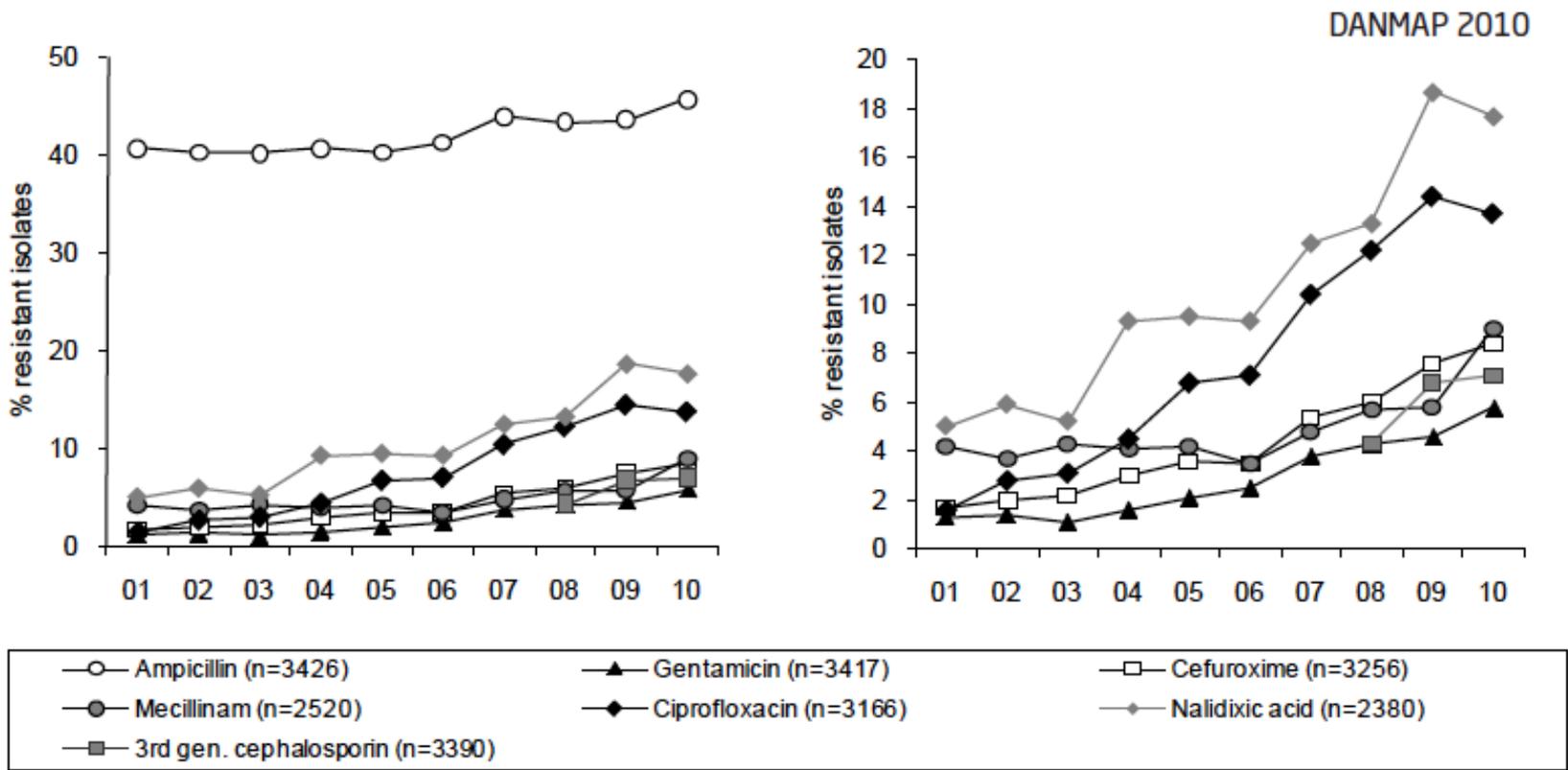
Year	Action
1998	Denmark bans all growth promoting antibiotics.
1999	EU bans growth promoting uses of tylosin, spiramycin, bacitracin, virginiamycin, carbadox, and olaquinox.
2002	Denmark bans most uses of fluoroquinolones.
2005	Denmark increases oversight of swine veterinarians.
2006	EU bans growth 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.

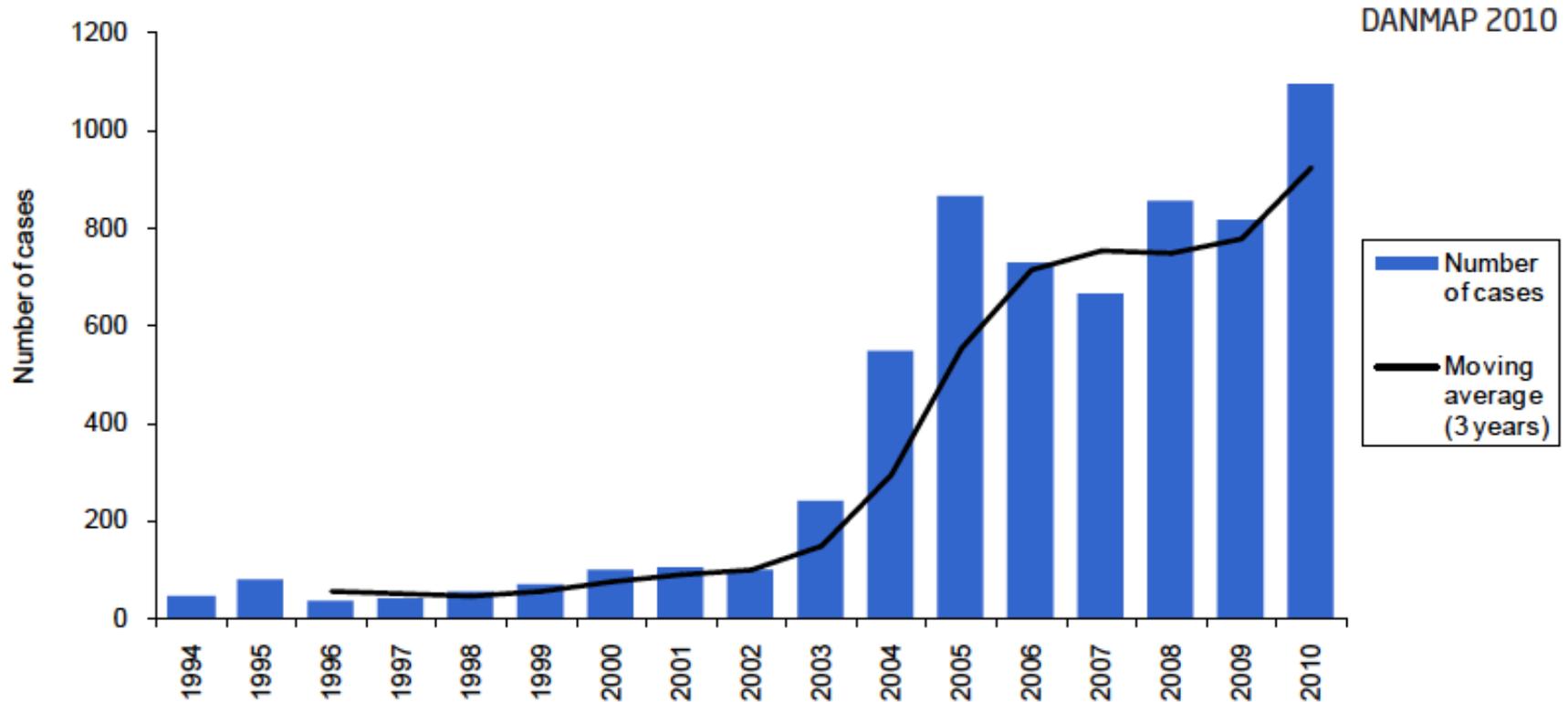
Figure 8.1. Resistance (%) in *Escherichia coli* blood isolates from humans, Denmark



# Bans Have Not Had Desired Impact on Human Health

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Figure 8.5. Number of MRSA cases, with a three years moving average, Denmark



# Ag. Therapeutic Uses of Antibiotics in Denmark Increased

Figure 4.2. Consumption of antimicrobial agents in sows, weaner pigs<sup>(a)</sup>, finishers<sup>(b)</sup> and total pig production<sup>(c)</sup>, given as Animal Daily Doses (ADDs), Denmark

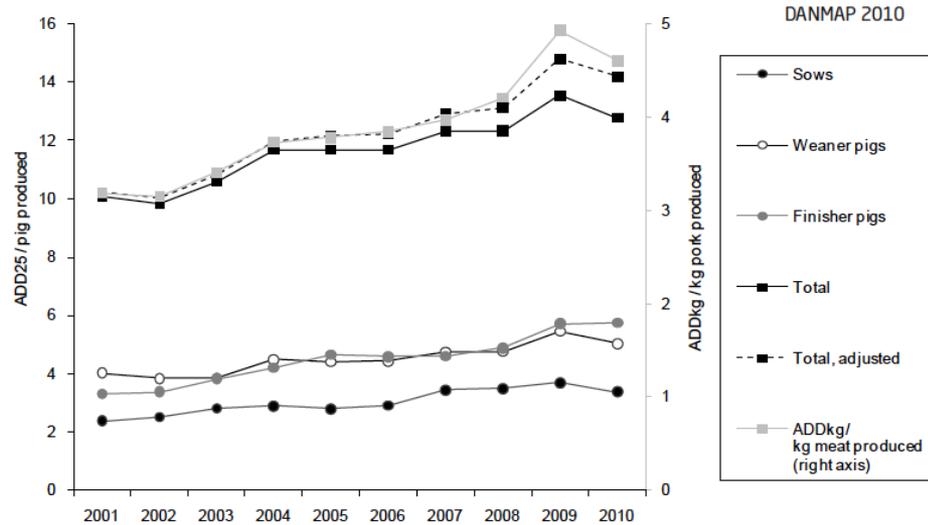
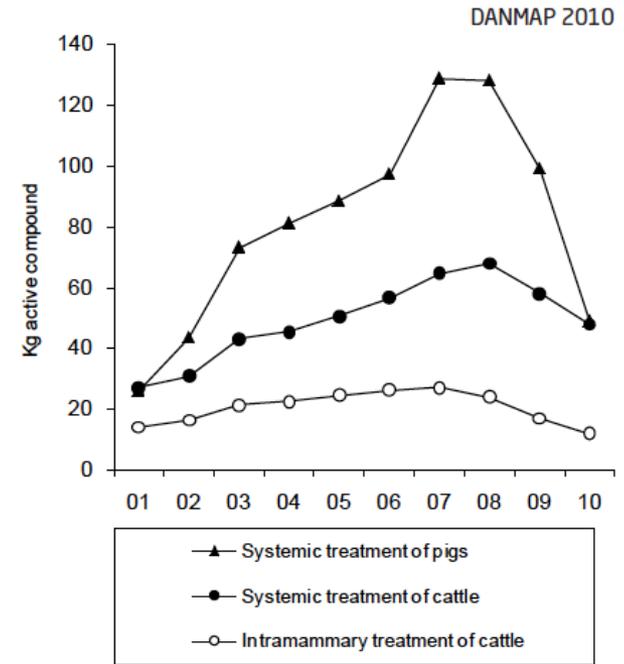


Figure 4.3. Consumption of 3rd and 4th generation cephalosporins in pigs and cattle, Denmark



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# Pressure to Adopt EU-like Regulations Continues

- **Advocacy groups continue campaigns.**
- **In 2012 a federal judge ordered the FDA to initiate withdrawal proceedings for growth-promoting uses of antibiotics including penicillin and tetracycline.**
- **In 2012 the FDA issued guidelines for the the judicious use of medically important antibiotics.**

# GAO Report 11-801

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GAO

United States Government Accountability Office

Report to the Ranking Member,  
Committee on Rules, House of  
Representatives

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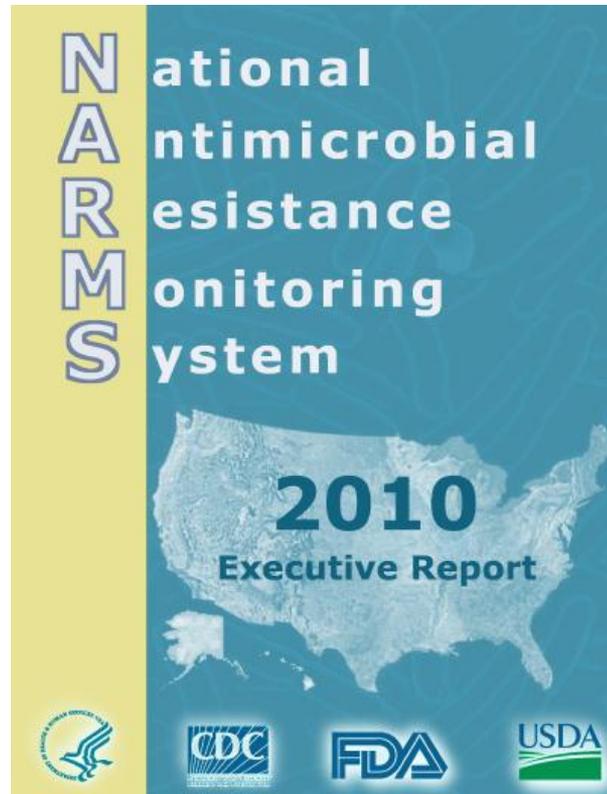
September 2011

## ANTIBIOTIC RESISTANCE

Agencies Have Made  
Limited Progress  
Addressing Antibiotic  
Use in Animals

# GAO Report 11-801: Antibiotic Resistance

- GAO found that the current National Antimicrobial Resistance Monitoring System (NARMS) is inadequate since samples are not representative.
- NARMS is an interagency program lead by FDA, involving CDC and USDA.



# GAO Report 11-801: Antibiotic Resistance

- GAO found that the current National Antimicrobial Resistance Monitoring System (NARMS) is inadequate since samples are not representative.

Agency	Sampled Matrix	Salmonella	Campylobacter	E. coli	Enterococcus	Shigella
USDA	Chicken at processing (carcass and meat)	Yes	Yes	Yes	Yes	No
USDA	Turkey at processing (carcass and meat)	Yes	No	No	No	No
USDA	Cattle/Beef at processing (carcass and meat)	Yes	No	No	No	No
USDA	Swine at processing (carcass)	Yes	No	No	No	No
FDA	Retail chicken breasts (10 states)	Yes	Yes	4 states	4 states	No
FDA	Retail pork chops (10 states)	Yes	No	4 states	4 states	No
FDA	Retail ground turkey (10 states)	Yes	Yes	4 states	4 states	No
FDA	Retail ground beef (10 states)	Yes	No	4 states	4 states	No
CDC	Humans (clinical samples, nationwide)	Yes	10 states	O157 only	No	Yes

- FDA’s retail meat testing from 10 or 4 states is not representative.
- USDA’s samples can not be used for trend analysis since they are obtained from targeted, non-representative sampling.
  - HACCP verification testing performed by FSIS is source.
- USDA’s carcass sampling does not represent production environment.

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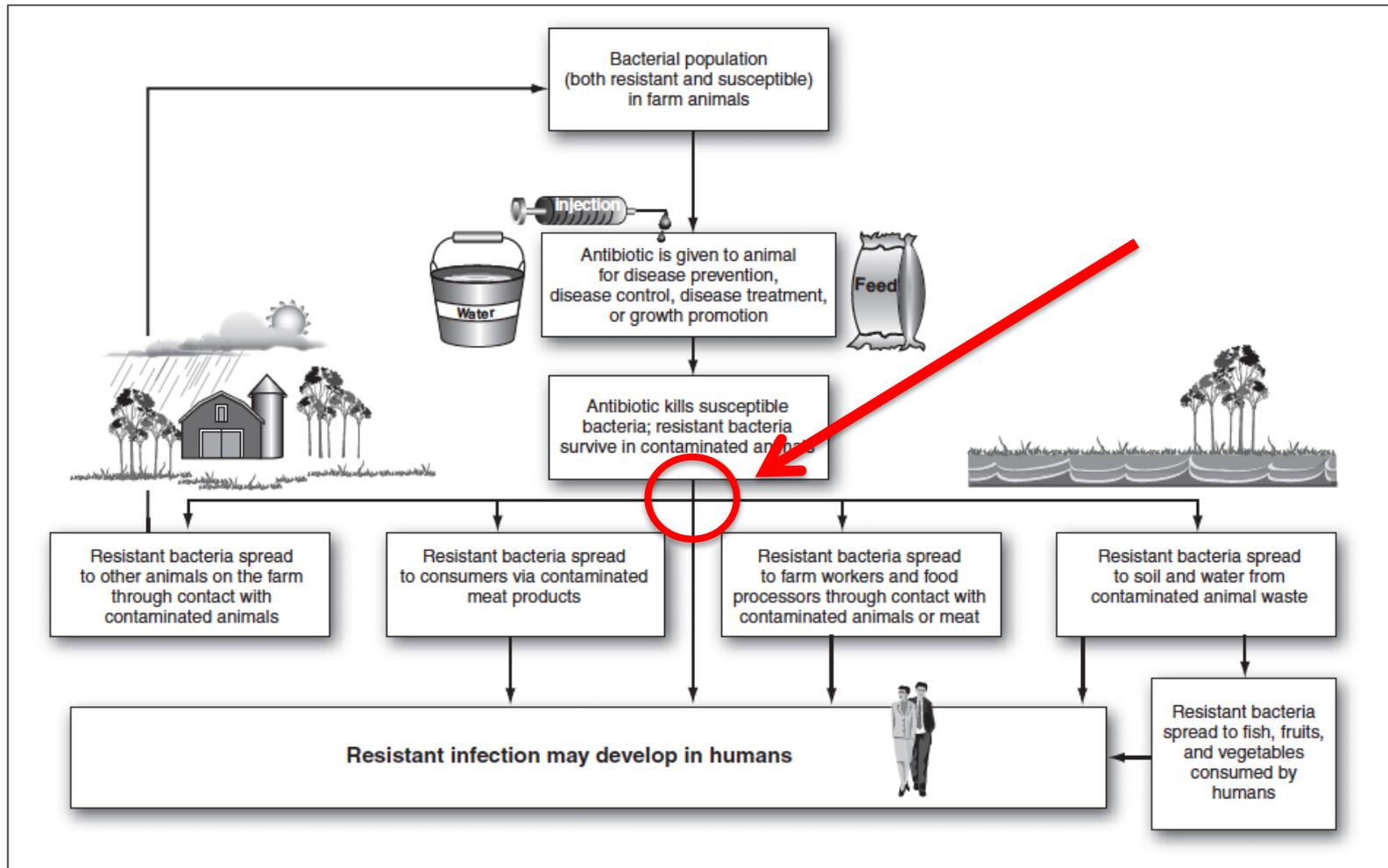
- GAO found that the current National Antimicrobial Resistance Monitoring System (NARMS) is inadequate since samples are not representative.
- Report also found that NARMS does not collect data pertaining to **antibiotic use** and **resistance at animal production facilities**.

# GAO Recommendations

- To “...enhance surveillance of antibiotic-resistant bacteria in food animals...modify NARMS sampling to make the data more representative of antibiotic resistance in food animals and retail meat throughout the US.”
- To “...identify potential approaches for collecting detailed data on antibiotic use in food animals, including the species in which antibiotics are used and the purpose for their use.”
- GAO report suggests that DANMAP program could serve as model for improving NARMS.

# Moving Monitoring Upstream

Figure 1: Potential Pathways for Spread of Antibiotic-Resistant Bacteria from Animals to Humans



# DANMAP & NARMS

## DANMAP Antibiotic Resistant Bacteria Monitoring

Entity	Sampled Matrix	Salmonella	Campylobacter	E. coli	Enterococcus	S. aureus
Animals	Healthy pigs, cattle, & chickens at slaughter	No	Yes	Yes	Yes	No
Animals	Diagnostic lab submissions	Typhimurium	No	O149 & F5	No	No
Animals	Targeted swine & chicken herds/flocks	Yes	No	No	No	No
Animals	Swine at processing (carcass)	Yes	No	No	No	No
Food	Beef	Yes, risk based	No	Yes	Yes	No
Food	Pork	Yes, risk based	No	Yes	Yes	No
Food	Chicken	Yes, risk based	Yes	Yes	Yes	No
Humans	Clinical samples	Yes	Yes	Yes	Yes	Yes

- DANMAP's resistance monitoring is statistically representative.
- **DANMAP includes very detailed monitoring of all antibiotic use in animals and humans.**
- FDA has funded pilot studies to investigate methods for sampling of animal production environments for antibiotic-resistant bacteria.
- FSIS issued public notice #13-13 on procedures for PHVs to sample cecal contents for antibiotic-resistant bacteria.

# Conclusions

- **Human infections complicated by antibiotic resistance are not going away nor are concerns about the contribution of antibiotic uses in animal agriculture.**
- **The EU & Denmark experiences illustrate that the problem will not be solved by simple solutions such as restrictions on agricultural uses of antibiotics based on the “Precautionary Principle.”**
- **The factors that contribute to antibiotic resistance transmission, amplification, persistence (ecology) are complex and understudied.**
- **The molecular mechanisms responsible for the physical transfer of MGEs (bacteriophage infection, lysis/lysogeny, transfer of conjugal plasmids, etc.) are very well understood due to 50+ years of intense study.**
- **Understanding of the ecology of antibiotic resistance is very limited and based on laboratory experiments.**
- **Studies on the ecology of antibiotic resistance in production environments may yield significant insights applicable to human medicine.**

# Research Needed to Inform Regulation

- **NARMS/DANMAP will never be enough.**
  - **NARMS and DANMAP only report on prevalence of phenotypic resistance.**
  - **NARMS and DANMAP do not explore genetic basis (genes) or ecology (population structures).**
- **New regulation is always on the horizon.**

## SCIENTIFIC OPINION

# Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum $\beta$ -lactamases and/or AmpC $\beta$ -lactamases in food and food-producing animals<sup>1</sup>

EFSA Panel on Biological Hazards (BIOHAZ)<sup>2, 3</sup>

European Food Safety Authority (EFSA), Parma, Italy

AmpC-producing bacteria related to food-producing animals. Prioritisation is complex, but it is considered that a highly effective control option would be to stop all uses of cephalosporins/systemically active 3<sup>rd</sup>/4<sup>th</sup> generation cephalosporins, or to restrict their use (use only allowed under specific circumstances). As co-resistance is an important issue, it is also of high priority to decrease the total antimicrobial use in animal production in the EU.

# Fecal Prevalence of ESC<sup>R</sup> *E. coli*

Month	No. Ceftiofur Injections	No. Other Ab Injections	Herd		IDS+TIO		Other+TIO	
			Period	Prev. ESC <sup>R</sup> <i>E. coli</i>	Period	Prev. ESC <sup>R</sup> <i>E. coli</i>	Period	Prev. ESC <sup>R</sup> <i>E. coli</i>
Pre-Sep.	10	23						
Sep.	10	13	Arrival	3.9% AB				
Oct.	52	1	IDS	5.5% AB	Pre-TIO	8.2% B		
					Post-TIO	92.0% A		
Nov.	14	2						
Dec.	4	2	Dec.	2.9% B	Dec.	6.1% B	Dec.	3.0% A
Jan.	0	5						
Feb.	6	0						
Mar.	3	0	Mar.	1.7% B	Mar.	0.0% B	Mar.	0.0% A
Apr.	1	0						
May	3	1	May	2.2% B	May	2.1% B	May	0.0% A
Jun.	3	0						
Jul.	4	0	Jul.	11.2% A	Jul.	2.1% B	Jul.	9.8% A

- IDS+TIO fecal prevalence of ESC<sup>R</sup> *E. coli* was highest shortly after injection.

- IDS+TIO fecal prevalences of ESC<sup>R</sup> *E. coli* were not higher than Herd prevalences during later sampling periods.

# Hide Prevalence of ESC<sup>R</sup> *E. coli*

Month	No. Ceftiofur Injections	No. Other Ab Injections	Herd		IDS+TIO		Other+TIO	
			Period	Prev. ESC <sup>R</sup> <i>E. coli</i>	Period	Prev. ESC <sup>R</sup> <i>E. coli</i>	Period	Prev. ESC <sup>R</sup> <i>E. coli</i>
Pre-Sep.	10	23						
Sep.	10	13	Arrival	15.0% A				
Oct.	52	1	IDS	11.7% A	Pre-TIO	8.2% AB		
					Post-TIO	26.0% A		
Nov.	14	2						
Dec.	4	2	Dec.	7.5% AB	Dec.	24.5% A	Dec.	9.1% AB
Jan.	0	5						
Feb.	6	0						
Mar.	3	0	Mar.	1.7% B	Mar.	0.0% B	Mar.	2.6% B
Apr.	1	0						
May	3	1	May	17.4% A	May	20.8% A	May	25.6% A
Jun.	3	0						
Jul.	4	0	Jul.	8.4% A	Jul.	0.0% B	Jul.	3.9% B

- Hide prevalence of ESC<sup>R</sup> *E. coli* **did not** increase while at the feedlot.



## Influence of Therapeutic Ceftiofur Treatments of Feedlot Cattle on Fecal and Hide Prevalences of Commensal *Escherichia coli* Resistant to Expanded-Spectrum Cephalosporins, and Molecular Characterization of Resistant Isolates

John W. Schmidt,<sup>a</sup> Dee Griffin,<sup>b</sup> Larry A. Kuehn,<sup>a</sup> Dayna M. Brichta-Harhay<sup>a</sup>

U.S. Department of Agriculture, Agricultural Research Service, Roman L. Hruska U.S. Meat Animal Research Center, Clay Center, Nebraska, USA<sup>a</sup>; Great Plains Veterinary Educational Center, School of Veterinary Medicine and Biomedical Sciences, University of Nebraska—Lincoln, Clay Center, Nebraska, USA<sup>b</sup>



# Foodborne urinary tract infections: a new paradigm for antimicrobial-resistant foodborne illness

Lora Nordstrom<sup>1</sup>, Cindy M. Liu<sup>1,2</sup> and Lance B. Price<sup>1,3\*</sup>

<sup>1</sup> Division of Pathogen Genomics, Center for Food Microbiology and Environmental Health, The Translational Genomics Research Institute, Flagstaff, AZ, USA

<sup>2</sup> Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>3</sup> School of Public Health and Health Services, George Washington University, Washington, DC, USA

## Edited by:

Axel Cloeckert, Institut National de la Recherche Agronomique, France

## Reviewed by:

Niels Frimodt-Møller, Hvidovre Hospital, Denmark

Jean-Yves Madec, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail, France

## \*Correspondence:

Lance B. Price, School of Public Health and Health Services, George Washington University, 2100 M Street NW, Suite 203A, Washington, DC 20037, USA; Division of Pathogen Genomics, Center for Food

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide. Disproportionately affecting women, UTIs exact a substantial public burden each year in terms of direct medical expenses, decreased quality of life, and lost productivity. Increasing antimicrobial resistance among strains of extraintestinal pathogenic *Escherichia coli* challenges successful treatment of UTIs. Community-acquired UTIs were long considered sporadic infections, typically caused by the patients' native gastrointestinal microbiota; however, the recent recognition of UTI outbreaks with probable foodborne origins has shifted our understanding of UTI epidemiology. Along with this paradigm shift come new opportunities to disrupt the infection process and possibly quell increasing resistance, including the elimination of non-therapeutic antimicrobial use in food-animal production.

**Keywords:** antibiotics, antibiotic resistance, antimicrobial resistance, *Escherichia coli*, food contamination, poultry products, UPEC, urinary tract infections

# Research Needed to Inform Regulation & More

- **NARMS/DANMAP will never be enough.**
  - **NARMS and DANMAP on report on prevalence of phenotypic resistance.**
  - **NARMS and DANMAP do not explore genetic basis (genes) or ecology (population structures).**
- **New regulation is always on the horizon.**
- **Industry will have to demonstrate that antibiotic uses are judicious.**
- **Comprehensive, longitudinal studies on the impact of specific antibiotic uses (e.g., ionophores) on specific antibiotic resistant bacteria (e.g., macrolide resistant Enterococci) are lacking.**
- **This data gap is exploited by the opponents of animal agriculture.**
- **Research can demonstrate commitment to better understanding and combating antibiotic resistance.**

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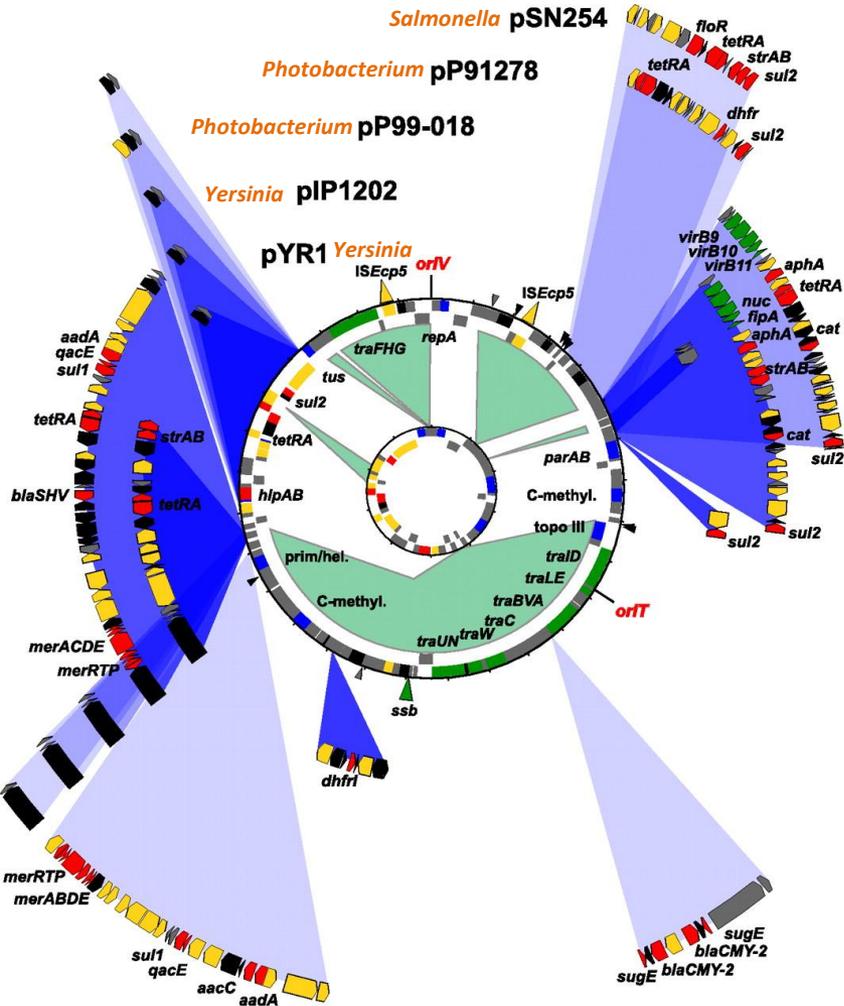
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# Mobile Genetic Elements

- **Mobile genetic elements (MGE) are segments of DNA that encode enzymes that facilitate the movement of DNA.**
- **MGEs include bacteriophage, transposons, plasmids, insertion sequences, and integrons.**
- **HGT is thought to be a dominant contributor to the spread of antibiotic resistance since highly conserved antibiotic resistance genes contained within MGEs have been isolated from distantly related bacteria.**

# Broad Host Range IncA/C Multidrug Resistance Plasmid



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

- Genes for horizontal transfer.
- Genes that confer resistance to:
  - Cephalosporins (*bla<sub>CMY-2</sub>*)
  - Chloramphenicol (*floR*)
  - Tetracycline (*tetRA*)
  - Streptomycin (*strAB*)
  - Sulfonamides (*sul1* & *sul2*)

## • Transposition/recombination

• “Backbone” sequences of IncA/C plasmids from diverse hosts are highly conserved.

IncA/C MDR plasmids have been isolated from:

Genus	Family/Order	Class
<i>Serratia</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Escherichia</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Klebsiella</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Providencia</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Salmonella</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Yersinia</i>	Enterobacteriaceae	Gammaproteobacteria
<i>Photobacterium</i>	Vibrionaceae	Gammaproteobacteria
<i>Vibrio</i>	Vibrionaceae	Gammaproteobacteria
<i>Aeromonas</i>	Aeromonadaceae	Gammaproteobacteria

**Figure 6.1. Resistance (%) in *Salmonella* Typhimurium<sup>(a)</sup> from pigs, Denmark**

