Antibiotic Resistance at the Intersection of Animal and Human Health

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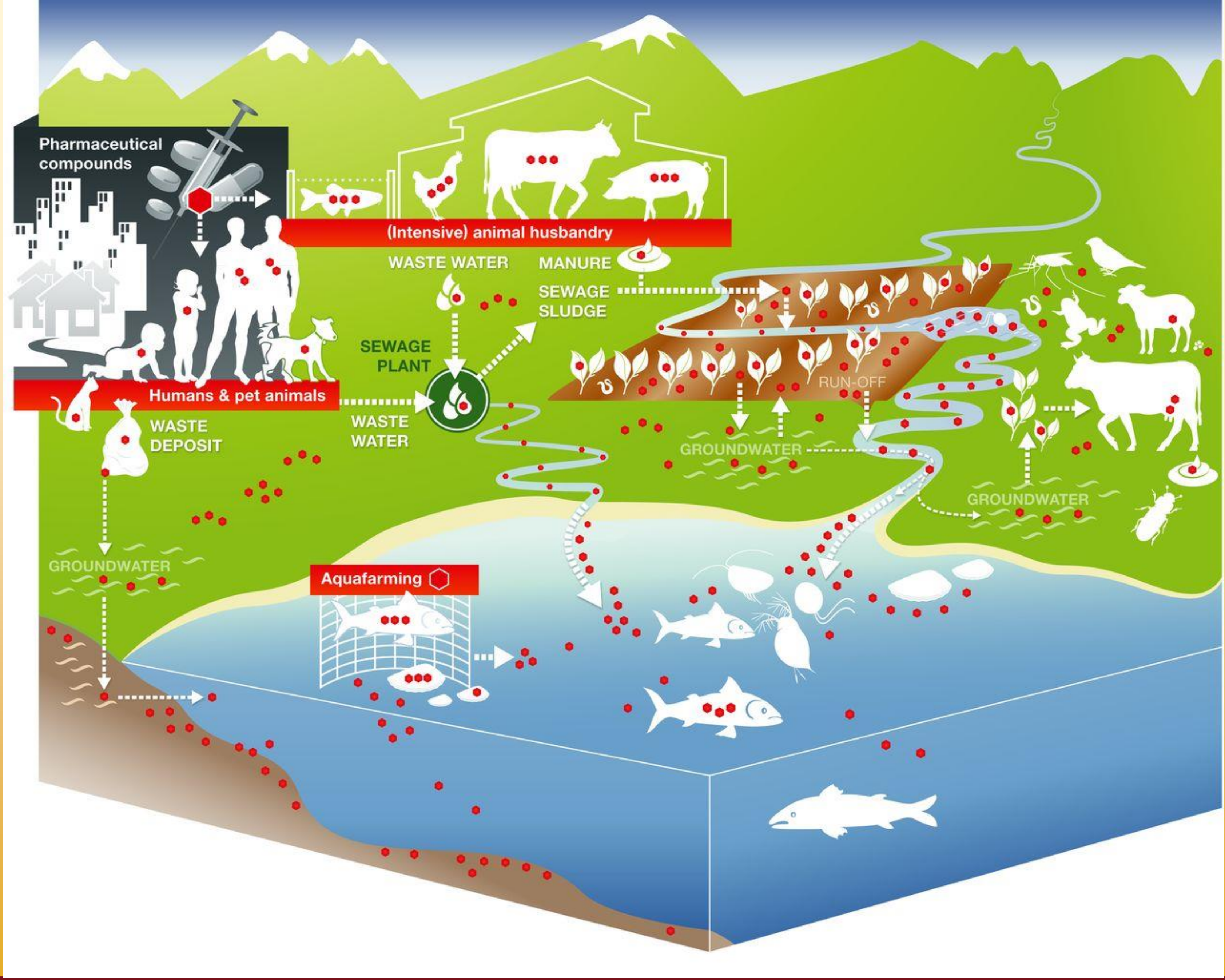
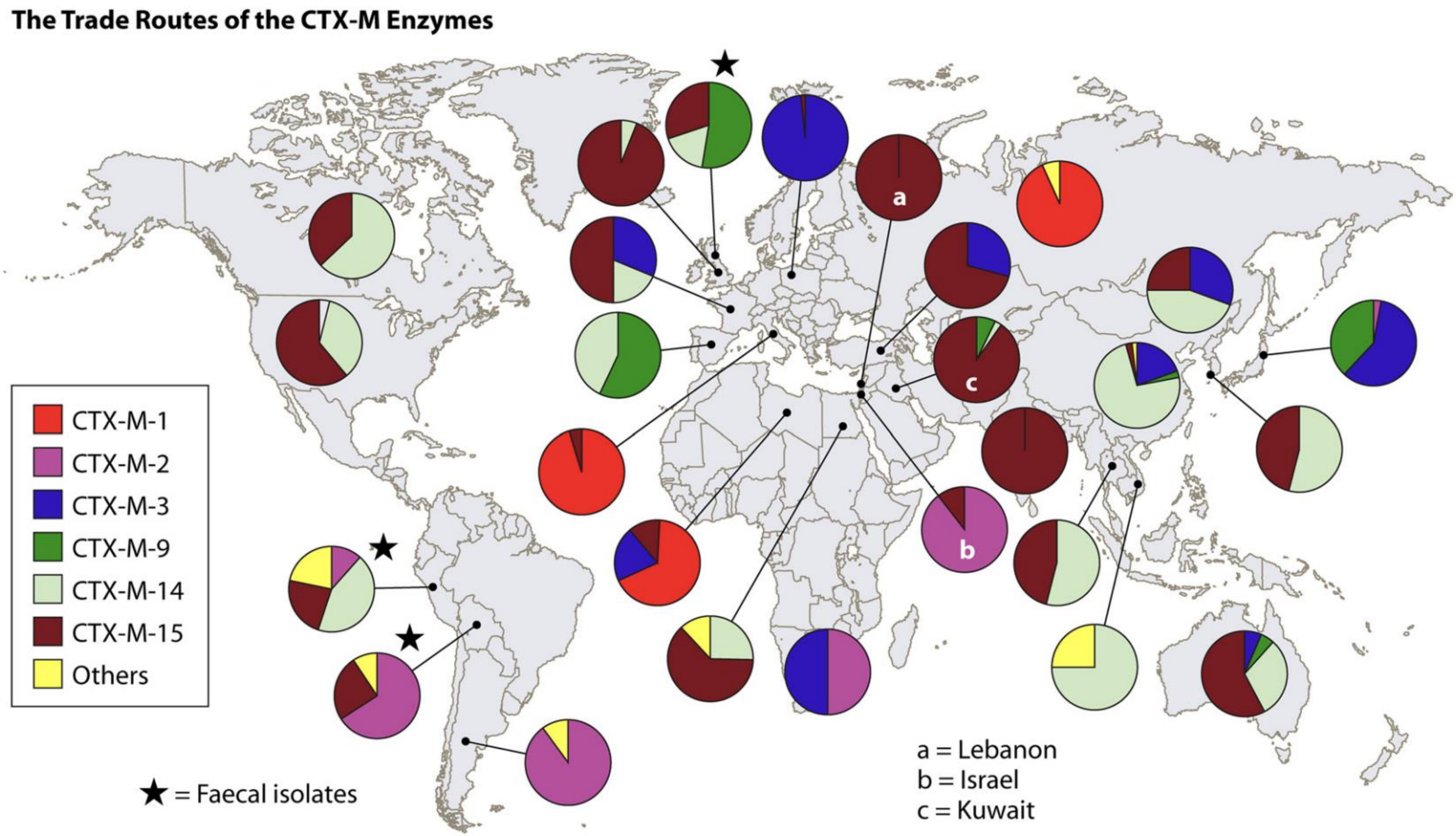
Driven to Discover®


80% OF ALL ANTIBIOTICS
ARE USED ON
FACTORY FARM
ANIMALS
MEATWITHOUTDRUGS.ORG


Pharmaceutical compounds
(Intensive) animal husbandry
WASTE WATER
MANURE
SEWAGE SLUDGE
SEWAGE PLANT
Humans & pet animals
WASTE WATER
WASTE DEPOSIT
RUN-OFF
GROUNDWATER
GROUNDWATER
GROUNDWATER
Aquafarming

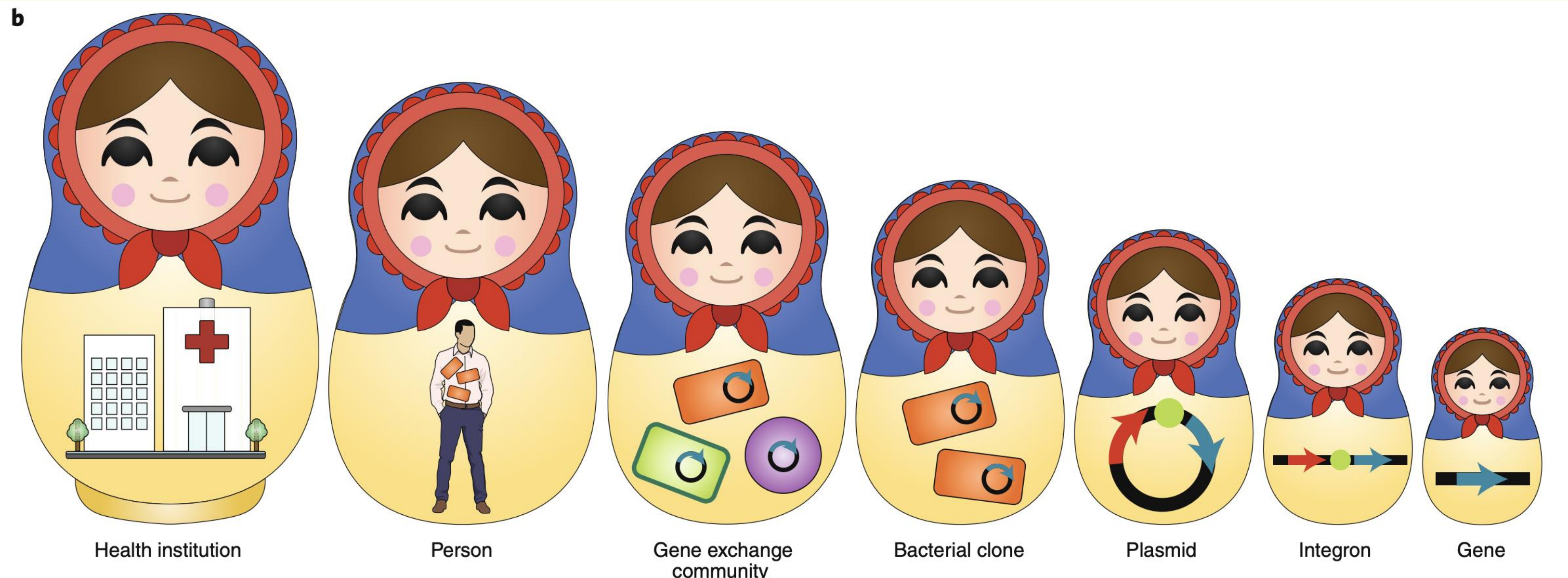
This is a global problem



Origins and Evolution of Antibiotic Resistance

Julian Davies* and Dorothy Davies

This is a multi-layered problem



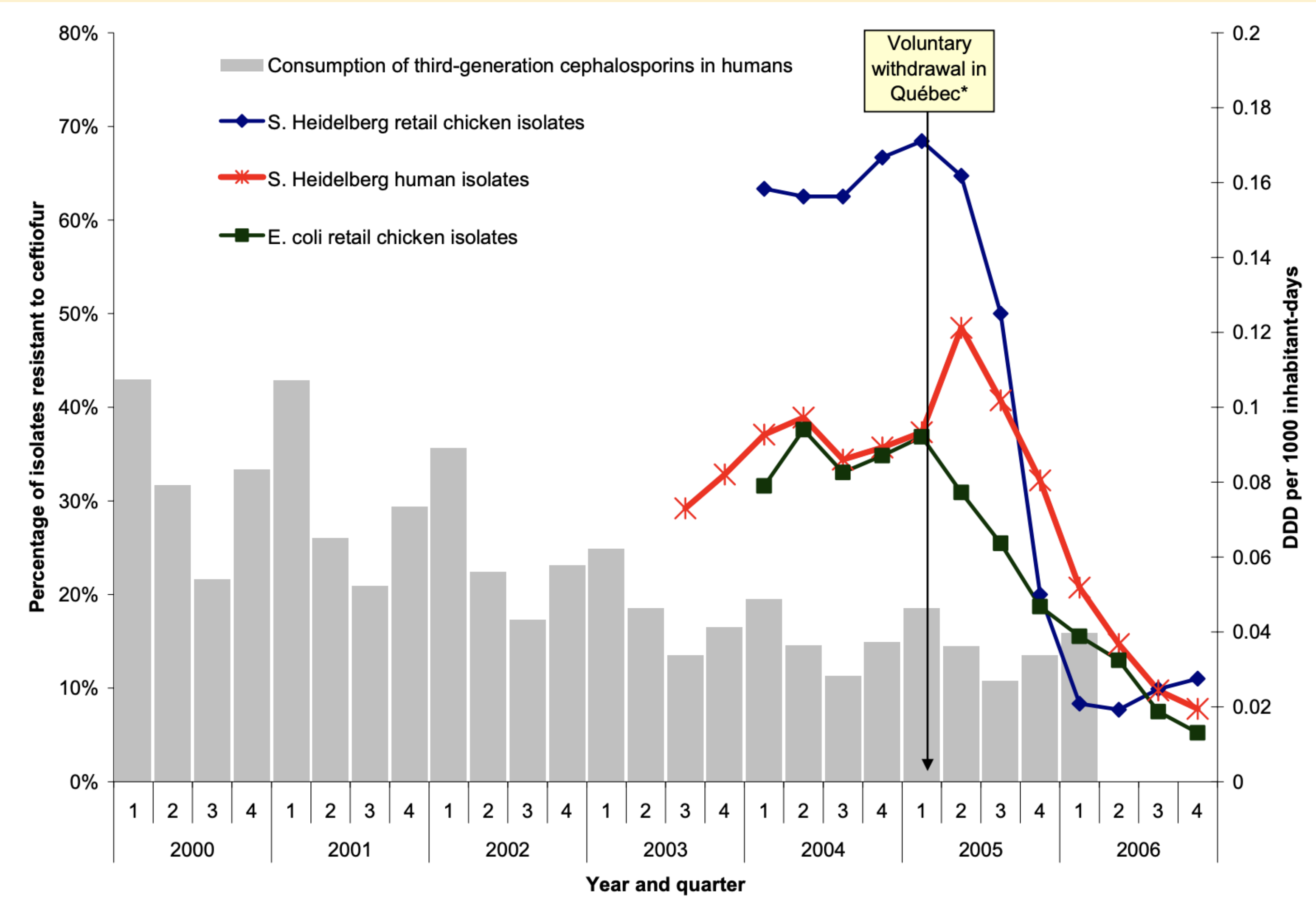
Defining and combating antibiotic resistance from One Health and Global Health perspectives

Sara Hernando-Amado[1], Teresa M. Coque[2], Fernando Baquero[2] and José L. Martínez[1*]

How to reduce the burden of AMR?

- Modify therapy
  - New Abx, policy, evidence-based cycling, modify existing approaches, better separation of animal vs human Abx
- Reduce selective pressure
  - More surveillance, less environmental impact, reduce use, more vaccinations
- Reduce transmission
  - Risk assessments, better hygiene, trade control, integrated One Health surveillance
- Restore populations
  - Probiotics, CRISPR-based systems, phage, microbial transplantation?

Some actions have rapid effect…



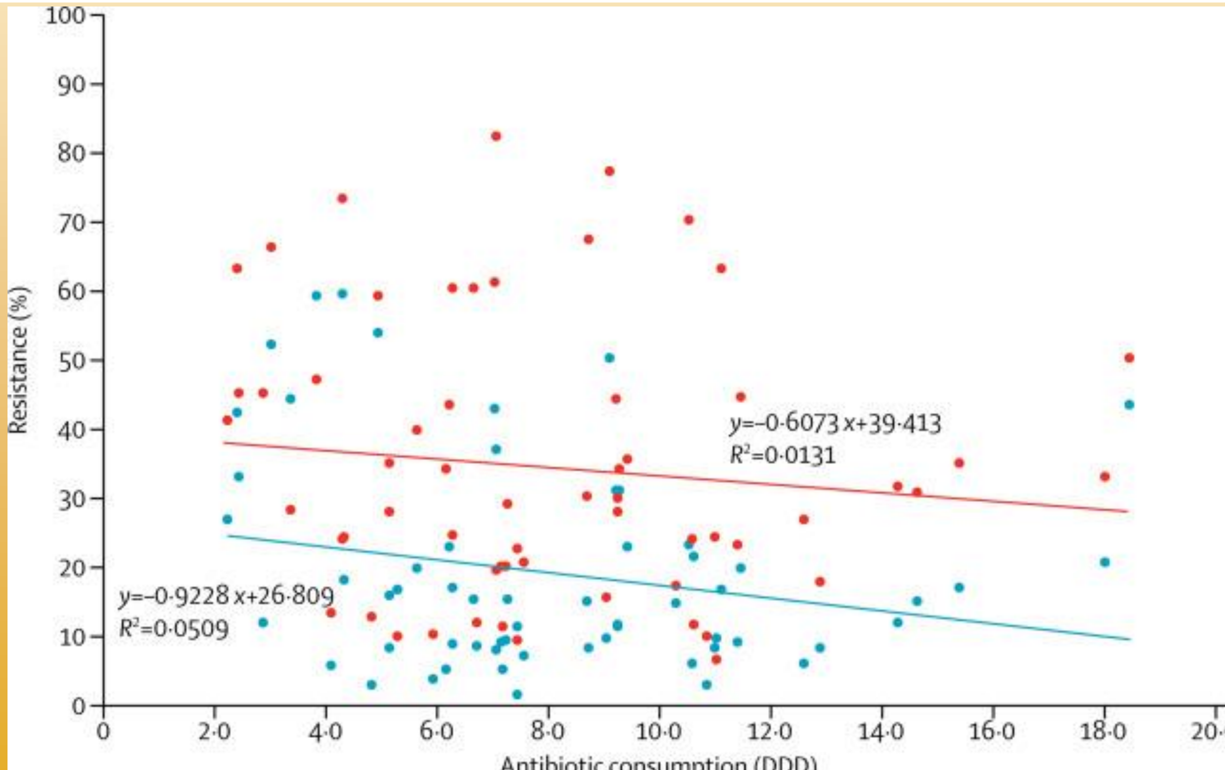
Public Health Agency of Canada Agence de santé publique du Canada Canada

Salmonella Heidelberg – Ceftiofur-Related Resistance in Human and Retail Chicken Isolates

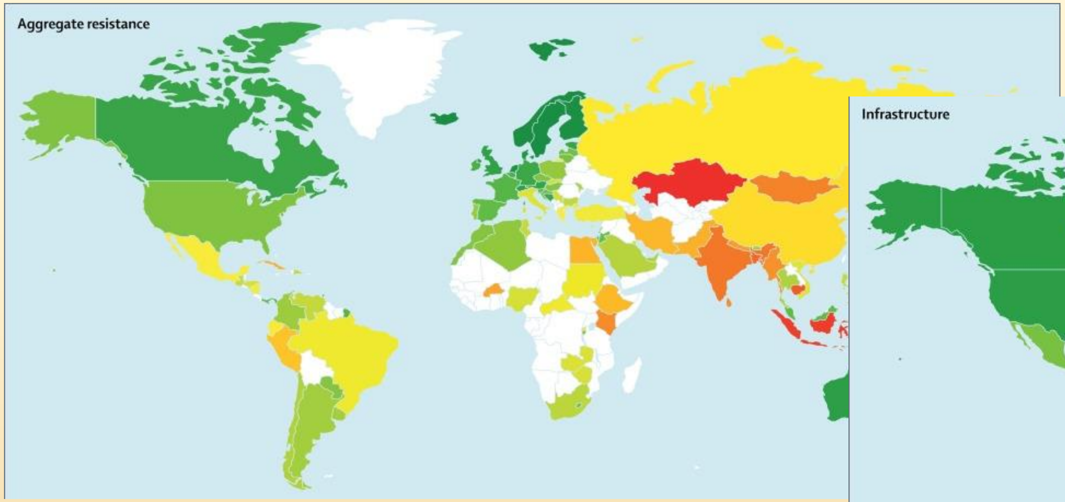
The global picture on AMR is less clear…

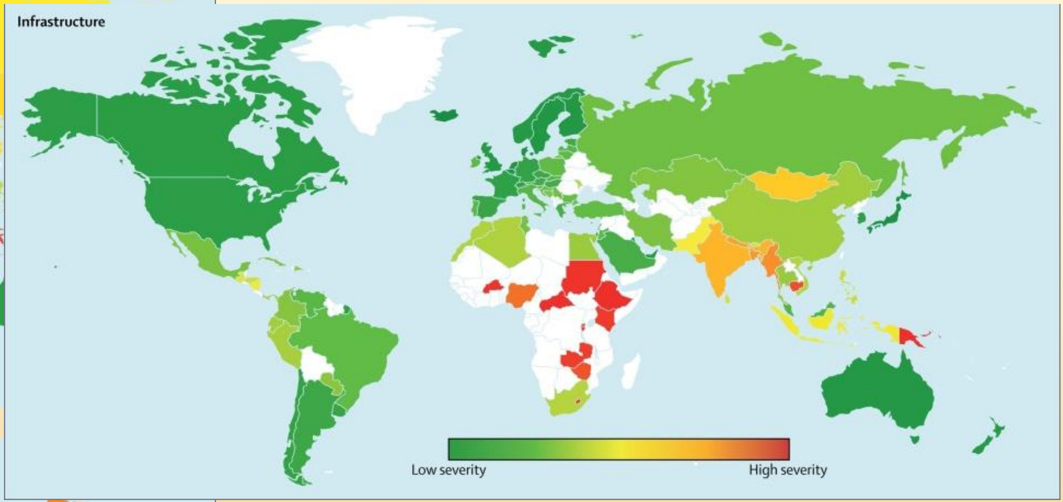
Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

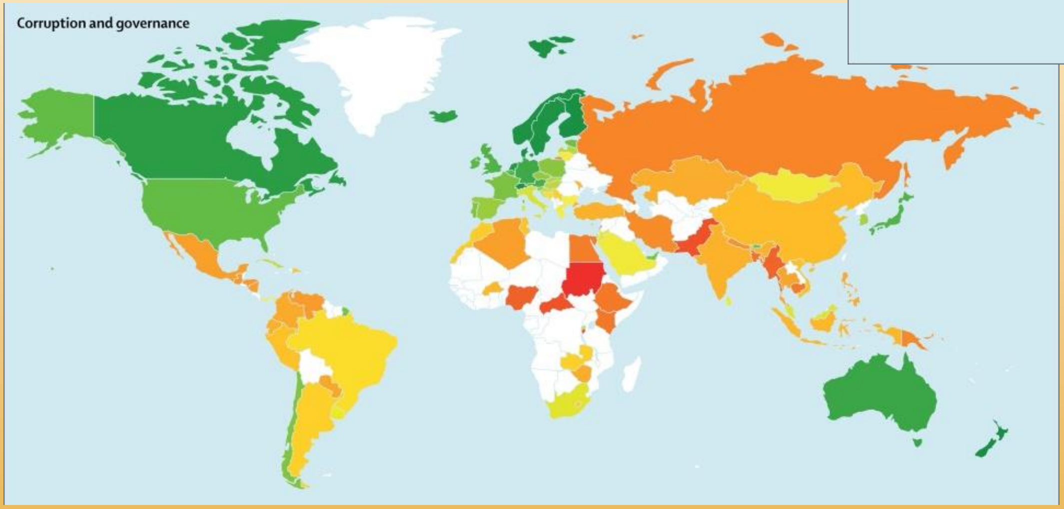
Peter Collignon, John J Beggs, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan



Collignon et al., Lancet Planet Health, 2018







"Reduction of antibiotic consumption will not be sufficient to control antimicrobial resistance because contagion-the spread of resistant strains and resistance genes-seems to be the dominant contributing factor. Improving sanitation, increasing access to clean water, and ensuring good governance, as well as increasing public health-care expenditure and better regulating the private health sector are all necessary to reduce global antimicrobial resistance."

Collignon et al., Lancet Planet Health, 2018

Classification of antibiotics

- Non-Medically Important Antibiotics
  - Those antibiotic classes NOT used in human medicine
- Medically Important Antibiotics
  - Those antibiotic classes used in human medicine
  - Critically Important Antibiotics (WHO)
    - The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people
    - The antimicrobial class is used to treat infections in people caused by either (1) bacteria that may be transmitted to humans from non-human sources or (2) bacteria that may acquire resistance genes from non-human sources

Antibiotic approvals in U.S.

- Growth promotion / feed efficiency
  - Use of antimicrobial substances to increase the rate of weight gain and/or the efficiency of feed utilization
- Disease prevention
  - Use of an antimicrobial(s) in healthy animals considered to be at risk of infection
- Disease control
  - Use of an antimicrobial(s) in animals exposed to an infectious disease or illness
- Disease treatment
  - Use of an antimicrobial(s) for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness

Changes in USA, Jan. 1, 2017 Veterinary Feed Directive

- Elimination of the growth promotion label for medically important antibiotics
- Disease prevention still exists
- Prescriptions are required by veterinarian for all medically important antibiotic use
- This was a voluntary action by pharmaceutical companies and animal agriculture

Antibiotics used in U.S. broiler production

Medically important

Route of Administration	Drug Class	Classification	Active Ingredient
Injectable			
	Aminoglycosides	Highly Important	Gentamicin
Feed			
	Diaminopyrimidines	Critically Important	Ormetoprim
	Streptogramins	Highly Important	Virginiamycin
	Sulfonamides	Critically Important	Sulfadimethoxine
	Tetracyclines	Highly Important	Chlortetracycline
			Oxytetracycline
Water			
	Aminoglycosides	Highly Important	Neomycin
			Spectinomycin
	Lincosamides	Highly Important	Lincomycin
	Macrolides	Critically Important	Tylosin
	Natural penicillins	Highly Important	Penicillin G
	Sulfonamides	Critically Important	Sulfadimethoxine
			Sulfamerazine
			Sulfamethazine
			Sulfaquinoxaline
	Tetracyclines	Highly Important	Chlortetracycline
			Oxytetracycline
			Tetracycline

Non-medically important

Route of Administration	Drug Class	Active Ingredient
Feed		
	Glycolipids	Bambermycins
	Ionophores	Lasalocid
		Monensin
		Narasin
		Salinomycin
	Orthosomycins	Avilamycin
	Polypeptides	Bacitracin
Water		
	Polypeptides	Bacitracin

Estimates of On-Farm Antimicrobial Usage in Broiler Chicken and Turkey Production in the United States, 2013 – 2017

Randall S. Singer, DVM, MPVM, PhD
Mindwalk Consulting Group, LLC

Leah Porter
Mindwalk Consulting Group, LLC

Antibiotic use in U.S. broiler production

	Antimicrobial Usage in Broilers (kg of antimicrobial)			% Change	
Antimicrobial Class	2013	2016	2017	2013-2017	2016-2017
Aminoglycosides	1,651	837	508	-69%	-39%
Lincosamides	3,584	4,360	2,604	-27%	-40%
Macrolides	8,048	10,591	900	-89%	-92%
Penicillins	17,309	27,955	17,398	1%	-38%
Sulfonamides	5,221	1,915	1,892	-64%	-1%
Tetracyclines	107,633	22,103	15,366	-86%	-30%

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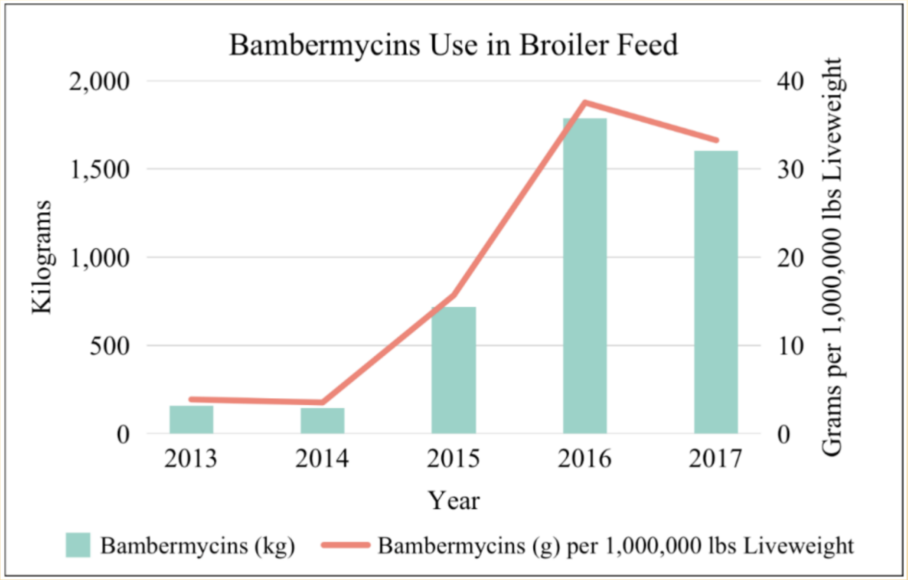
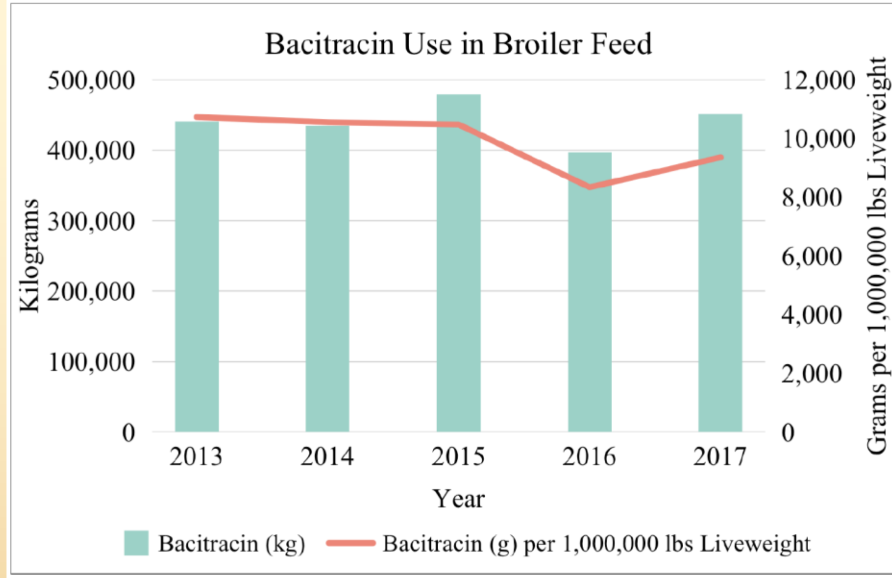
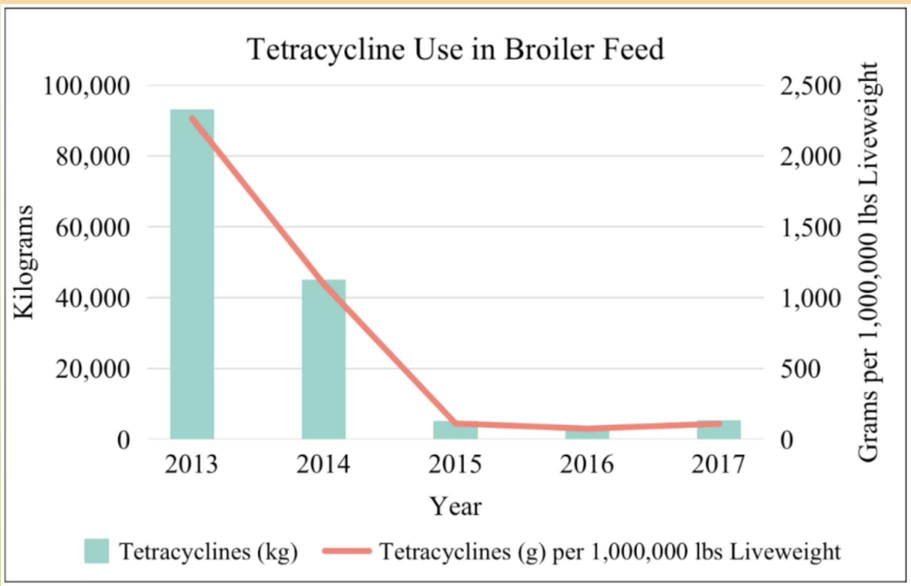
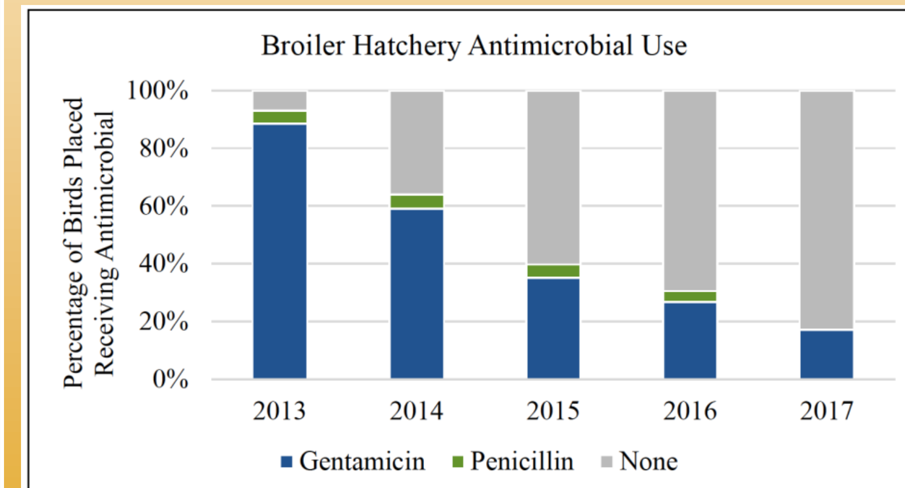

Bambermycins Use in Broiler Feed
Kilograms
2,000
1,500
1,000
500
0
Grams per 1,000,000 lbs Liveweight
40
30
20
10
0
2013
2014
2015
2016
2017
Year
Bambermycins (kg)
Bambermycins (g) per 1,000,000 lbs Liveweight


Bacitracin Use in Broiler Feed
Kilograms
500,000
400,000
300,000
200,000
100,000
0
Grams per 1,000,000 lbs Liveweight
12,000
10,000
8,000
6,000
4,000
2,000
0
2013
2014
2015
2016
2017
Year
Bacitracin (kg)
Bacitracin (g) per 1,000,000 lbs Liveweight


Tetracycline Use in Broiler Feed
Kilograms
100,000
80,000
60,000
40,000
20,000
0
Grams per 1,000,000 lbs Liveweight
2,500
2,000
1,500
1,000
500
0
2013
2014
2015
2016
2017
Year
Tetracyclines (kg)
Tetracyclines (g) per 1,000,000 lbs Liveweight


Broiler Hatchery Antimicrobial Use
Percentage of Birds Placed Receiving Antimicrobial
100%
80%
60%
40%
20%
0%
2013
2014
2015
2016
2017
Gentamicin
Penicillin
None

Antibiotic use in U.S. turkey production

Antimicrobial Class	Antimicrobial Usage in Turkeys (kg of antimicrobial)			% Change	
	2013	2016	2017	2013-2017	2016-2017
Aminoglycosides	11,382	9,278	6,579	-42%	-29%
Amphenicols	27	87	153	461%	76%
Cephalosporins	19	8	0	-100%	-100%
Lincosamides	4,364	5,424	2,847	-35%	-48%
Macrolides	246	320	693	182%	117%
Penicillins	399,003	384,933	280,901	-30%	-27%
Sulfonamides	21,782	15,888	20,851	-4%	31%
Tetracyclines	186,624	164,662	111,836	-40%	-32%

Estimates of On-Farm Antimicrobial Usage in Broiler Chicken and Turkey Production in the United States, 2013 – 2017

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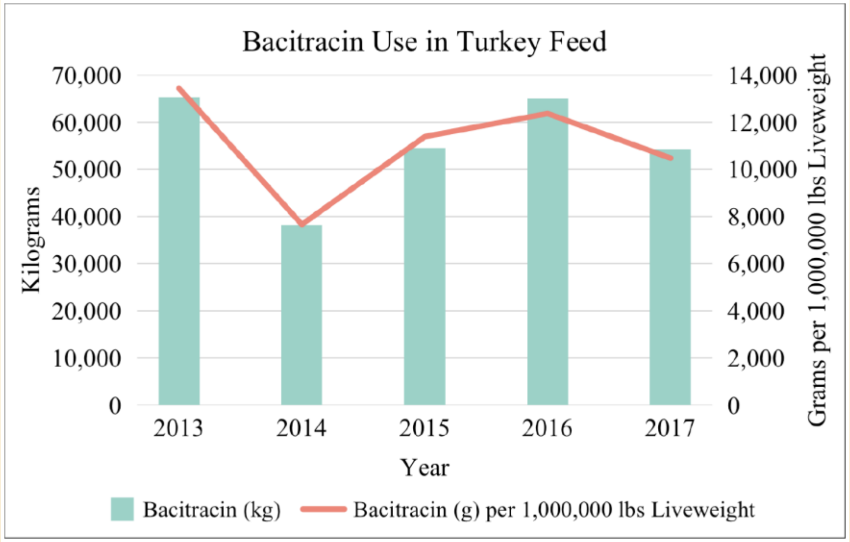
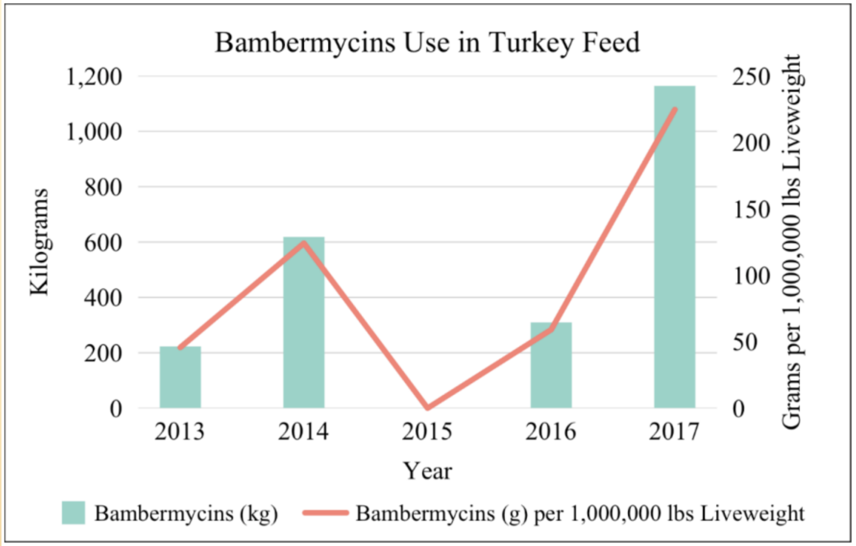
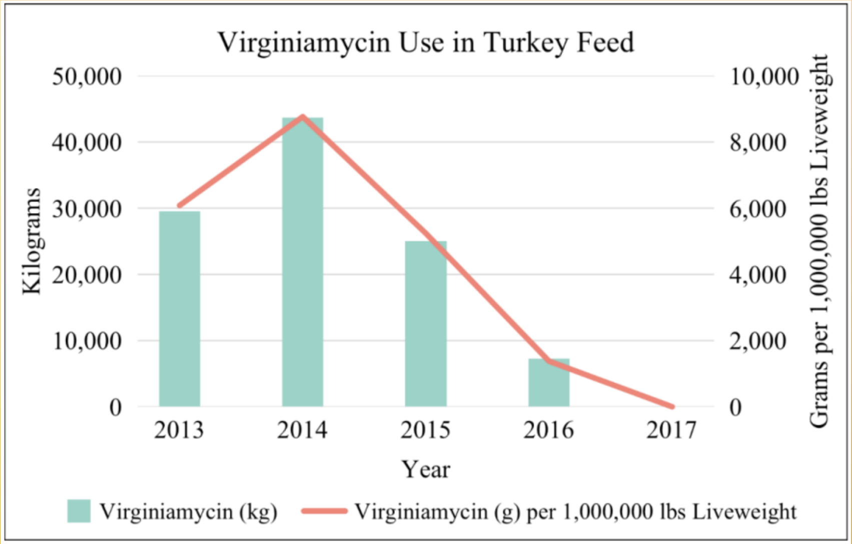
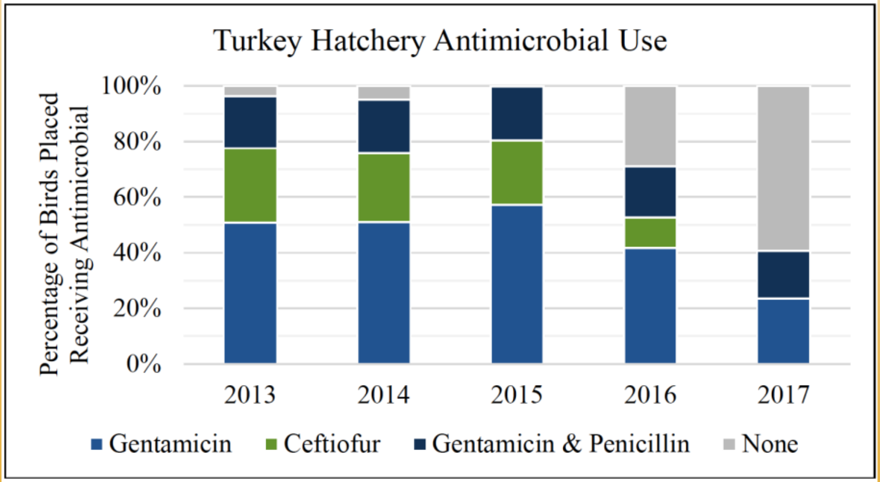

Bacitracin Use in Turkey Feed
Kilograms
Grams per 1,000,000 lbs Liveweight
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
2013
2014
2015
2016
2017
Year
Bacitracin (kg)
Bacitracin (g) per 1,000,000 lbs Liveweight


Bambermycins Use in Turkey Feed
Kilograms
Grams per 1,000,000 lbs Liveweight
1,200
1,000
800
600
400
200
0
250
200
150
100
50
0
2013
2014
2015
2016
2017
Year
Bambermycins (kg)
Bambermycins (g) per 1,000,000 lbs Liveweight


Virginiamycin Use in Turkey Feed
Kilograms
Grams per 1,000,000 lbs Liveweight
50,000
40,000
30,000
20,000
10,000
0
10,000
8,000
6,000
4,000
2,000
0
2013
2014
2015
2016
2017
Year
Virginiamycin (kg)
Virginiamycin (g) per 1,000,000 lbs Liveweight


Turkey Hatchery Antimicrobial Use
Percentage of Birds Placed Receiving Antimicrobial
100%
80%
60%
40%
20%
0%
2013
2014
2015
2016
2017
Gentamicin
Ceftiofur
Gentamicin & Penicillin
None

Why we don’t want blanket reduction targets

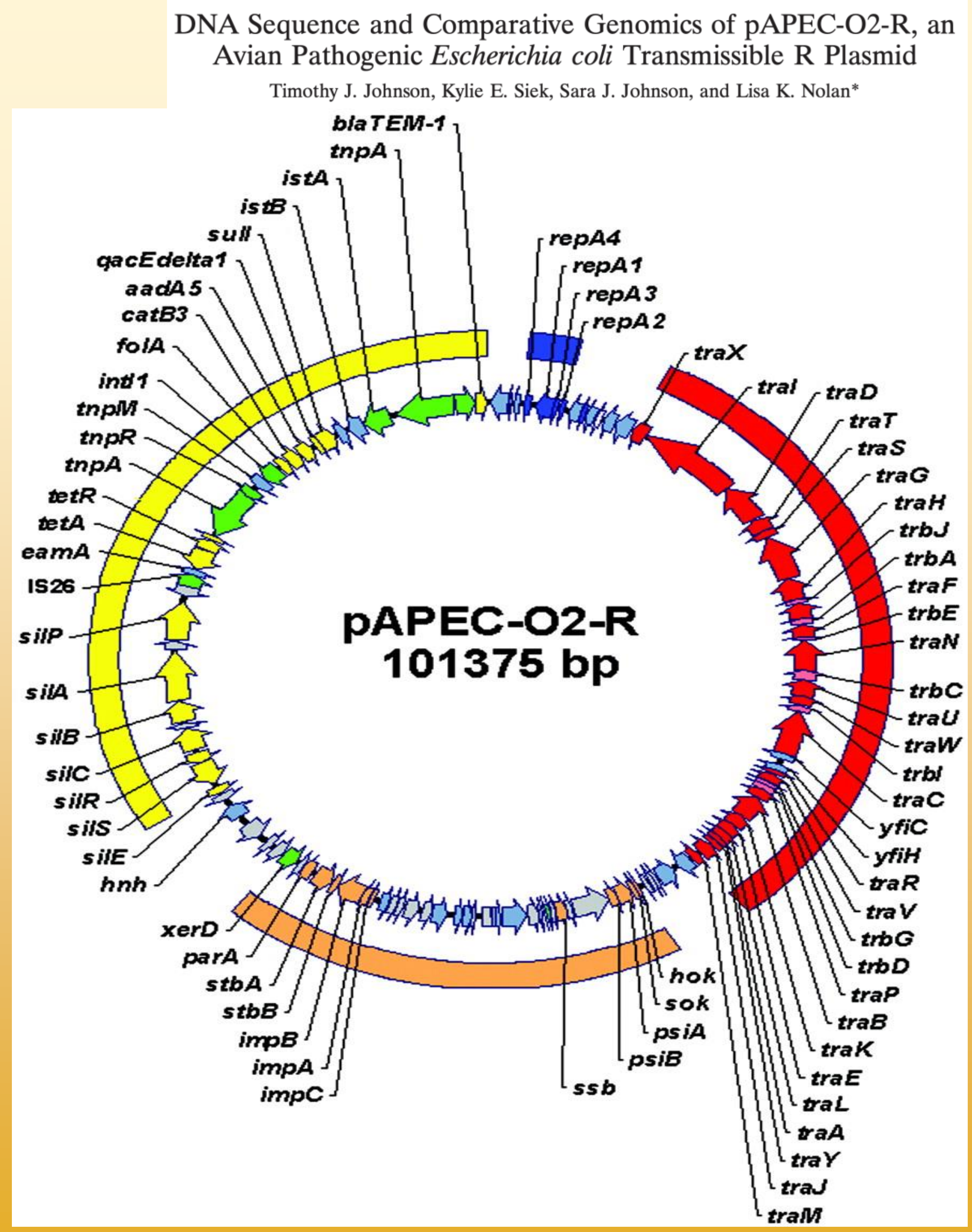
Treatment of *E. coli* diseases in poultry

	Sulfadimethoxine	Tetracycline
Number of packs of drug	25 packs	31 packs
Active drug per pack	480 g / pack (gallon)	1,400 g / pack
Total active drug (g)	12,000 g	43,400 g
Active drug per bird	480 mg / bird	1,736 mg / bird
Active drug per kg body weight (BW)	150.9 mg / kg BW	545.9 mg / kg BW
Active drug per kg per day	30.2 mg / kg BW / day	109.2 mg / kg BW / day
Animal-Days of therapy	125,000	125,000
Therapeutic regimens	25,000	25,000

The Game Changer – avian *E. coli*

The game changer

- Laying hen clinical *E. coli* from Iowa
- Resistance to 6 classes of Abx
- Class 1 integron
- Heavy metal resistance
- Disinfectant resistance
- Ubiquitous



What is avian colibacillosis?

- Range of localized and systemic infections
- Etiology (cause) is *E. coli*
- Death results from systemic infection
- Prior to death, many “entry points” exist for *E. coli*:
  - Airborne
  - Ascending (reproductive)
  - Skin breaks
  - In ovo or during hatch

APEC = avian pathogenic *E. coli*

frontiers in
VETERINARY SCIENCE

PERSPECTIVE ARTICLE
published: 14 October 2014
doi: 10.3389/fvets.2014.00005

Is the concept of avian pathogenic *Escherichia coli* as a single pathotype fundamentally flawed?

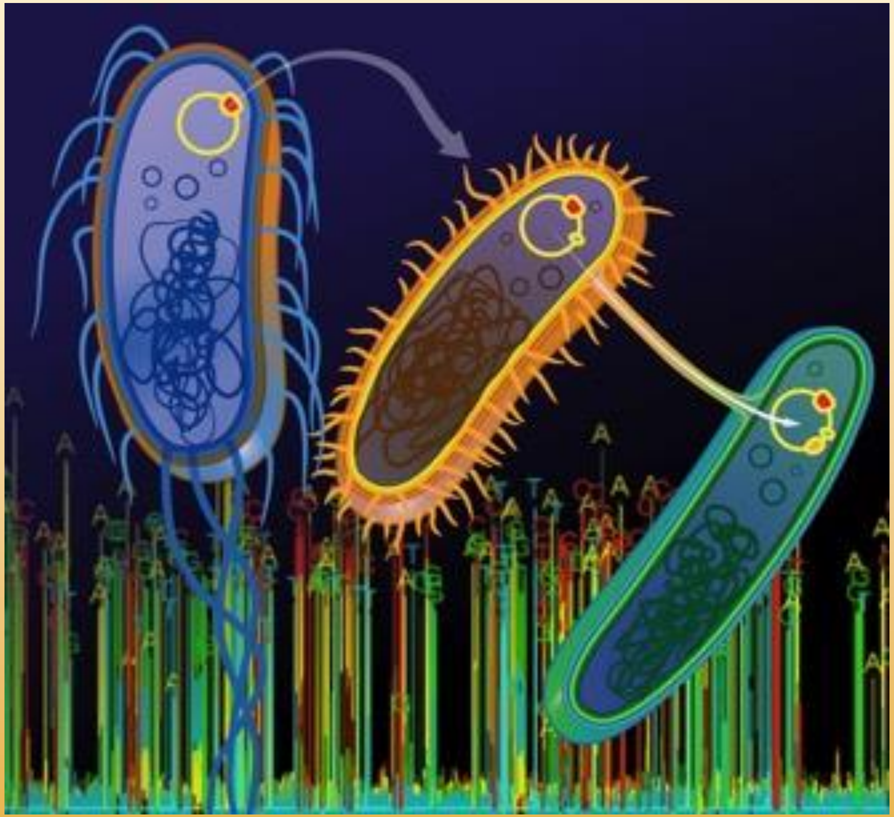
Charlotte Collingwood[1], Kirsty Kemmett[1], Nicola Williams[2] and Paul Wigley[1]*

[1] *Department of Infection Biology, Institute of Infection and Global Health, School of Veterinary Science, University of Liverpool, Neston, UK*
[2] *Department Epidemiology and Population Health, Institute of Infection and Global Health, School of Veterinary Science, University of Liverpool, Neston,*

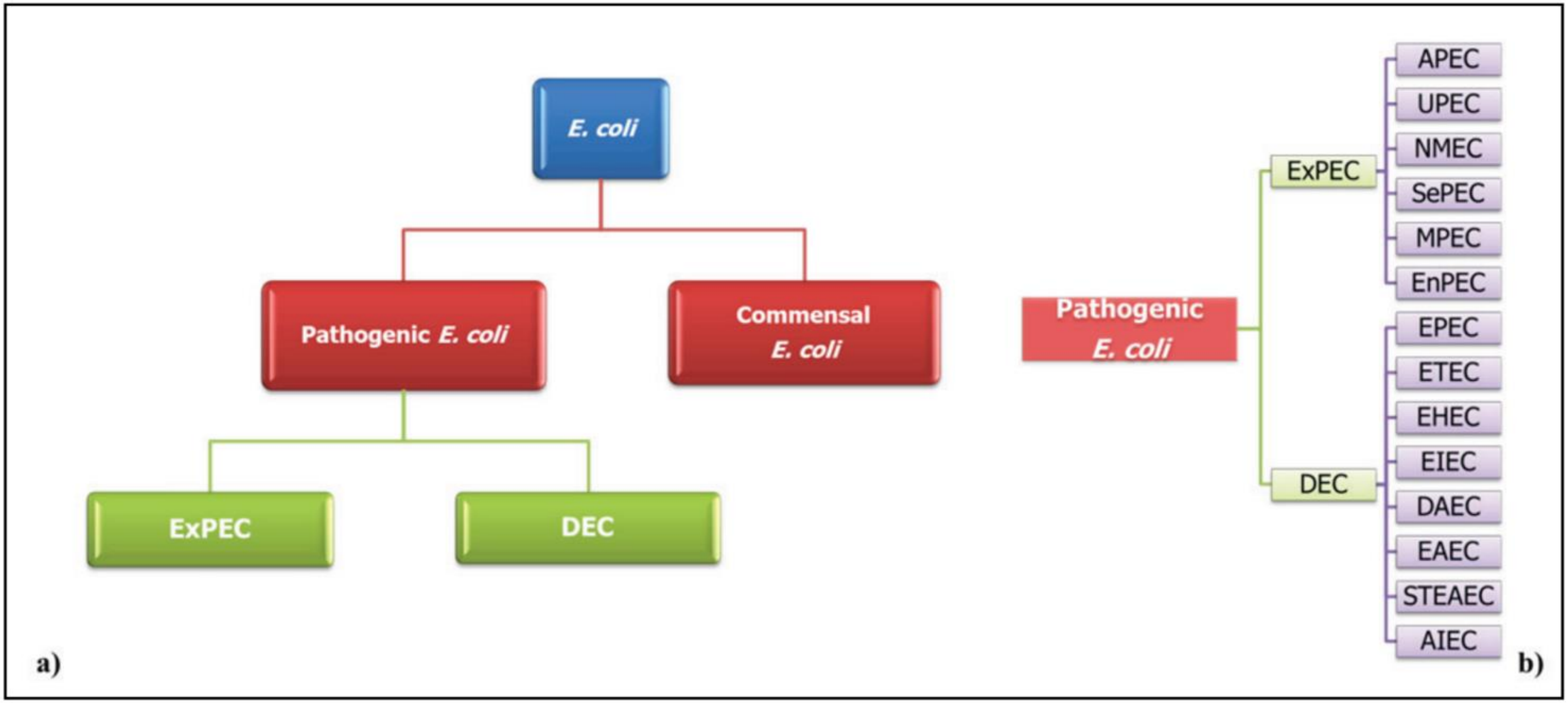
In conclusion, we believe that *E. coli* disease in the chicken cannot be simply defined as being caused by a single pathotype of *E. coli*. In particular, colibacillosis is perhaps better defined as disease caused by *E. coli* rather than by Avian Pathogenic *E. coli*, and that the term APEC be reserved for the smaller number of well-defined "bona fide" pathogenic isolates with a range of defined virulence determinants that can reproduce disease in animal models. There are APEC, but not all disease-associated with *E. coli* in the chicken is caused by APEC.

What is a plasmid?

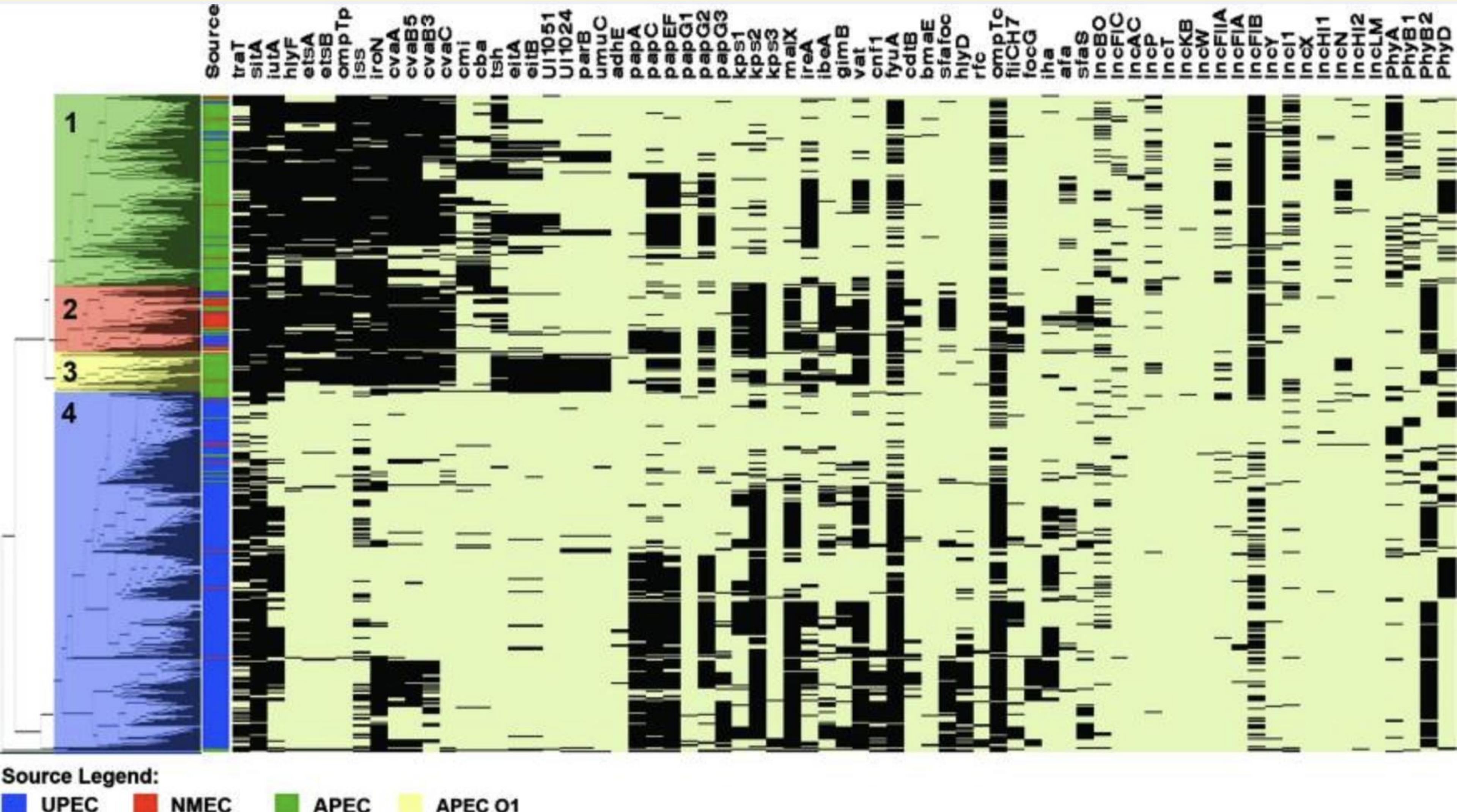
- “Extra” DNA
- Self-replicating
- Sometimes transmissible
- Circular
- Most *E. coli* pathotypes are defined by their plasmids
- APEC is defined by a single plasmid



E. coli pathotypes



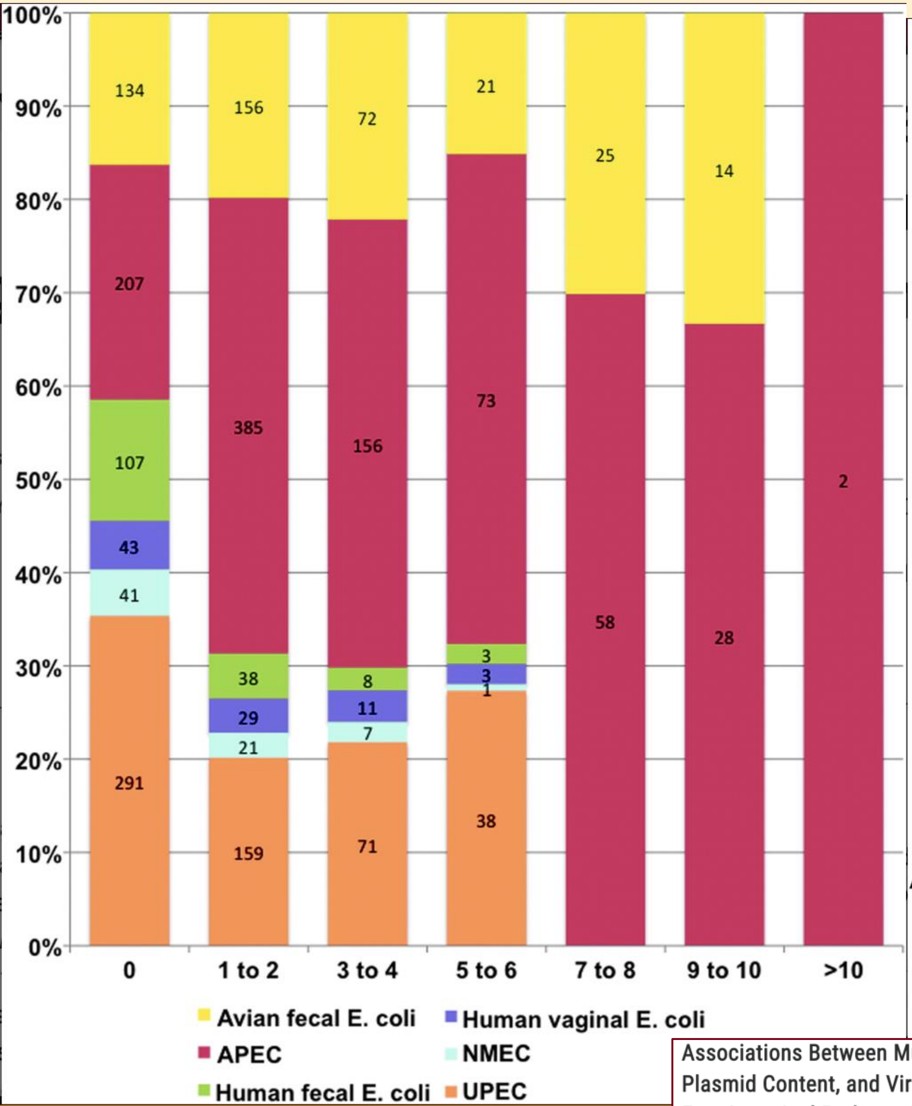
APEC are similar to *some* human ExPEC

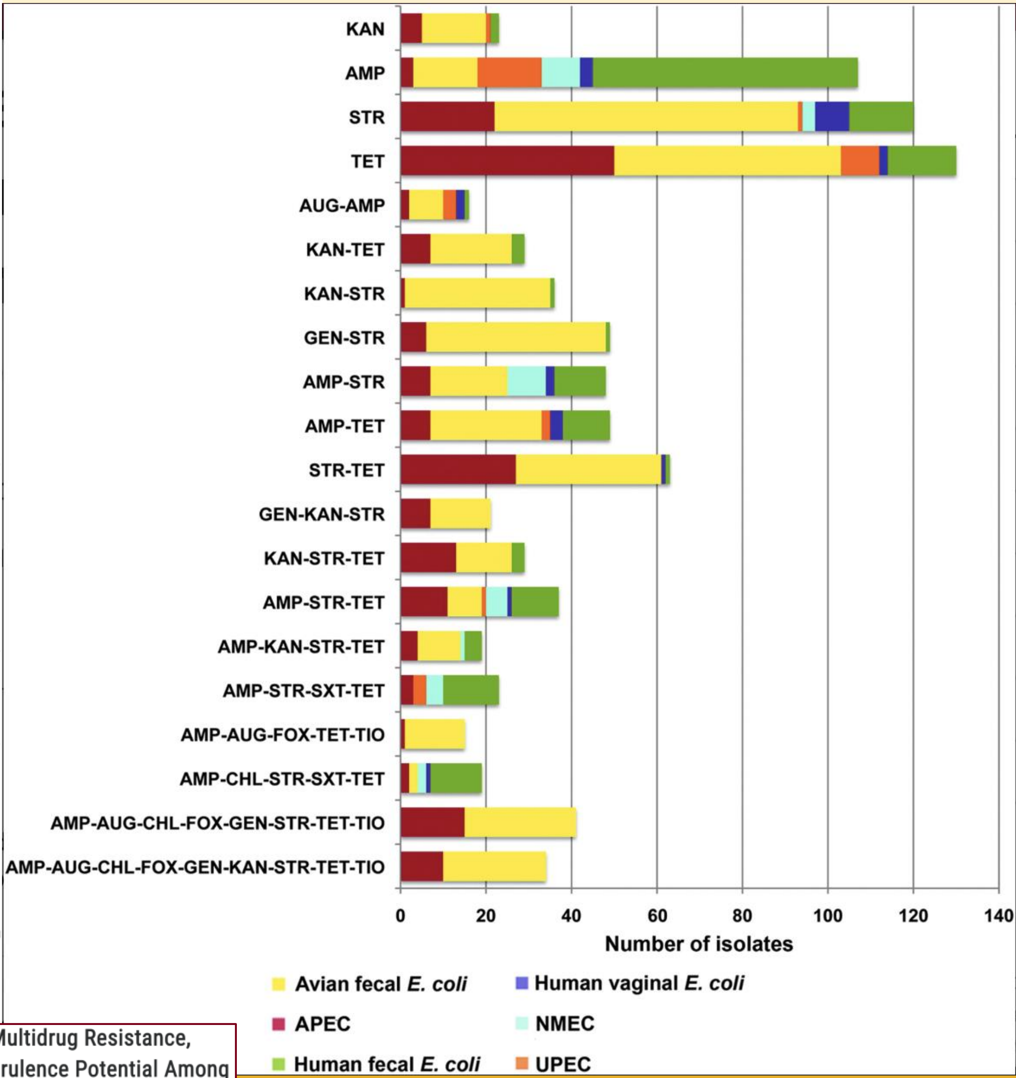


Comparison of Extraintestinal Pathogenic *Escherichia coli* Strains from Human and Avian Sources Reveals a Mixed Subset Representing Potential Zoonotic Pathogens[∇]

Timothy J. Johnson,[1,2] Yvonne Wannemuehler,[2] Sara J. Johnson,[2] Adam L. Stell,[1] Curt Doetkott,[3] James R. Johnson,[4] Kwang S. Kim,[5] Lodewijk Spanjaard,[6] and Lisa K. Nolan[2]*

APEC are MDR





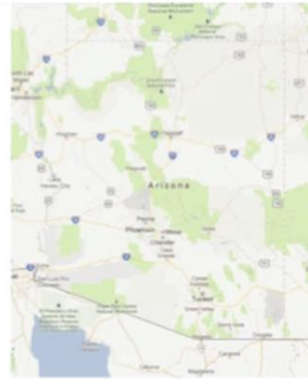
Associations Between Multidrug Resistance, Plasmid Content, and Virulence Potential Among Extraintestinal Pathogenic and Commensal *Escherichia coli* from Humans and Poultry

Timothy J. Johnson, Catherine M. Logue, James R. Johnson, Michael A. Kuskowski, Julie S. Sherwood, H. John Barnes, Chitrita DebRoy, Yvonne M. Wannemuehler, Mana Obata-Yasuoka, Lodewijk Spanjaard, and Lisa K. Nolan

Foodborne urinary tract infections (FUTIs): Colonizing opportunistic pathogens (COPs)

- Eat undercooked chicken or touch contaminated surfaces
- Touch your mouth with your fingers
- Get colonized with drug resistant *E. coli* from the chicken
- Time goes on
- Get a UTI

Flagstaff, AZ

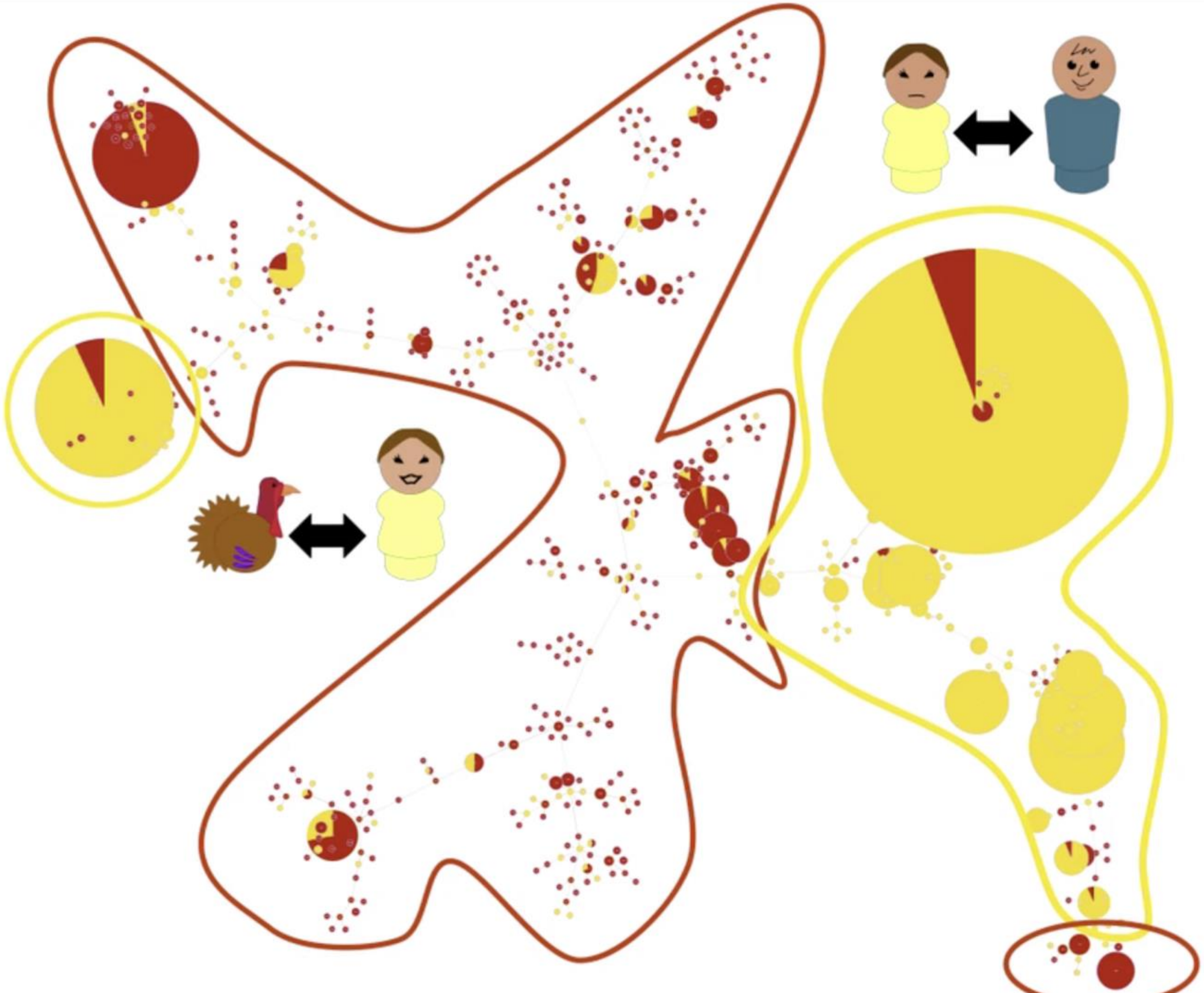


- Sampled *E. coli* for 1 year
- All brands chicken, turkey and pork
  - All stores
  - All brands
  - ~2500 retail meats
- All bladder and kidney infections
  - ~1500 infections

Lance B. Price, PhD

Professor,
George Washington University

Director,
Center for Food Microbiology and Environmental Health,
Translational Genomics Research Institute (TGen)



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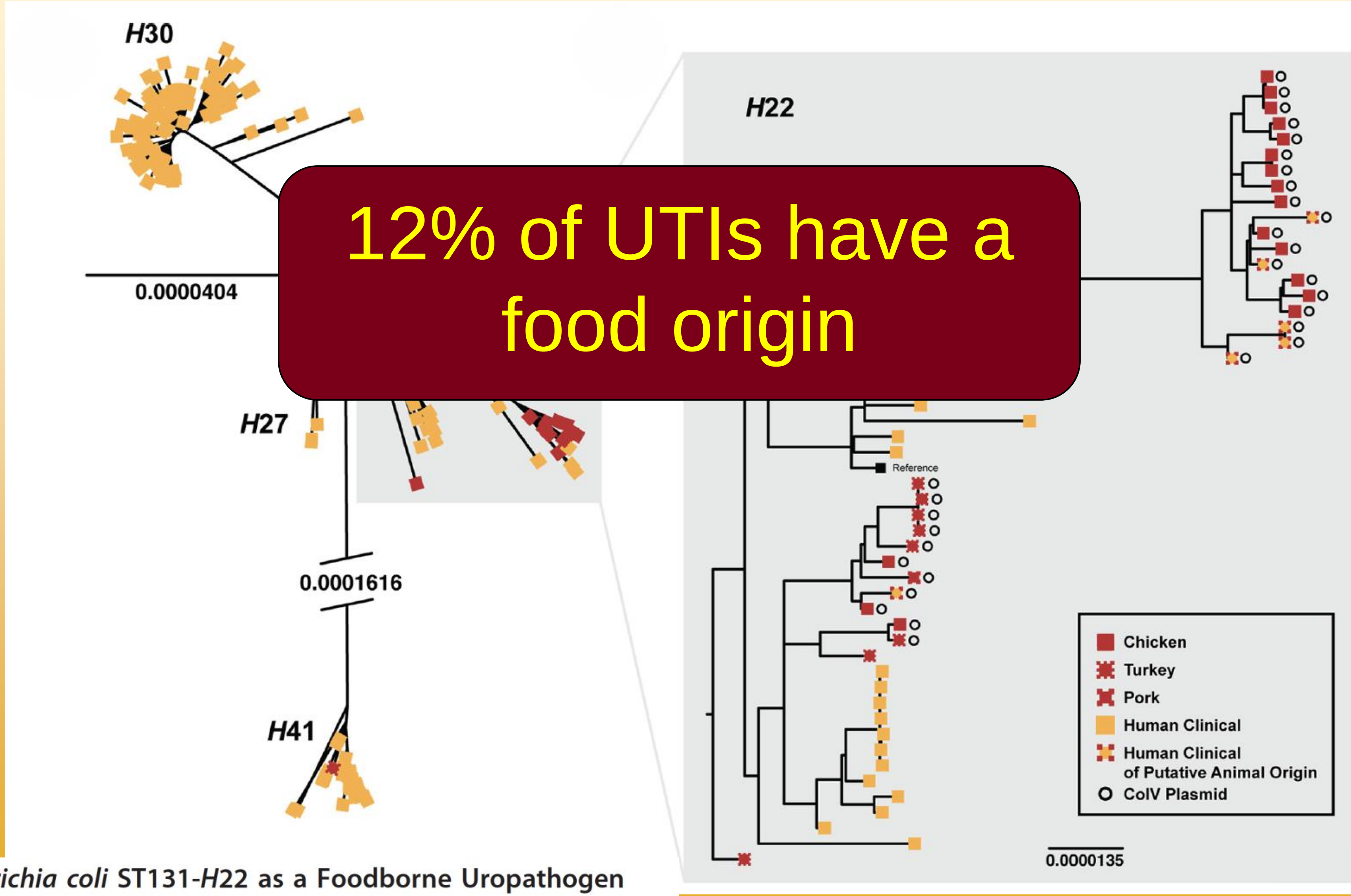
Translational Genomics Research Institute (TGen)

Host-adaptive markers provide higher resolution

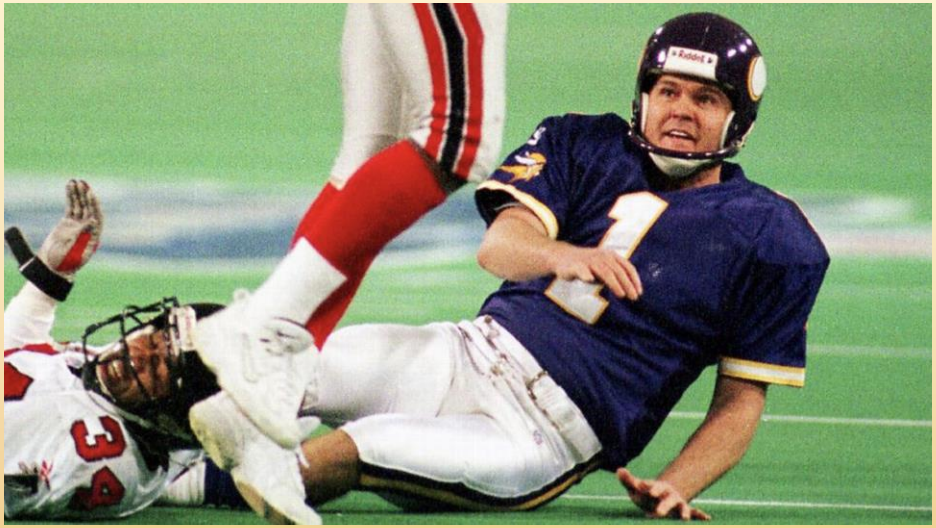


12% of UTIs have a food origin

Escherichia coli ST131-*H22* as a Foodborne Uropathogen

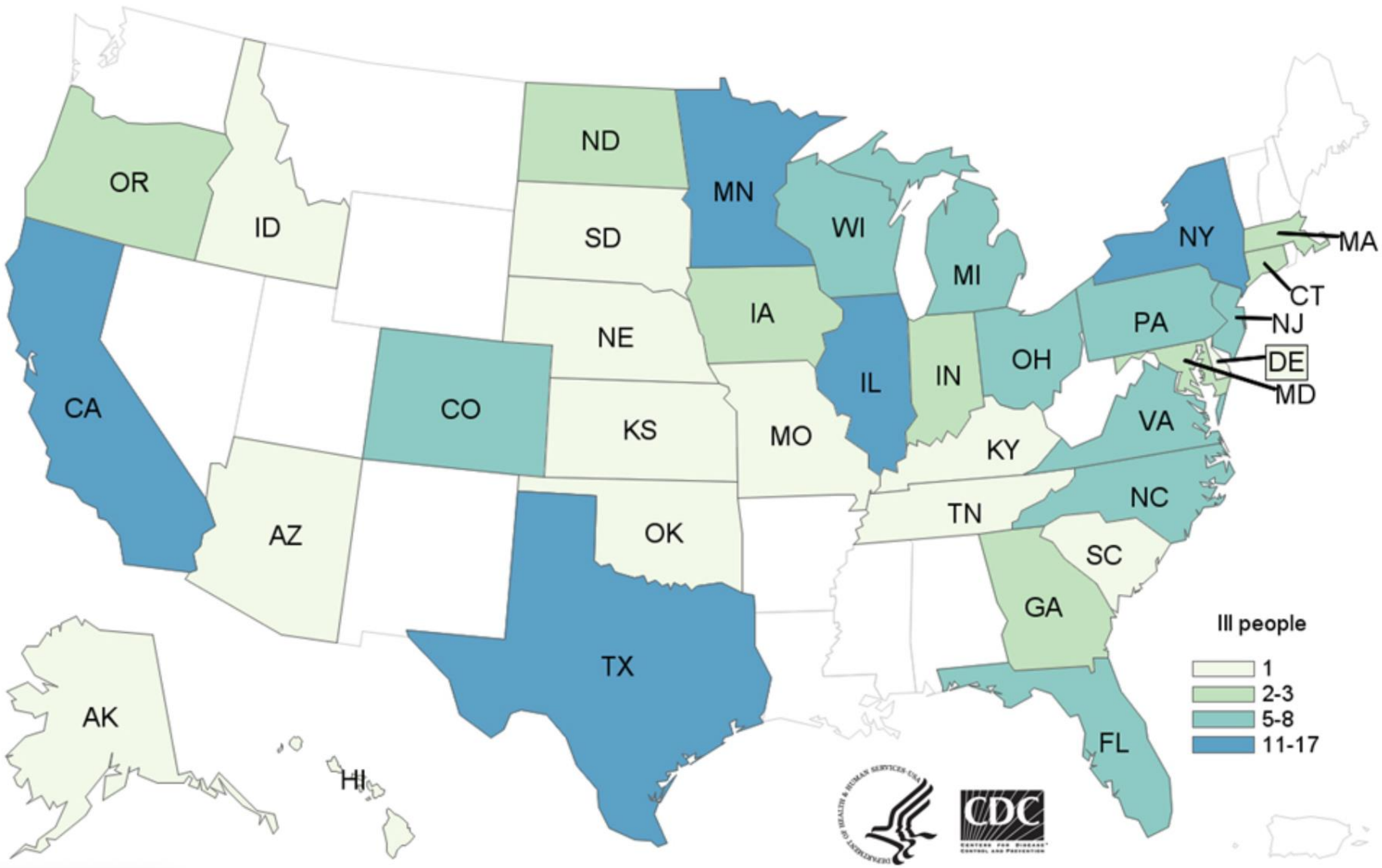
Cindy M. Liu,[a,b,c] Marc Stegger,[a,d] Maliha Aziz,[a,c] Timothy J. Johnson,[e] Kara Waits,[c] Lora Nordstrom,[c] Lori Gauld,[f] Brett Weaver,[c,f] Diana Rolland,[f] Sally Statham,[c] Joseph Horwinski,[c] Sanjeev Sariya,[a] Gregg S. Davis,[a] Evgeni Sokurenko,[g] Paul Keim,[b] James R. Johnson,[h,i] Lance B. Price[a,c]

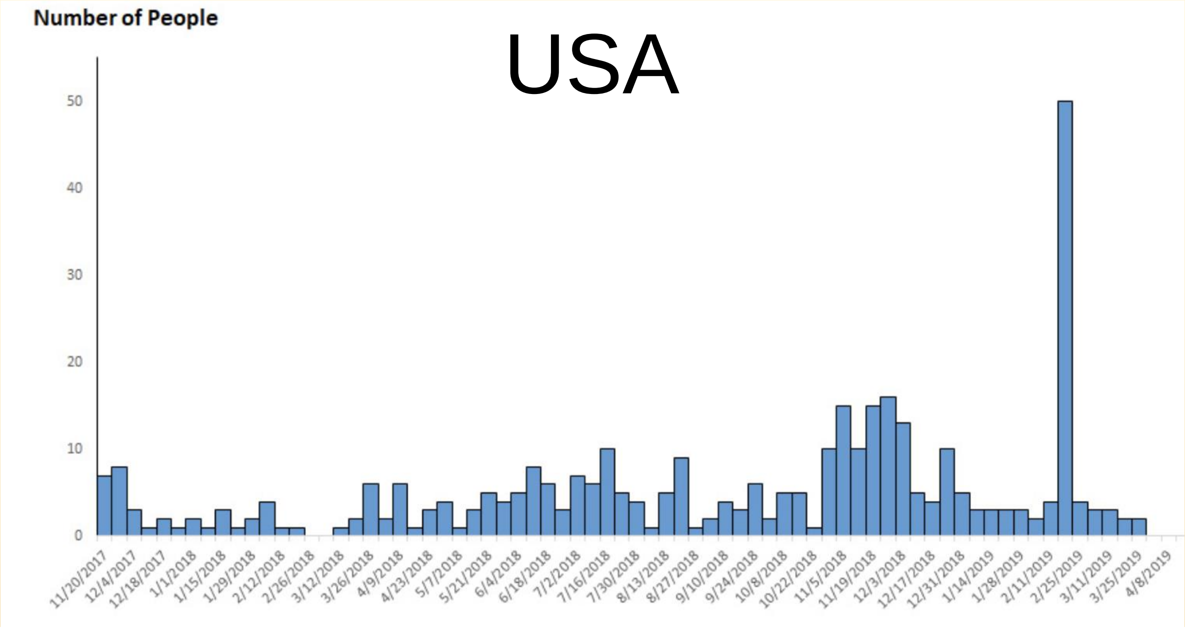
Game Changer #2 – *Salmonella* Reading



Salmonella Reading outbreak: raw turkey products, no single company, multi-state, multi-country

People infected with the outbreak strain of *Salmonella* Reading, by state of residence, as of November 5, 2018 (n=164)




USA
Number of People
0
10
20
30
40
50
11/20/2017
12/4/2017
12/18/2017
1/1/2018
1/15/2018
1/29/2018
2/12/2018
2/26/2018
3/12/2018
3/26/2018
4/9/2018
4/23/2018
5/7/2018
5/21/2018
6/4/2018
6/18/2018
7/2/2018
7/16/2018
7/30/2018
8/13/2018
8/27/2018
9/10/2018
9/24/2018
10/8/2018
10/22/2018
11/5/2018
11/19/2018
12/3/2018
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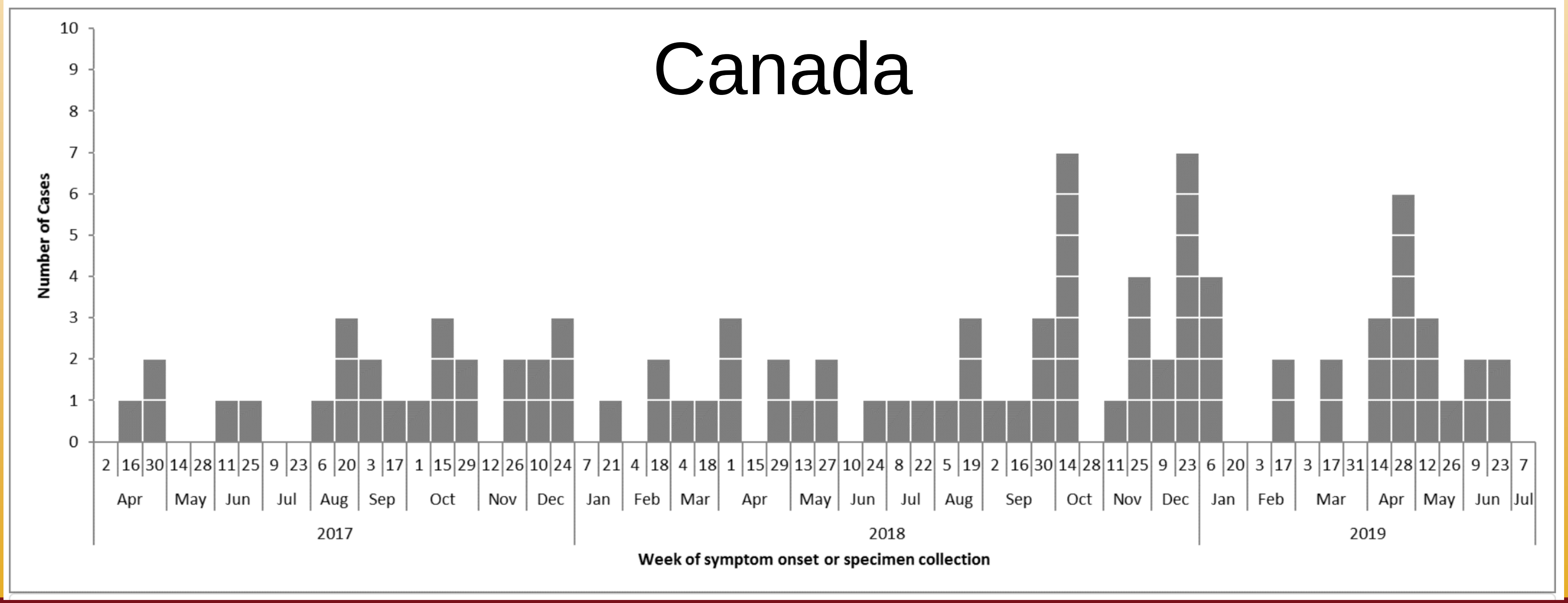
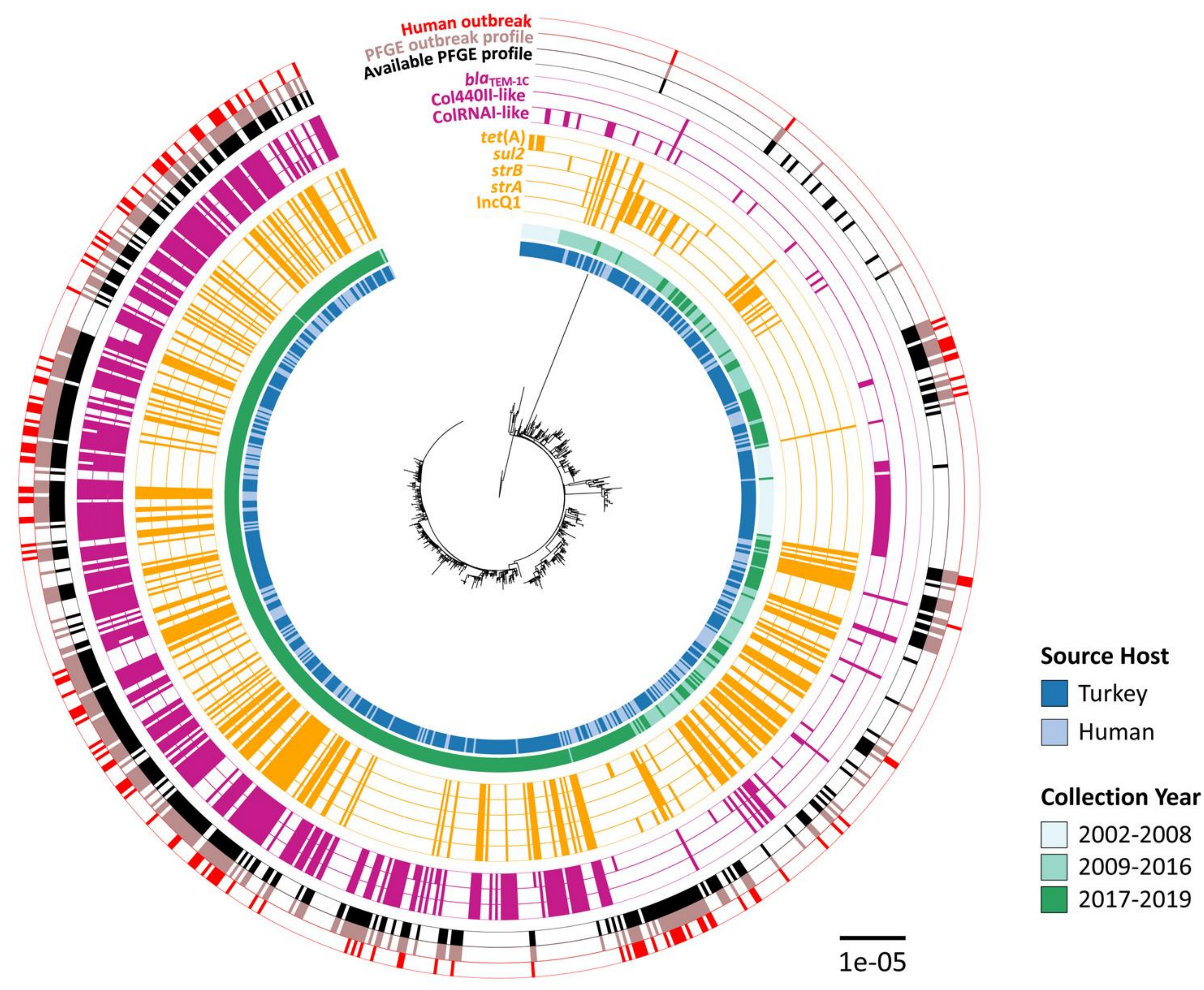
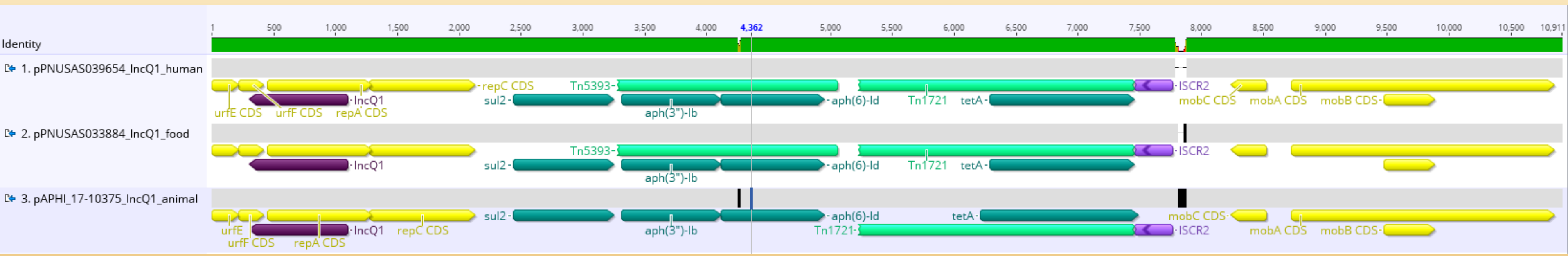
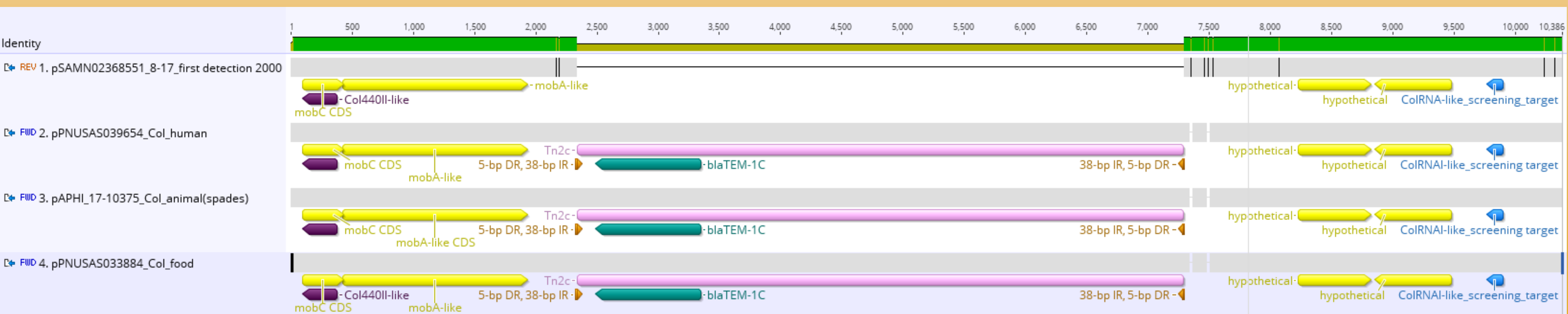
3/11/2019
3/25/2019
4/8/2019


Canada
Number of Cases
0
1
2
3
4
5
6
7
8
9
10
2 16 30 14 28 11 25 9 23 6 20 3 17 1 15 29 12 26 10 24 7 21 4 18 4 18 1 15 29 13 27 10 24 8 22 5 19 2 16 30 14 28 11 25 9 23 6 20 3 17 3 17 31 14 28 12 26 9 23 7
Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul
2017
2018
2019
Week of symptom onset or specimen collection


Human outbreak
PFGE outbreak profile
Available PFGE profile
blaTEM-1C
Col440II-like
ColRNAI-like
tet(A)
sul2
strB
strA
IncQ1
1e-05
Source Host
Turkey
Human
Collection Year
2002-2008
2009-2016
2017-2019

Resistance pattern	Resistance genes		Plasmids
ASSuT	*bla*$_{\text{TEM-1C}}$	*strAB sul2 tetA*	IncQ1 + Col440II
A	*bla*$_{\text{TEM-1C}}$		Col440II
SSuT		*strAB sul2 tetA*	IncQ1





Simple explanation? Resistance

- Biofilm formation
- Adherence/invasion in avian cells
- Adherence/invasion in human cells
- Environmental survival
- Fitness during enrichment
- Resistance to disinfectants
- Work in progress – pointing towards plasmids conferring some or all of these traits

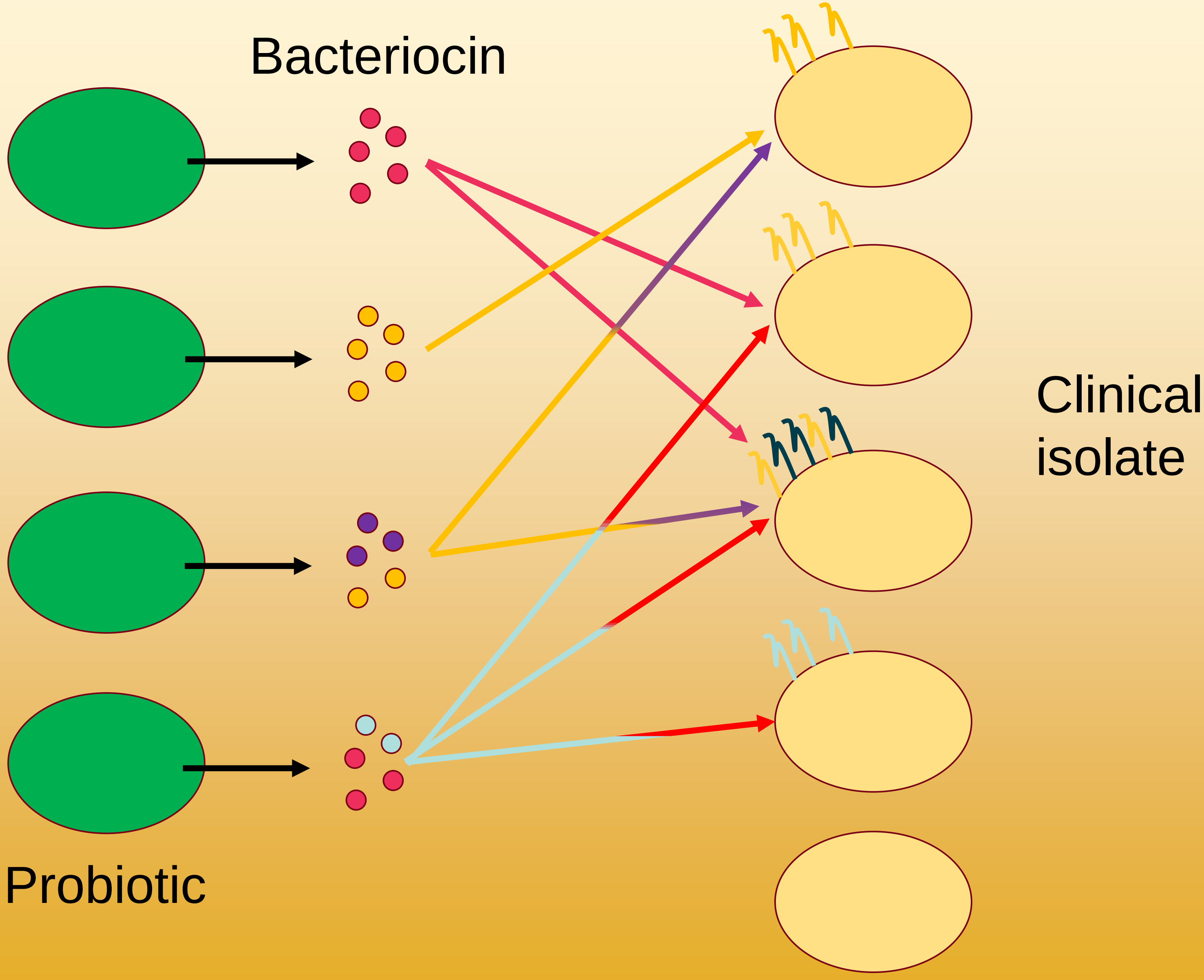
Where do we go from here?
Alternative products to control pathogens and sustain health

How do you choose your probiotics?

Probiotics: approaches

- Generally there are two concepts:
  - Continuously feed (most direct fed microbials)
  - Target at specific times (hatch, movement, disease challenge, vaccination)
- Generally there are two approaches:
  - Find a probiotic strain with the right properties, don't care if it colonizes
  - Find colonizing strains that will stick around

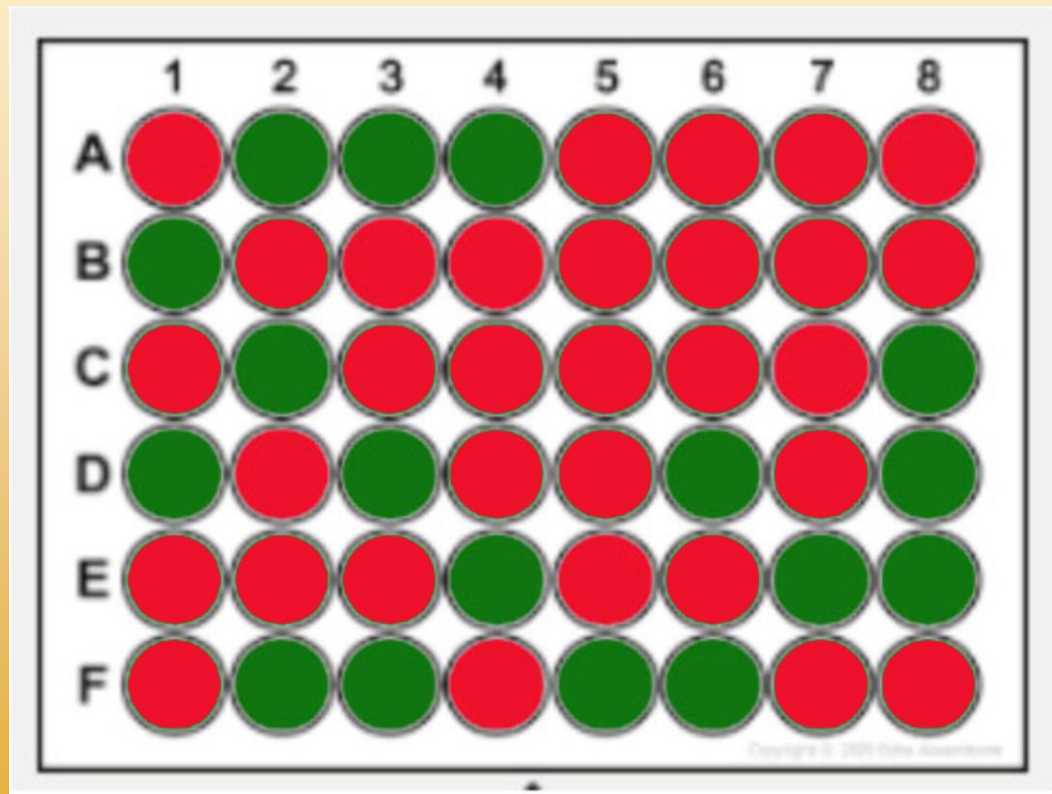
Probiotics tailored to target specific strains



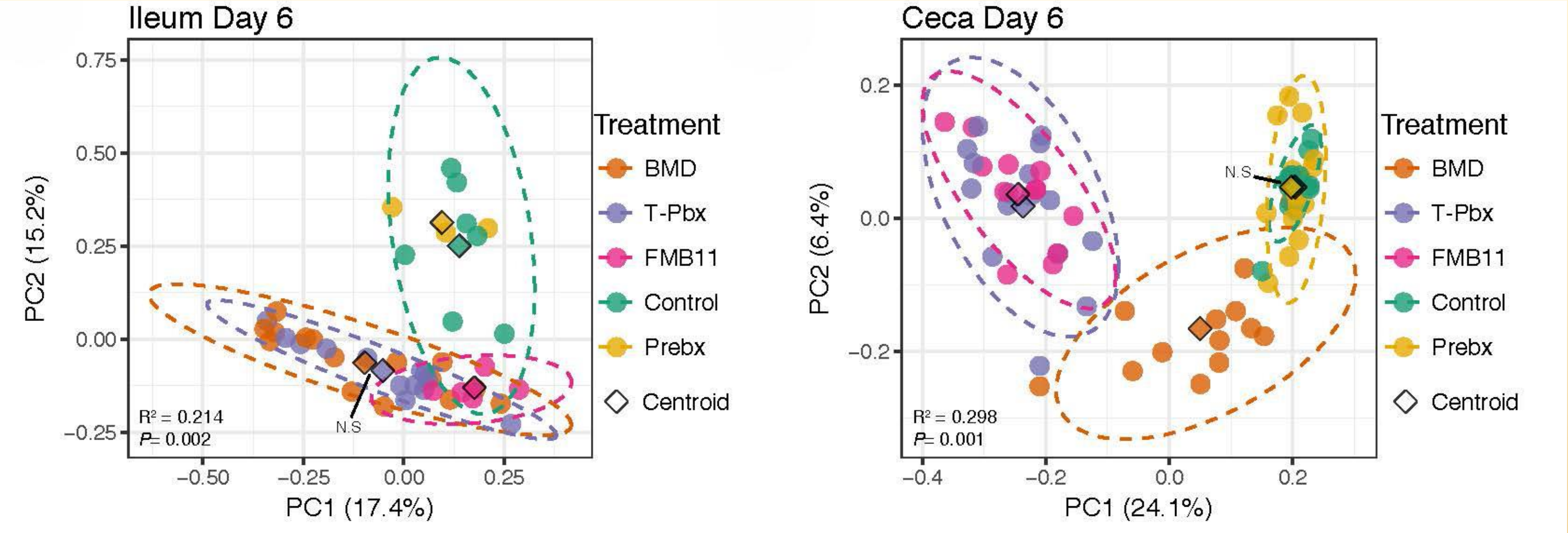
Resistance is not limited to antibiotics

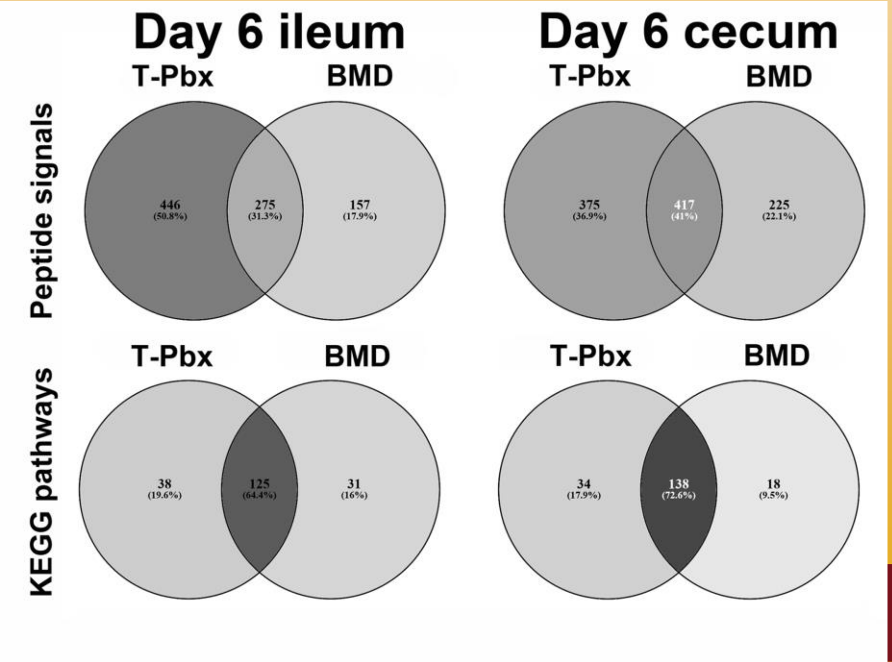
Probiotic supernatant

APEC strain



Host-tailored probiotics can mimic effects of antibiotic growth promoters





What is the future for feed additives or antibiotic alternatives?

- Better surveillance
  - Genome-based
  - Farm-specific
  - Proactive
  - Judicious
  - Multi-pronged
  - Uses math and modeling

“Next-gen” product workflow

1. Surveillance of the pathogens on farm through high resolution techniques (whole genome sequencing)
2. Identification of common problematic pathogen clones
3. Creation of a custom product targeting those clones
4. Continued surveillance of pathogen following implementation
5. Prediction of the next “shift”
6. Switching of product at least every 1-2 years

<u>This only works if all 6 steps are followed!</u>

ANIMALS

PEOPLE

Minnesota

ONE HEALTH

Antibiotic Stewardship Collaborative

ENVIRONMENT

WORKING TOGETHER TO

PROTECT HEALTH & PRESERVE ANTIBIOTICS

GCC 3016 Antibiotic resistance: How can we avoid the apocalypse?

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