STATENS SERUM INSTITUT

Genomes, host markers and resistance genes in *E. coli* from a One Health perspective

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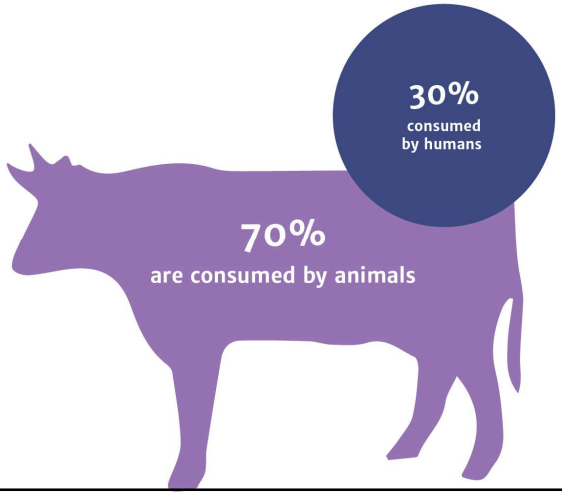
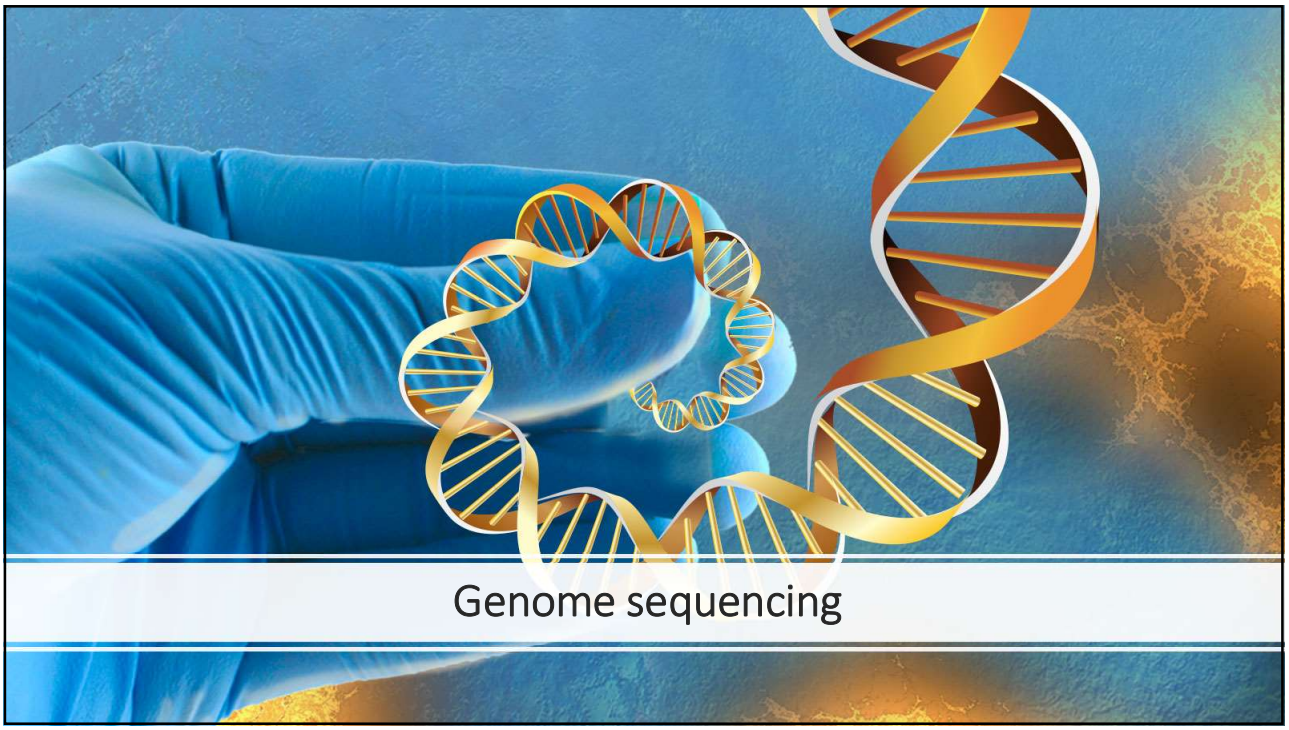
Improving antimicrobial stewardship is key to decrease resistance

But were do we focus our efforts?

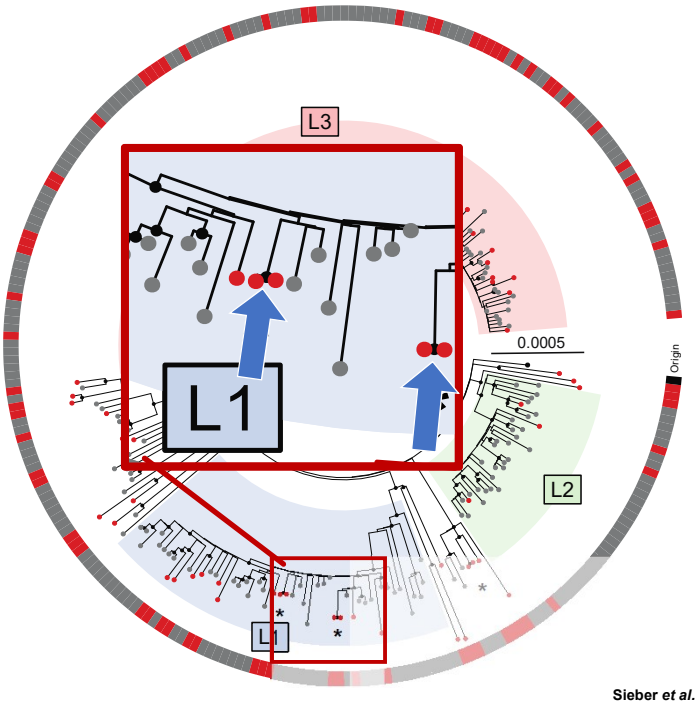


Identifying transmission/ population overlap



Identifying overlap

"Outbreak–like" approach:
Define/evalute cut-off to determine relatedness



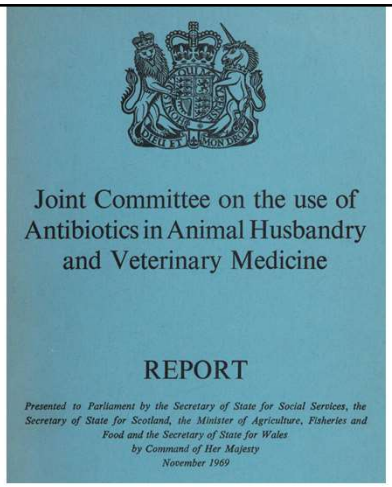
Sieber *et al.* 2019

One Health concept was not recently conceptualized

- Commissioned by the British Parliament, the Swann report (1969) reported:

  "….the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health."

  "….recommended that only antibiotics which "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms" should be usable for growth promotion."


Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine

REPORT

Presented to Parliament by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food and the Secretary of State for Wales by Command of Her Majesty November 1969

Letter | Published: 04 March 1976

Spread of antibiotic-resistant plasmids from chicken to chicken and from chicken to man

STUART B. LEVY, GEORGE B. FITZGERALD & ANN B. MACONE

Lancet Infect Dis 2019

Extended-spectrum β-lactamase-producing *Escherichia coli* in human-derived and foodchain-derived samples from England, Wales, and Scotland: an epidemiological surveillance and typing study

Michaela J Day, Katie L Hopkins, David W Wareham, Mark A Toleman, Nicola Elviss, Luke Randall, Christopher Teale, Paul Cleary, Camilla Wiuff, Michel Doumith†, Matthew J Ellington, Neil Woodford, David M Livermore*

Lancet Planet Health 2019:
3: 357–69

Attributable sources of community-acquired carriage of *Escherichia coli* containing β-lactam antibiotic resistance genes: a population-based modelling study

Lapo Mughini-Gras, Alejandro Dorado-García, Engeline van Duijkeren, Gerrita van den Bunt, Cindy M Dierikx, Marc J M Bonten, Martin C J Bootsma, Heike Schmitt, Tine Hald, Eric G Evers, Aline de Koeijer, Wilfrid van Pelt, Eelco Franz, Dik J Mevius, Dick J J Heederik*, on behalf of the ESBL Attribution Consortium*

Added value of this study

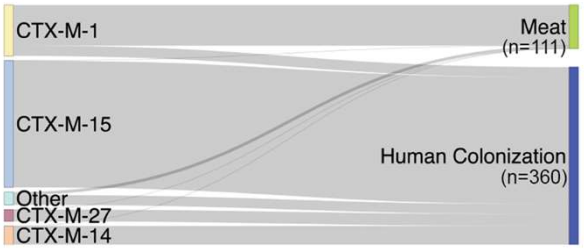
This study shows … bacteraemias in … colonists and in … ESBL types, they are largely distinct from those in food animals and retail food.

Implications of all the available evidence

Our study shows the complex links of ESBL-producing and pAmpC-producing *E coli* among humans, animal sources, the food chain, and the environment. Because humans are estimated to be the most important source in the open community, hygiene and responsible use of antibiotics in health care and veterinary medicine remain important pillars of prevention. Although the direct contributions of animals, food, and surface freshwater were estimated to be smaller, they entail large reservoirs of infection, contamination, and dissemination of ESBLs and pAmpCs to which humans remain continuously exposed and subsequently contribute to further spread of ESBLs and pAmpCs among individuals. Therefore, continuous monitoring of antimicrobial resistance in humans, animals, and other sources is crucial to detect changes in trends and dynamics, underpinning the need for longitudinal studies, because carriage of ESBLs and pAmpCs is temporal and the importance of some sources might fluctuate over time.

Implications of all the available evidence

… ts aim to achieve a … nfections by 2020. … lue to ESBL-*E coli* is especially desirable, given their incidence (>5000 cases per year) and the treatment challenges. Our findings show that actions on the food chain, however desirable for animal husbandry, are unlikely to contribute to reductions in human infection. Better potential control points are prevention of transmission by good post-toilet hygiene (eg, in care homes) and prevention of severe infection through good patient care and rapid effective treatment of initial uncomplicated urinary tract infections, which precipitate most of the bacteraemias. Vaccines might also be a future solution.



Focus on resistant isolates!

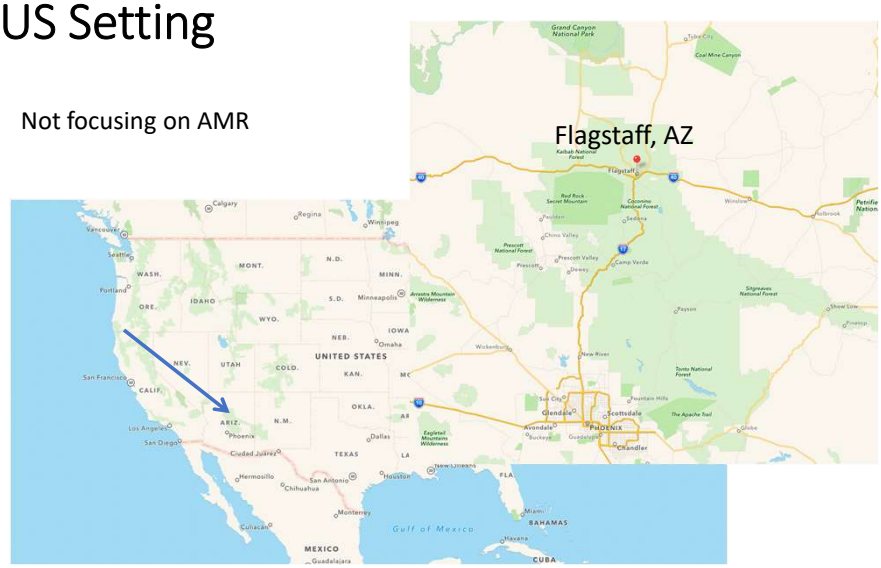
We struggle with the enormous underlying diversity of the food-animal *E. coli* populations

US: >8 billions broilers on ~230,000 farms

How many samples would you want?

US Setting

Not focusing on AMR



Flagstaff UTI Study

- Simultaneously collected meat and urine *E. coli* isolates for an entire year
  - all brands of chicken, turkey, and pork from all stores (n=2452)
  - all urine isolates from the only hospital (n=1257)

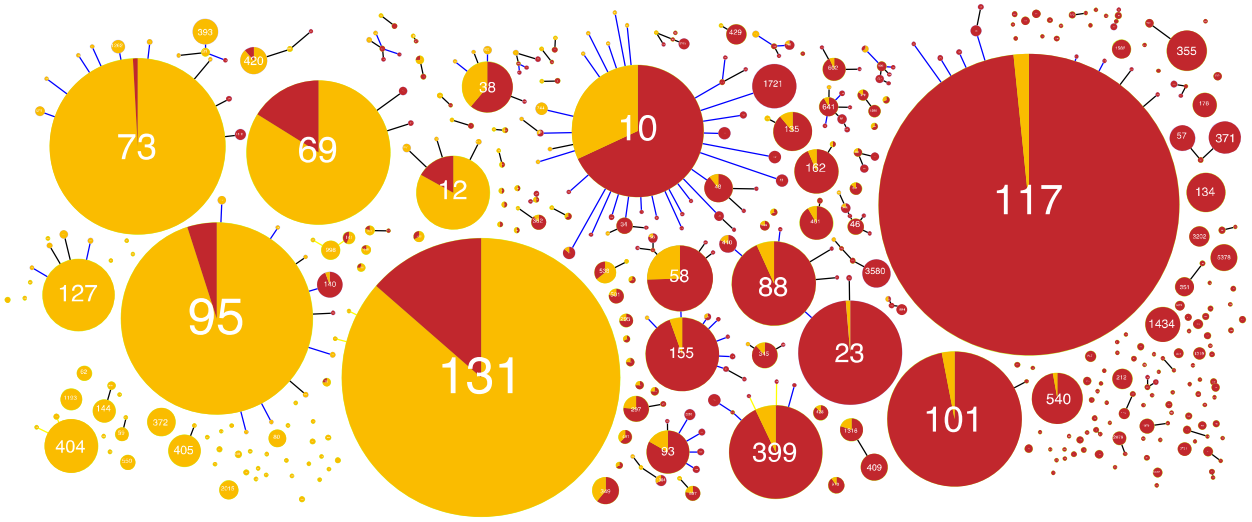
Initial 3-step approach

#1: Sequence genomes

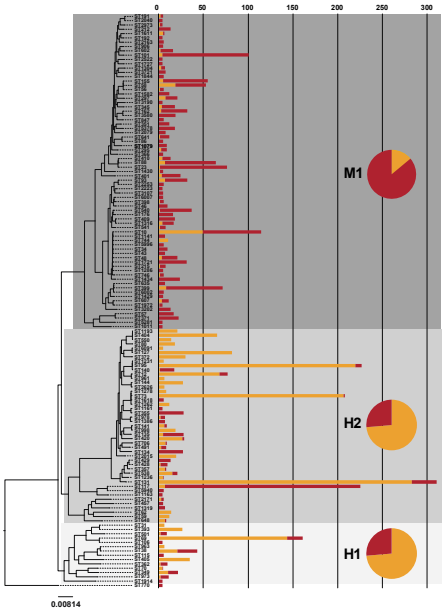
#2: Extract MLST

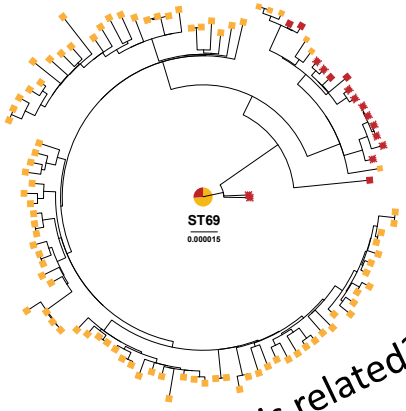
#3: WG-SNP phylogeny on each ST

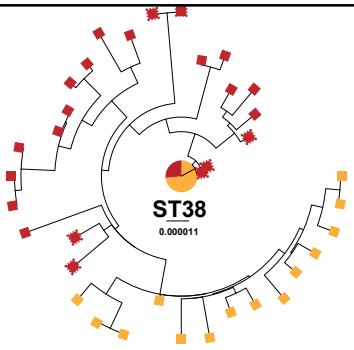
3000 isolates; 443 STs

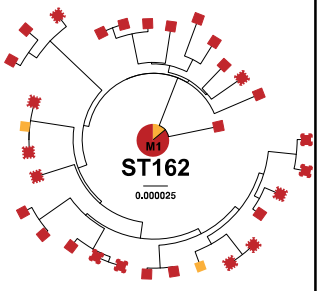


“Outbreak tools” to investigate relatedness



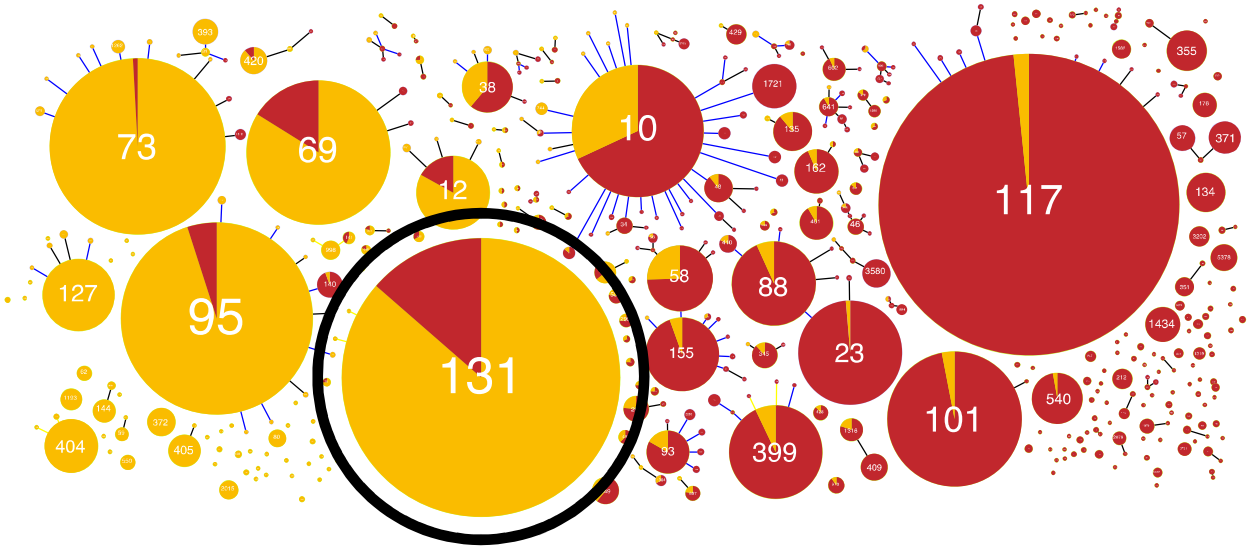


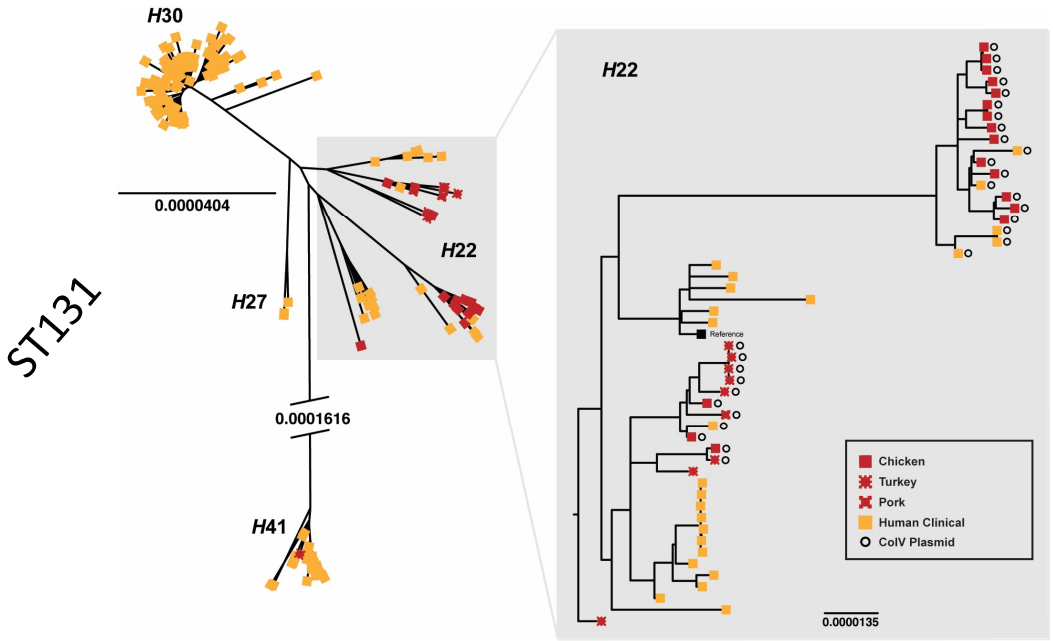




Still, what is related?

443 STs

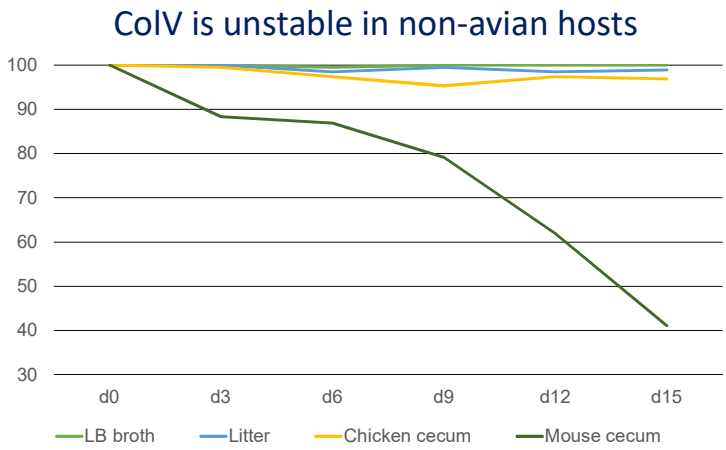




Liu *et al.* 2018

ColV plasmids as host marker?

- 63% Chicken *E. coli*
- 64% Turkey *E. coli*
- 5% Human *E. coli*



The instability of ColV plasmids outside of the avian host could inform epidemiologic investigations

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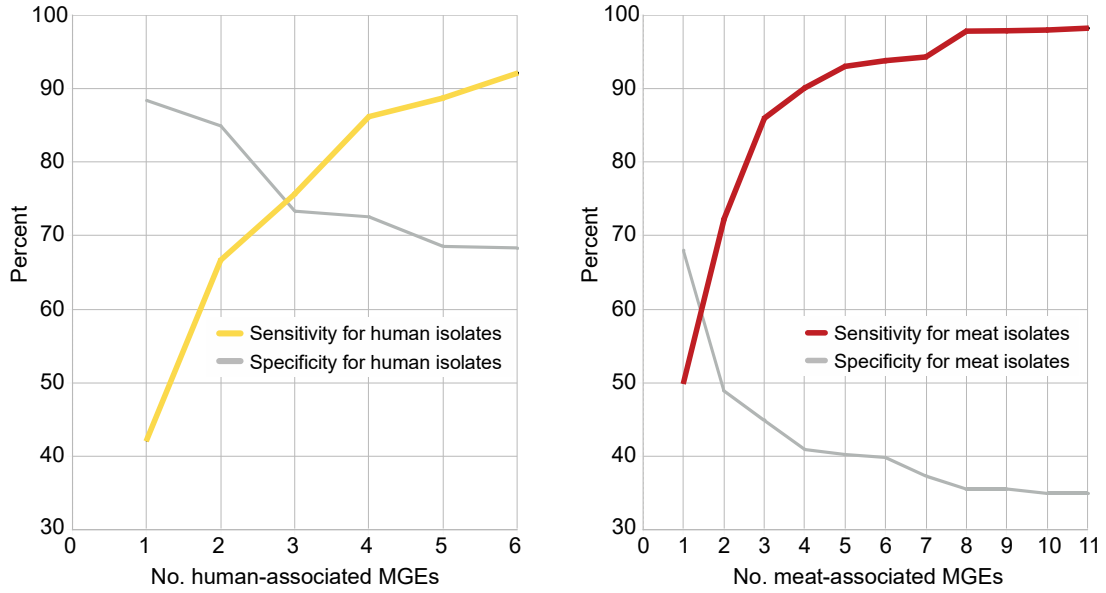
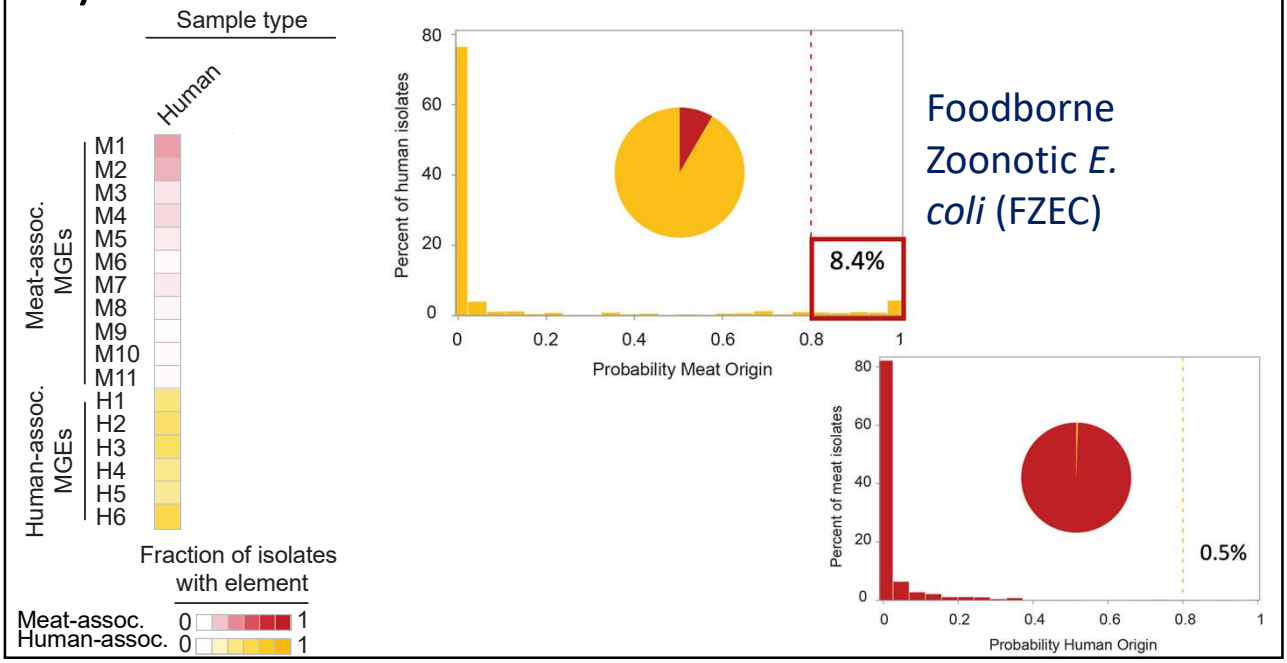
E. coli populations adapt to different vertebrate host by shedding and acquiring host-adaptive mobile genetic elements

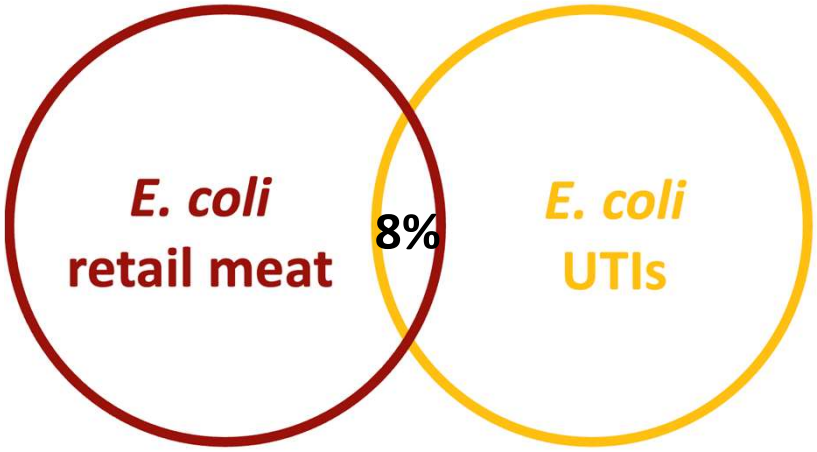
Host-associated mobile genetic elements



Bayesian Latent Class Model



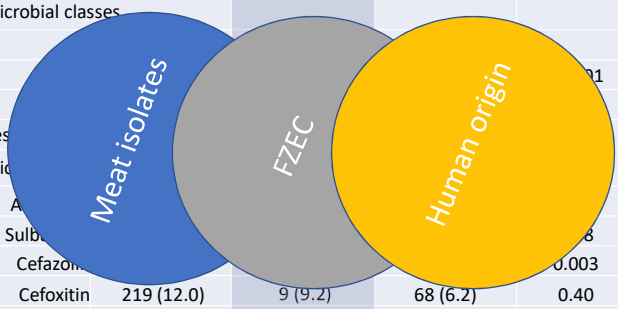
Foodborne Zoonotic *E. coli* (FZEC)



>1/2 million urinary tract infections per year in the US may be FZEC

AMR?

		Human-Clinical Isolates (n = 1,188)			
	A. Meat Isolates[a] (n = 1827)*	B. FZEC[b] (n = 98)	C. Human origin[c] (n = 1090)	p-value	
		n (% of isolates)		A vs B	B vs C
Resistance to antimicrobial classes					
				01	0.22
					0.03
Multi-drug res					0.02
Resistance to antimi					
A					<0.001
Ampicillin Sulb				8	<0.001
Cefazol				0.003	0.46
Cefoxitin	219 (12.0)	9 (9.2)	68 (6.2)	0.40	0.26
Ceftriaxone	185 (10.1)	2 (2.0)	31 (2.8)	0.01	0.64
Ciprofloxacin	1 (0.1)	6 (6.1)	204 (18.7)	<0.001	0.002
Gentamicin	442 (24.2)	6 (6.1)	54 (5.0)	<0.001	0.61
Tetracycline	912 (49.9)	29 (29.6)	265 (24.3)	<0.001	0.25
Trimethoprim Sulfamethoxazole	103 (5.6)	11 (11.2)	305 (28.0)	0.02	<0.001



So, we should not worry about antibiotic usage in livestock production in general?

- International efforts to curb antimicrobial resistance focuses on drug development, surveillance, and limiting unnecessary use
- <4% of Joint Programming Initiative for Antimicrobial Resistance (JPIAMR) funding is allocated towards identifying cost-effective environmental controls that curb microbial exchange
- Overlap in *E. coli* populations could be vastly different in low and middle-income countries where environmental controls such as WASH at the human-animal interface are lacking and where biosecurity in food-animal production is poor

Cambodia and food production

Cambodia is among the poorest countries in Southeast Asia and 76% its 16 million residents live in rural areas

Commercial livestock production has nearly doubled during the past decade, and >80% of livestock is raised by resource-constrained households in rural areas

Antibiotics administered to chickens and pigs included all antibiotics that are commonly used in human medicine - including third-generation cephalosporins, penicillins, fluoroquinolones, gentamicin, and co-trimoxazole

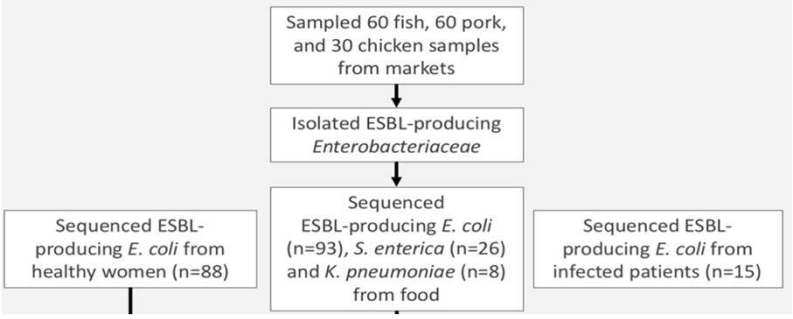
Opportunity of leaks between human communities and animals

- WASH conditions and animal husbandry practices in Cambodia suggest ample opportunity for bidirectional exchange of fecal-oral pathogens between humans and livestock
  - Open human defecation in common; 1/4 rural residents and 1/10 urban residents defecate in fields or other open spaces
  - Most livestock raised in rural and urban households roam freely
  - ~50% of livestock-owning households report dumping untreated animal manure directly into the environment
  - Cambodia has the lowest access to piped drinking water in Southeast Asia
  - Poor WASH practices along the food supply chain, including untreated animal manure for agricultural fertilization, habbit of eating undercooked chicken and fish

Study approach

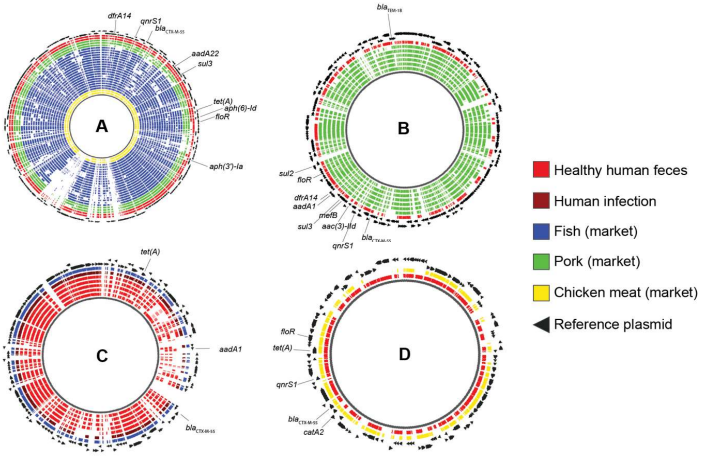
Genomics to investigate the spread of mobile resistance elements

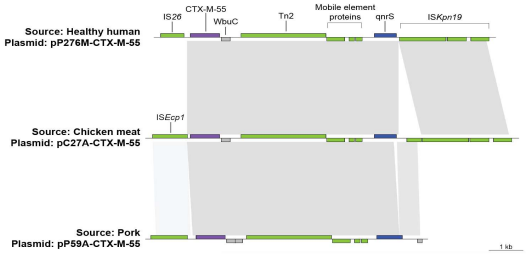
Focus on ESBL-producing gram-negative species



Results

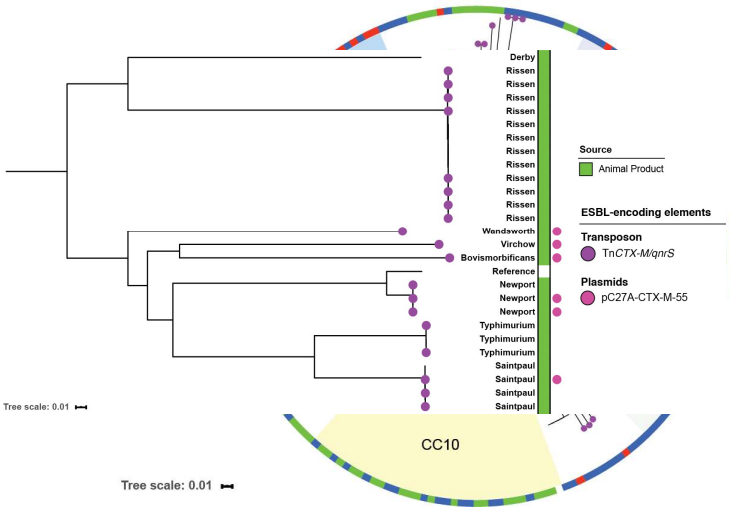
Using long-read sequencing, genomics from selected ESBL-producing *E. coli* isolates from the feces of healthy humans, pork meat and chicken





A $bla_{CTX\text{-}M\text{-}55}$-encoding transposon (Tn*CTX-M/qnrS)* was shared among three plasmids

Tn*CTX-M/qnrS* -transposon in the Cambodian *E. coli* collection



Widely prevalent among healthy humans (48%) and among food-origin ESBL-producing *E. coli* (58%), *S. enterica* (73%), and *K. pneumoniae* (13%)

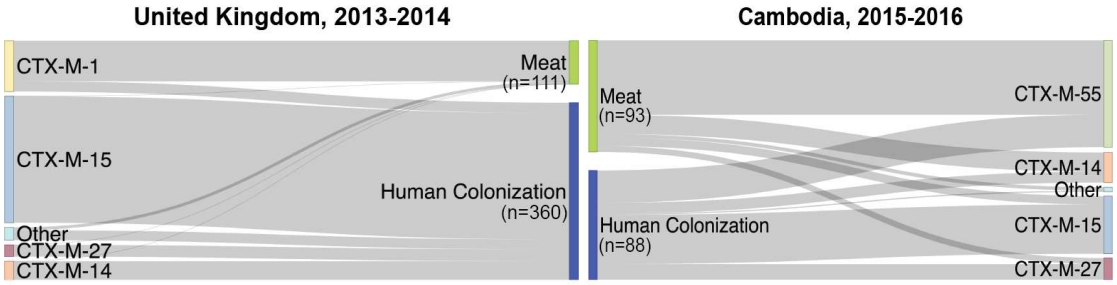
Screening EnteroBase retrieved 213 hits of *E. coli* belonging to multiple STs and 47 hit to *Shigella* spp. of various species

- (Sparse metadata) but almost exclusively detected among isolates of Asian origin

Overlap between populations

One-third of human-origin ESBL-producing *E. coli* strains encoded the $bla_{CTX\text{-}M\text{-}55}$ gene
- the predominant ESBL gene type among *E. coli* from meat and fish

Contrasting to findings from high-income countries



Outcome

AMR was not exclusively driven by the zoonotic transmission of specific bacterial clones; rather, frequent mixing of host-adapted strains likely allowed for the uptake of plasmids into diverse genetic contexts (a phenomenon others have observed in hospitals in high-income settings)

In settings where humans and food-animals are living in close proximity, a potential continuous, circular exchange of resistant bacteria selected through unregulated antibiotic use facilitates the exchange of resistance genes among bacteria in both sectors

Take home messages

- We could/should consider how we approach One-Health surveillance in Denmark
- One-Health is not “dead”
  - But likely more limited impact in terms of AMR in high-income countries, but 3.5 billion individuals reside in low- to middle-income countries