Campylobacter Ecology and Evolution:
Niche adaptation and resistance progression in *Campylobacter*

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UNIVERSITY OF BATH

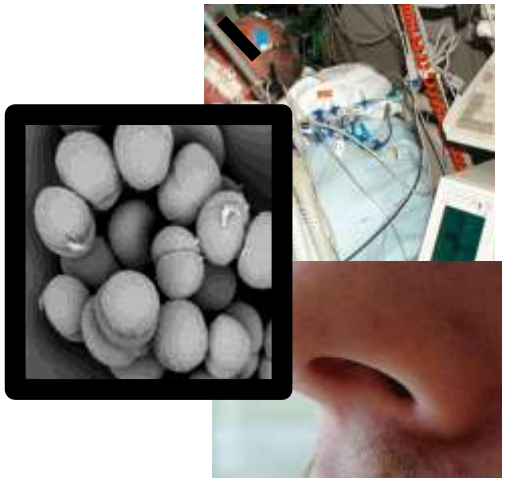
MRC Cloud Infrastructure for Microbial Bioinformatics

Milner Centre for EVOLUTION

Population genomics and evolution of bacteria

Host - Sheppard et al. (2013) *PNAS*
Biofilm – Pascoe et al. (2015) *Env Micro*
Surivival - Yahara et al. (2017) *Env Micro*

Pathogenicity – Monteil et al. (2016) *MGen.*

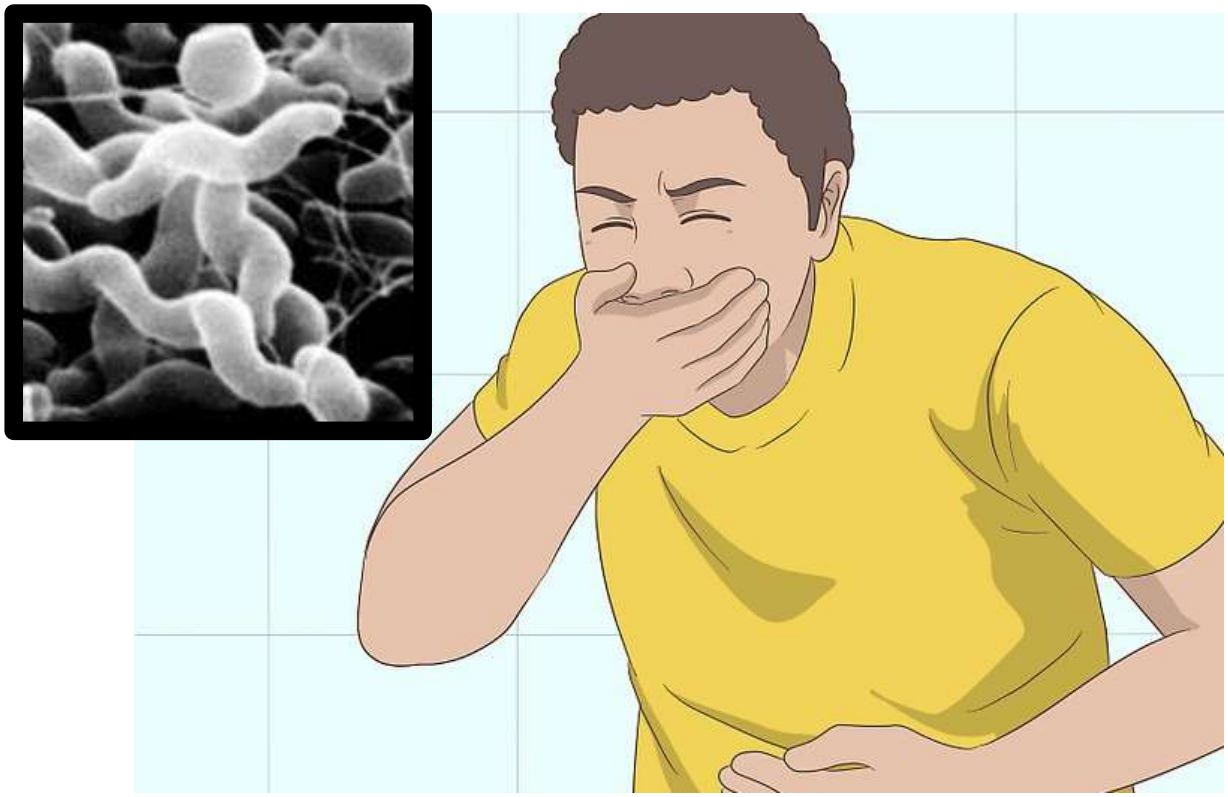


Pathogenicity – Meric et al. (2018) *NatComms.*

Pathogenicity – Bayliss et al. *In prep.*

Host/pathogen - Berthenet et al. (2018) *BMC Biology*

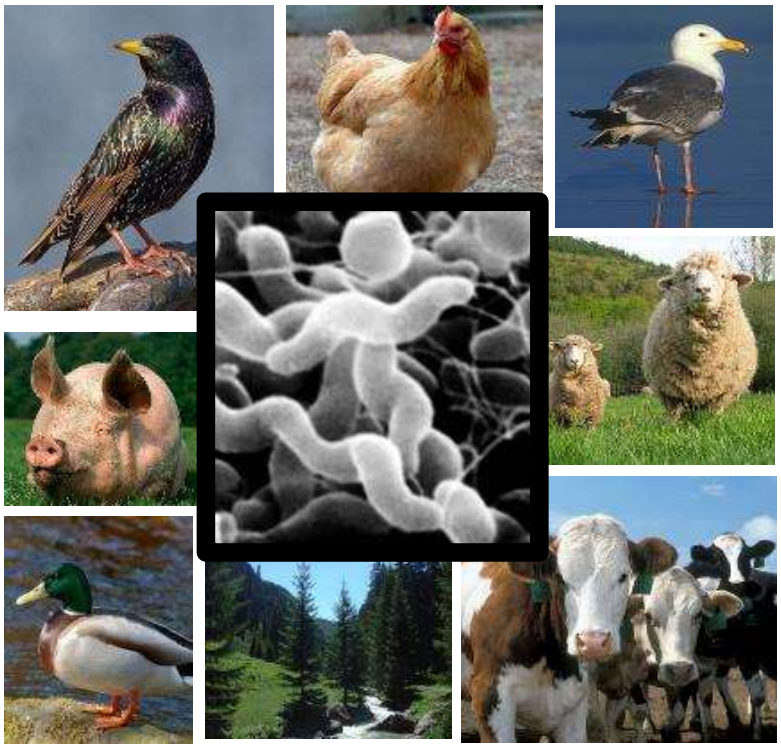
Campylobacter: among the most common causes of bacterial gastroenteritis

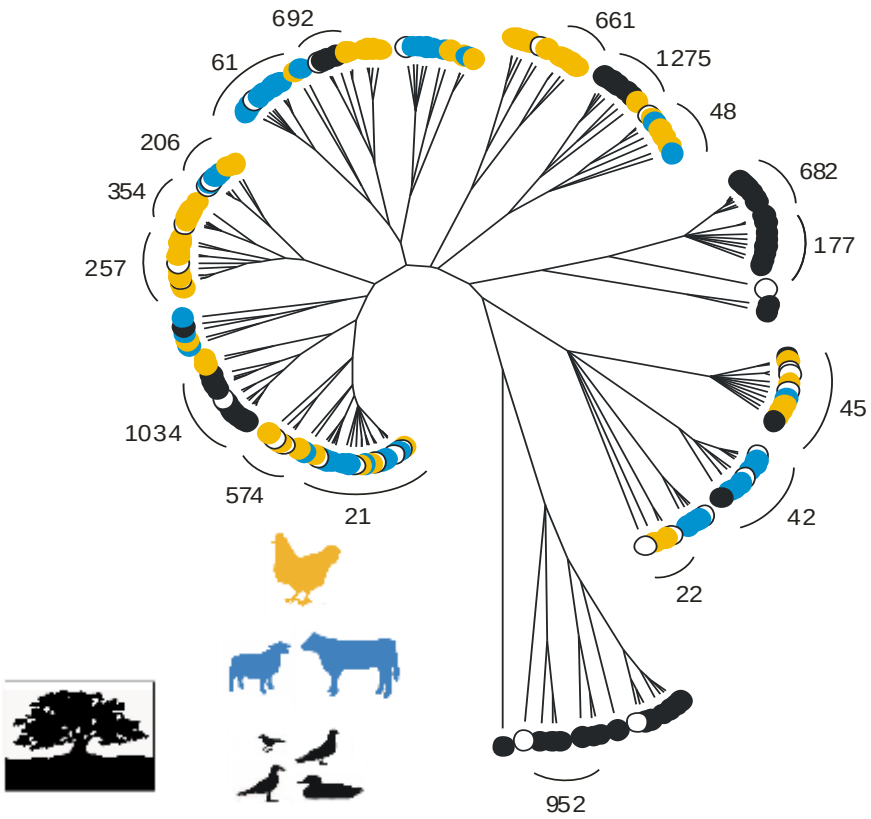


Antimicrobials used in persistent or severe cases but infection is usually self limiting (3-5) days.

Humans are a dead end host so where is the selection for resistance?

C. jejuni and *C. coli* principally inhabit animal guts





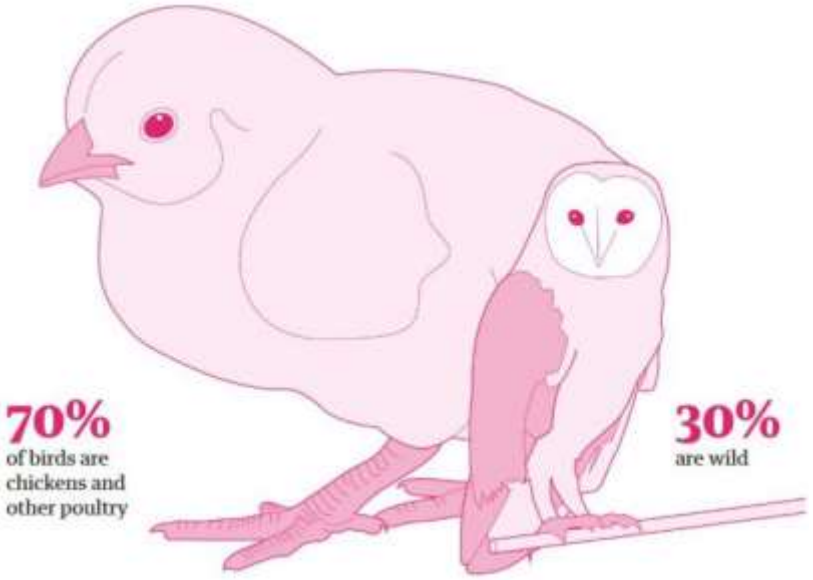
Where does human infection come from?

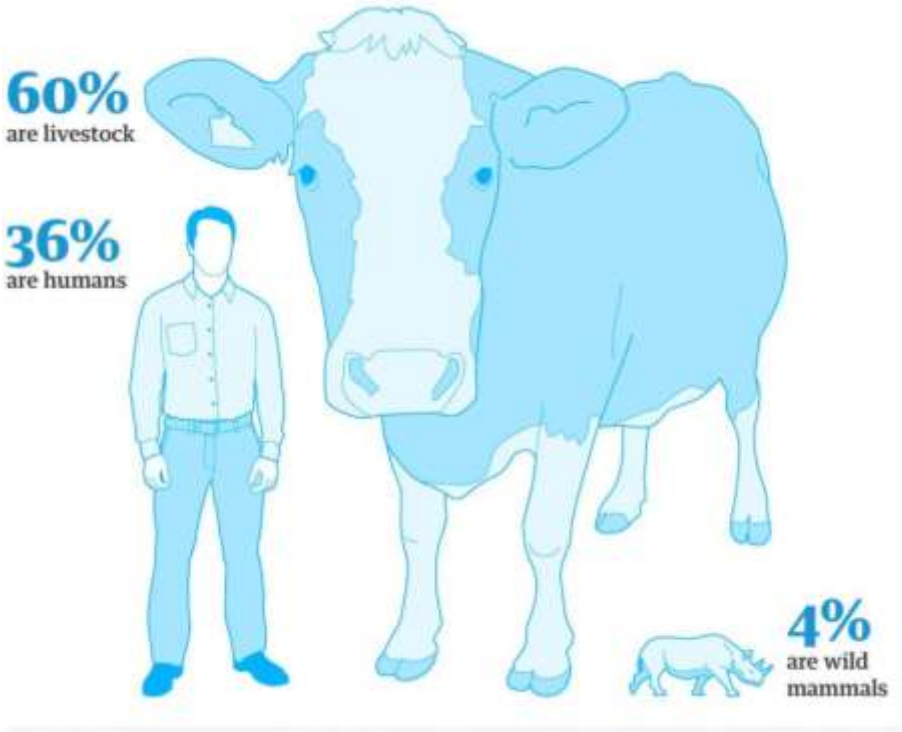
Is AMR acquired in animal hosts?

Sheppard et al. (2009) *Clinical Infectious Diseases* 48:1072–1078

Sheppard et al. (2010) *Applied Environmental Microbiology* 76, 5269-5277

Not all host animals are equal.





>20 billion chickens

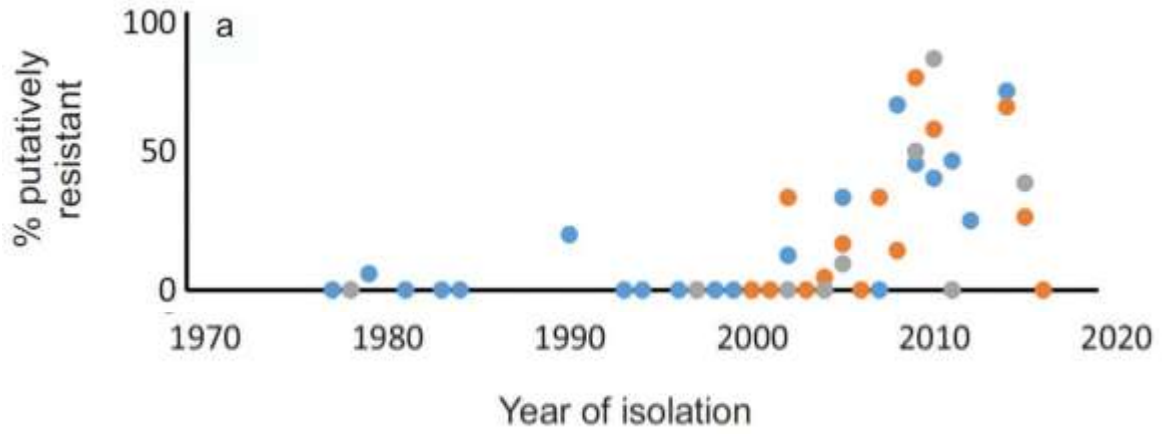
~1.5 billion cattle

Global use of antimicrobials in livestock production:

- Many of the same antimicrobial classes
- Global distribution networks
- Growth promoters and treatment of ‘sick animals’

Bar-On et al. (2018) 15 (25) 6506-6511.

The rise of AMR in *Campylobacter* from humans and animals coincides

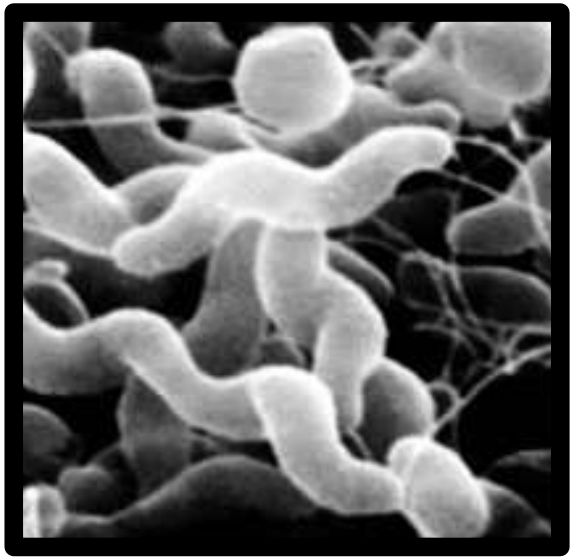


Trends in fluoroquinolone resistance in *Campylobacter*

Putative ciprofloxacin resistance in 1038 human (Blue), 670 chicken (Orange) and 136 ruminant (Grey) samples collected from 1978 to 2017.

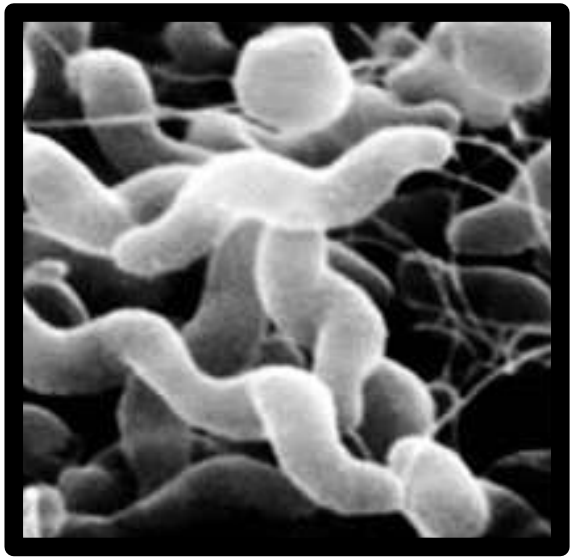
Sproston et al. (2018) *Microbial Genomics* 4; doi:10.1099/mgen.0.000198

Understanding the spread of AMR *Campylobacter*



1. Genomics and host adaptation
2. Clonal transmission
3. Gene pool transmission

Understanding the spread of AMR *Campylobacter*



1. Genomics and host adaptation
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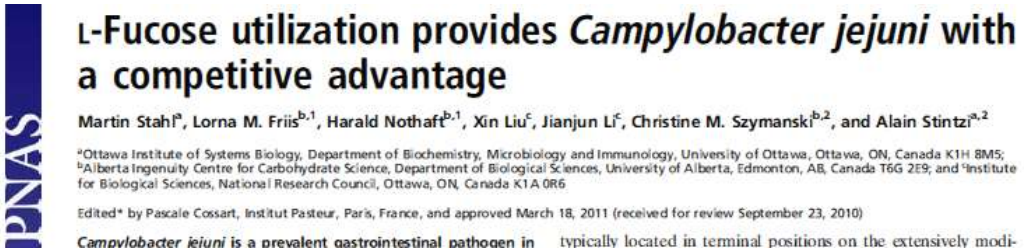
GWAS

Microbiology research is changing: top-down and bottom-up approaches

Bottom-up.

Starts with DNA sequence (genes) and tests the effect on the phenotype.



PNAS

L-Fucose utilization provides *Campylobacter jejuni* with a competitive advantage

Martin Stahl[a], Lorna M. Friis[b,1], Harald Nothaft[b,1], Xin Liu[c], Jianjun Li[c], Christine M. Szymanski[b,2], and Alain Stintzi[a,2]

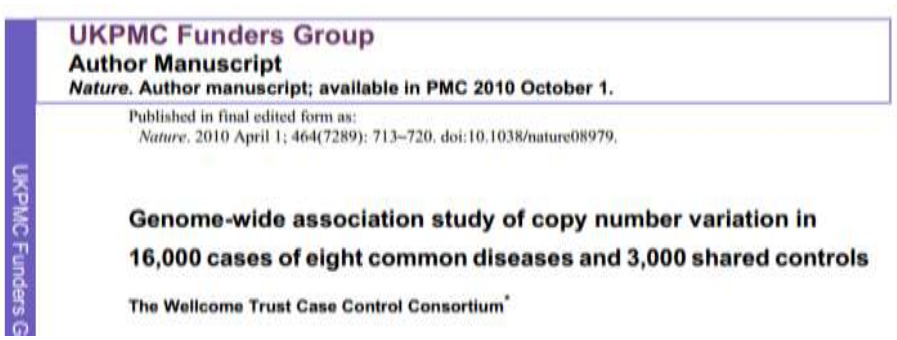
[a]Ottawa Institute of Systems Biology, Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, ON, Canada K1H 8M5; [b]Alberta Ingenuity Centre for Carbohydrate Science, Department of Biological Sciences, University of Alberta, Edmonton, AB, Canada T6G 2E9; and [c]Institute for Biological Sciences, National Research Council, Ottawa, ON, Canada K1A 0R6

Edited* by Pascale Cossart, Institut Pasteur, Paris, France, and approved March 18, 2011 (received for review September 23, 2010)

Campylobacter jejuni is a prevalent gastrointestinal pathogen in typically located in terminal positions on the extensively modi-

Top-down.

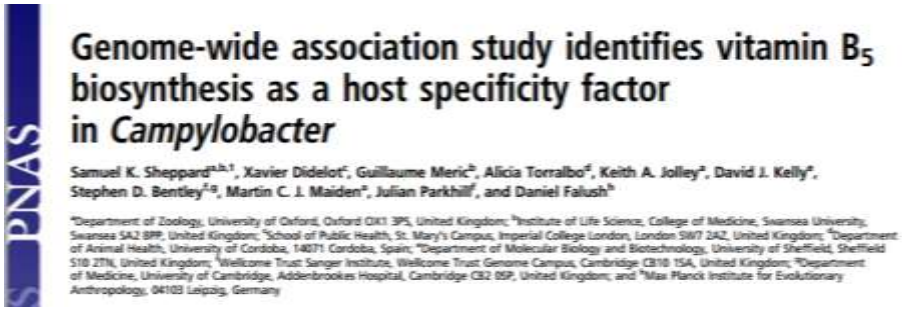
Starts with phenotype and associates it with particular genomic elements.



Published in final edited form as:
Nature. 2010 April 1; 464(7289): 713–720. doi:10.1038/nature08979.

Genome-wide association study of copy number variation in 16,000 cases of eight common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*



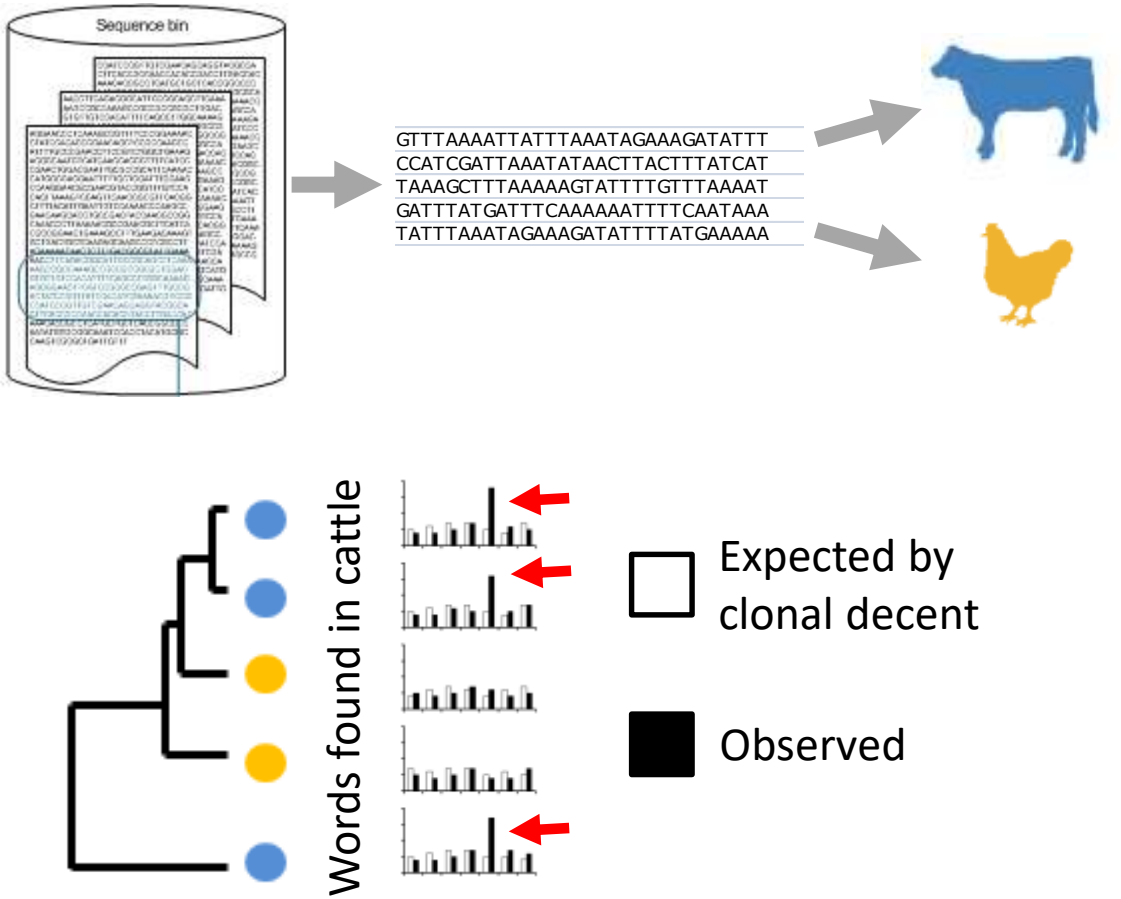
PNAS

Genome-wide association study identifies vitamin B_5 biosynthesis as a host specificity factor in *Campylobacter*

Samuel K. Sheppard[a,b,1], Xavier Didelot[c], Guillaume Meric[b], Alicia Torralbo[d], Keith A. Jolley[a], David J. Kelly[e], Stephen D. Bentley[f,g], Martin C. J. Maiden[a], Julian Parkhill[f], and Daniel Falush[h]

[a]Department of Zoology, University of Oxford, Oxford OX1 3PS, United Kingdom; [b]Institute of Life Science, College of Medicine, Swansea University, Swansea SA2 8PP, United Kingdom; [c]School of Public Health, St. Mary's Campus, Imperial College London, London SW7 2AZ, United Kingdom; [d]Department of Animal Health, University of Cordoba, 14071 Cordoba, Spain; [e]Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield S10 2TN, United Kingdom; [f]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge CB10 1SA, United Kingdom; [g]Department of Medicine, University of Cambridge, Addenbrookes Hospital, Cambridge CB2 0SP, United Kingdom; and [h]Max Planck Institute for Evolutionary Anthropology, 04103 Leipzig, Germany

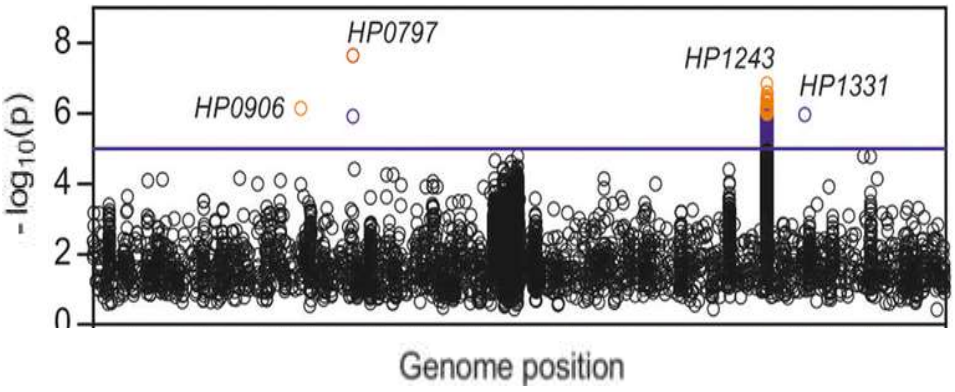
GWAS Association study Method (*Campylobacter*)

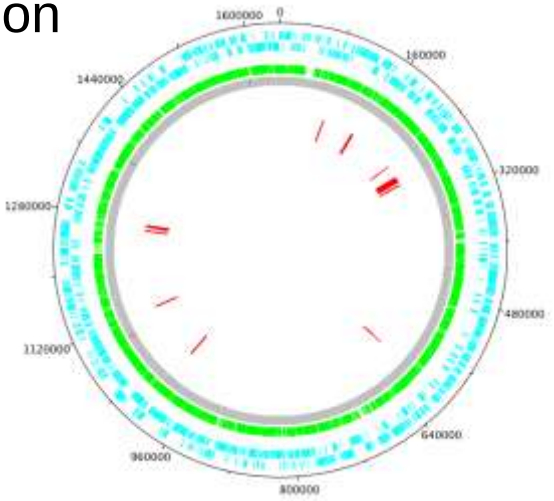


Sheppard et al.(2013) PNAS 110:11923-7.

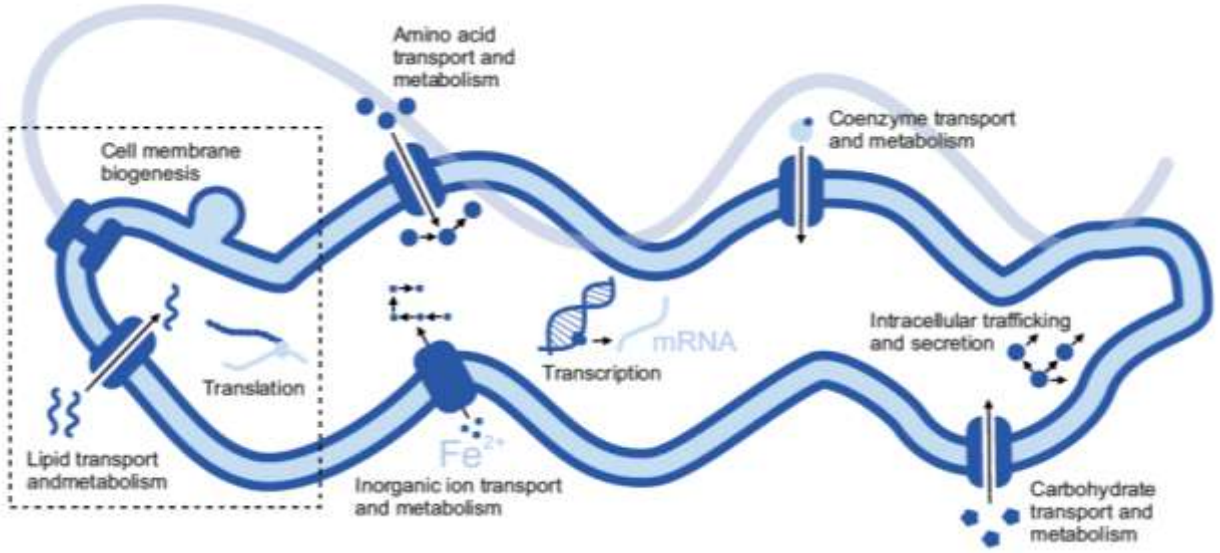
1. The genomics of host adaptation (Cattle)

Hot spots of host associated genetic variation



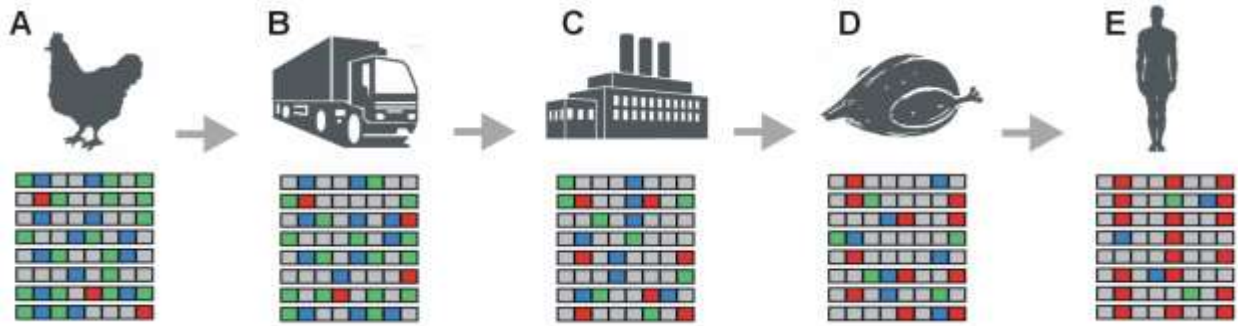


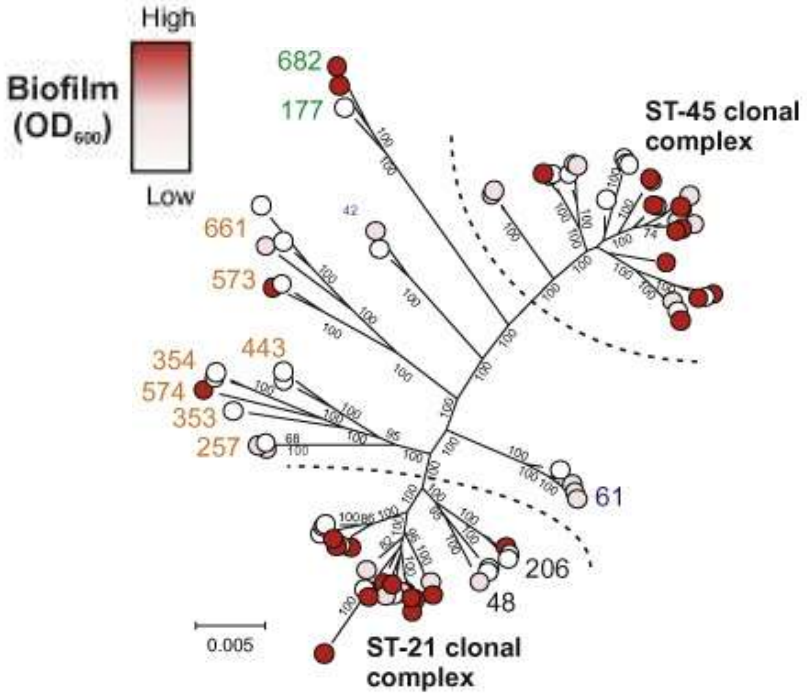
Genes underlying host adaptation



Sheppard et al.(2013) PNAS 110:11923-7.

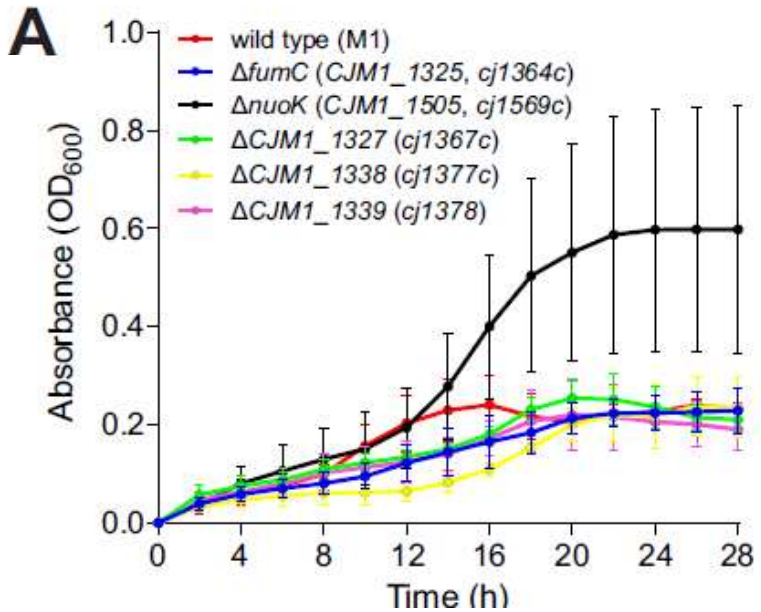
2. Survival through the food production chain





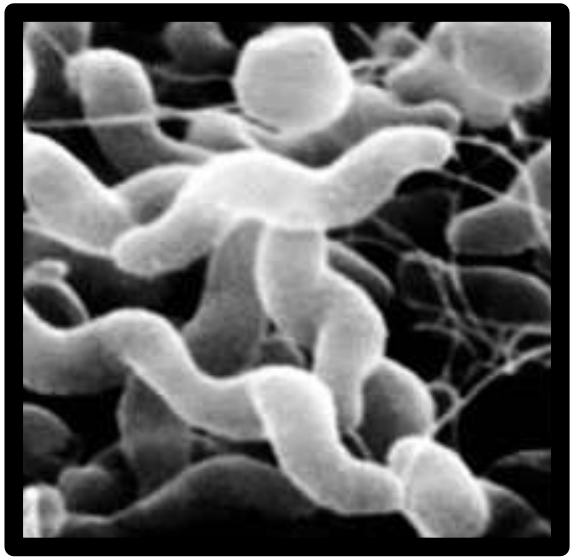
Pascoe (2015). Environmental Microbiology 17(11):4779-89.
Yahara et al (2017) Environmental Microbiology

Δ*nuoK* grows better in elevated oxygen



- *nuoK* is involved in NADH activity and switching from anaerobic to oxygen rich environment. Mutants grow better in enhanced O2

Understanding the spread of AMR *Campylobacter*



1. Genomics and host adaptation
2. Clonal transmission
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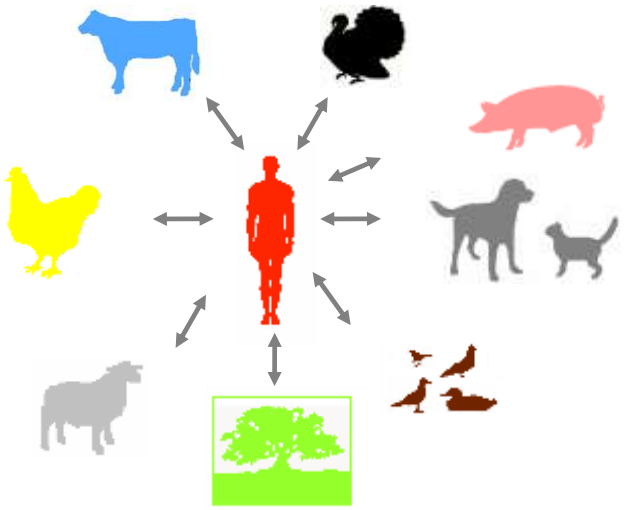
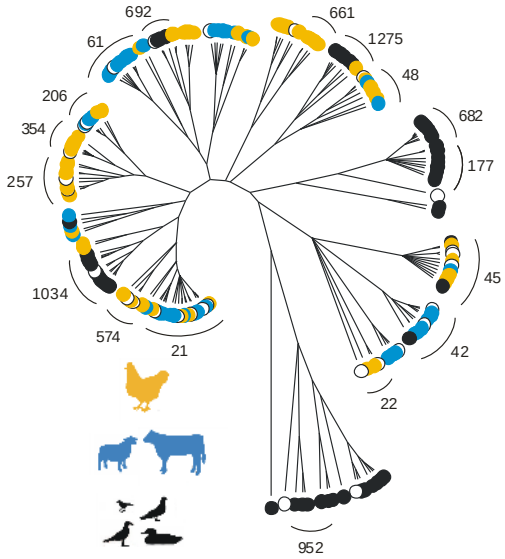
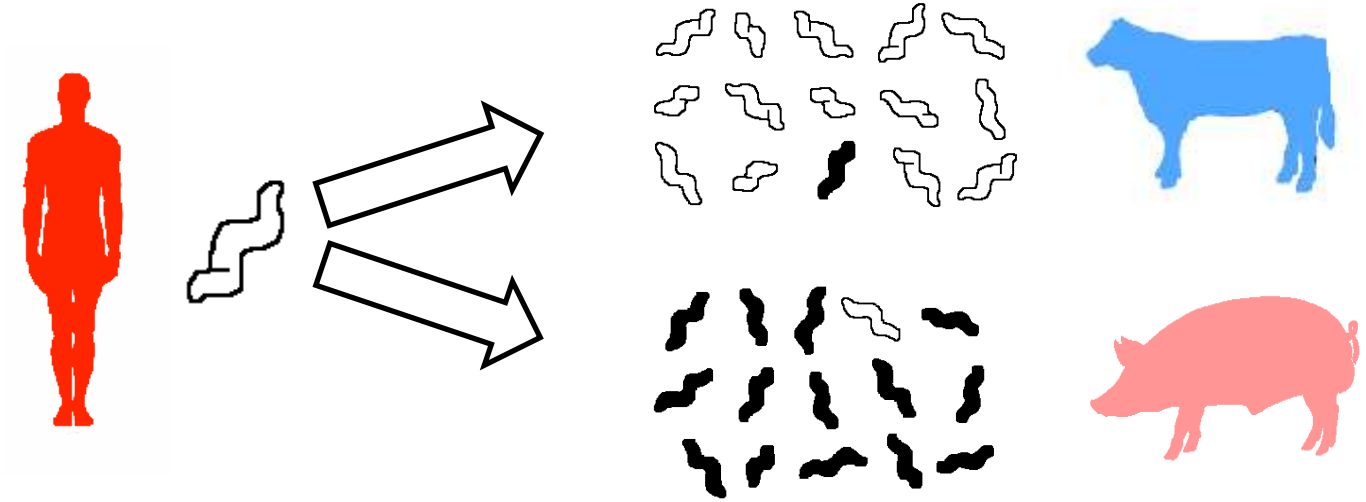
Campylobacter source attribution studies



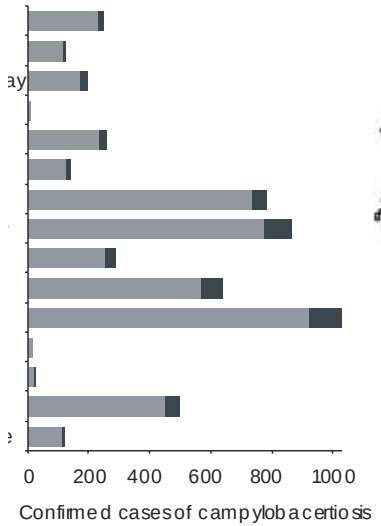
Several potential sources.

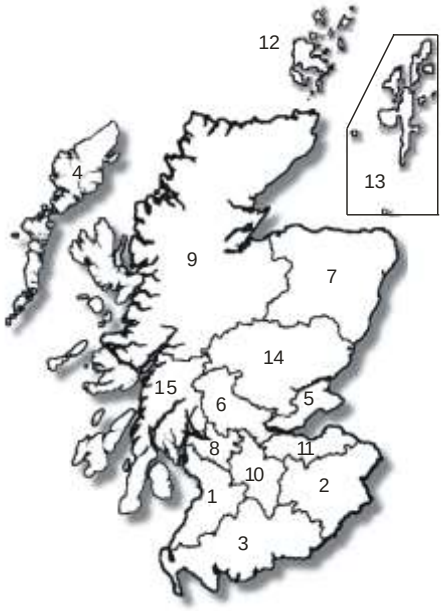


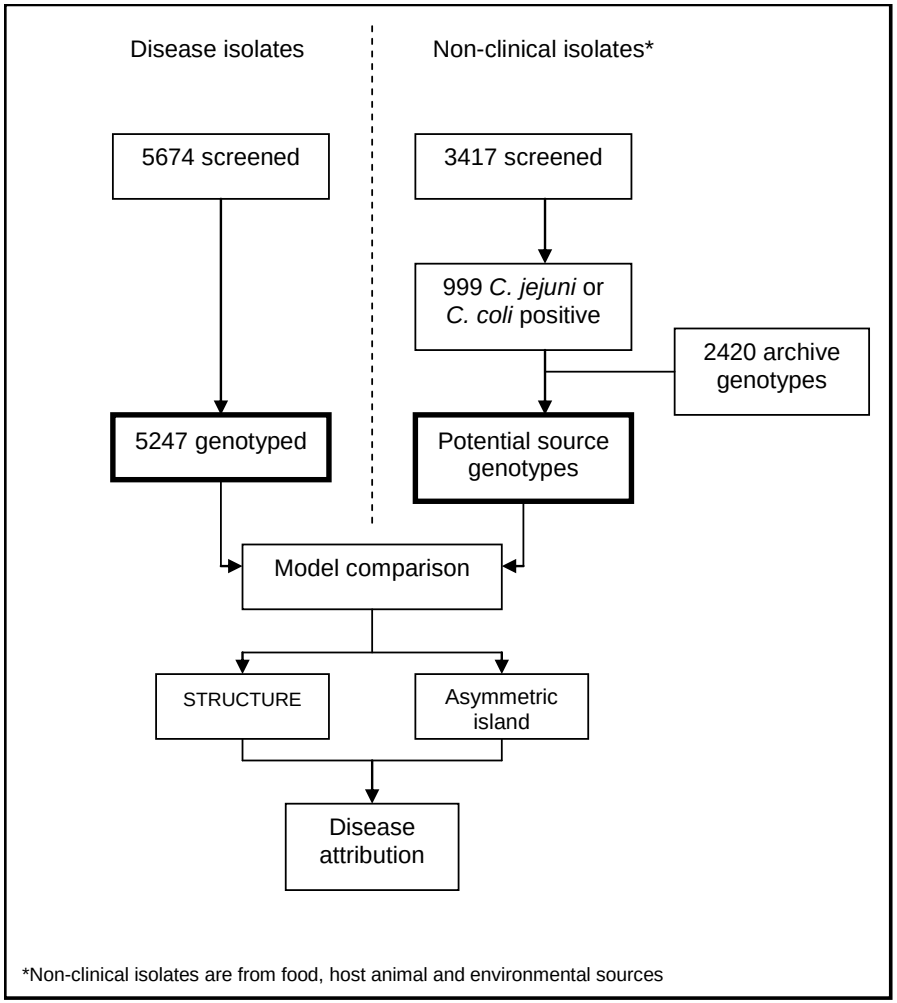
Different hosts have different *C. jejuni* types so disease can be attributed.



National attribution experiment

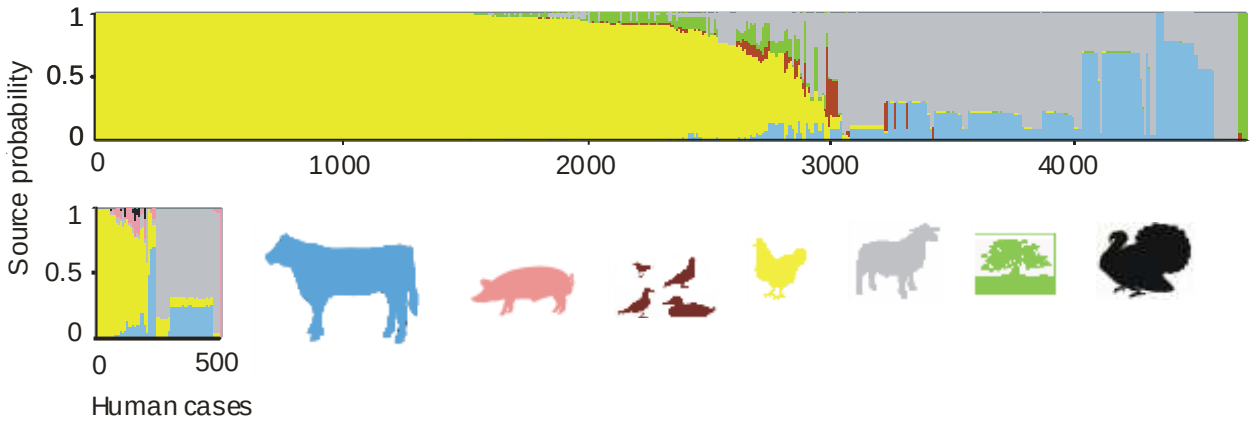




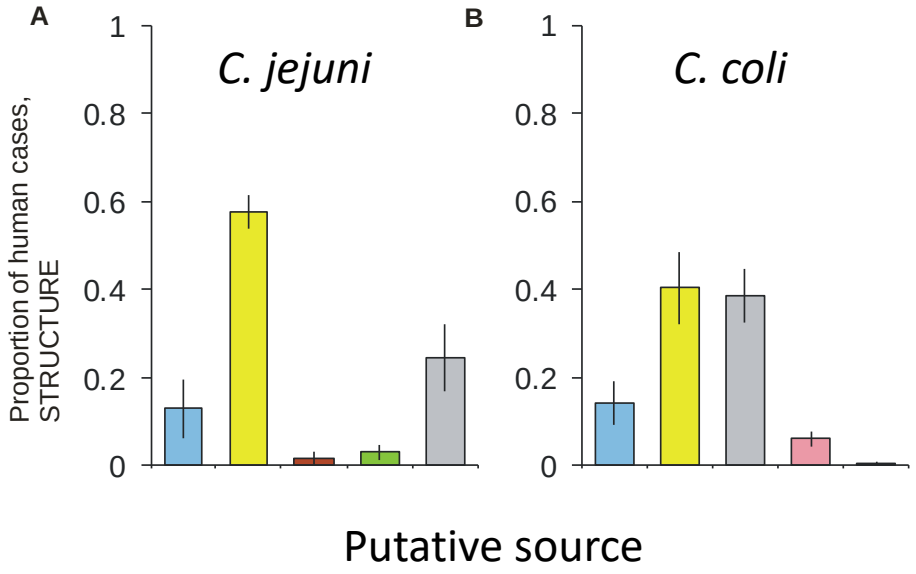


Sheppard et al. 2009 *Clinical Infectious Diseases* 48:1072–1078

Chicken is a major source of human infection



Assignment of clinical isolates to source using the Bayesian clustering algorithm - STRUCTURE.



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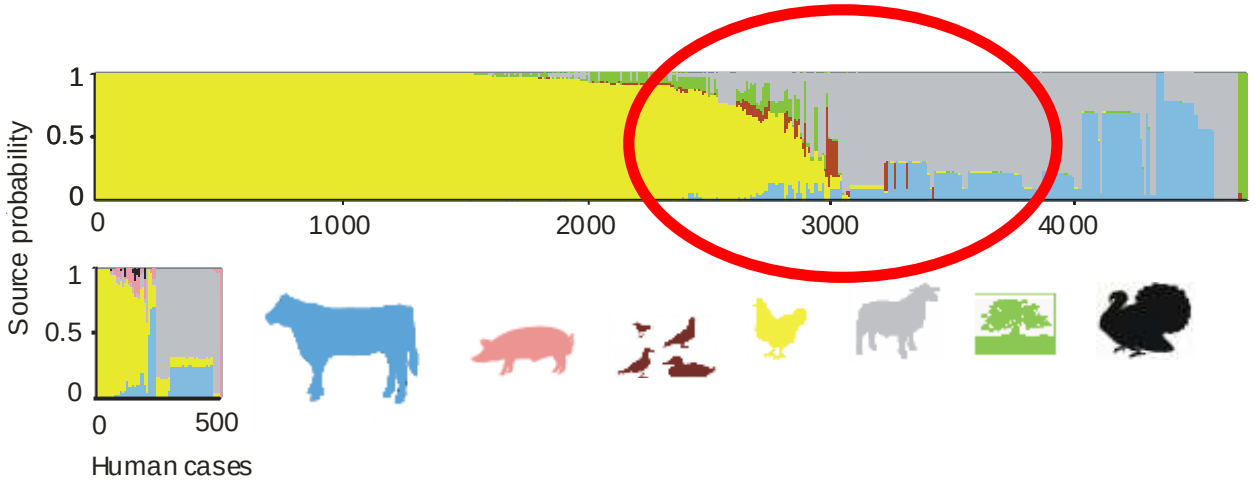

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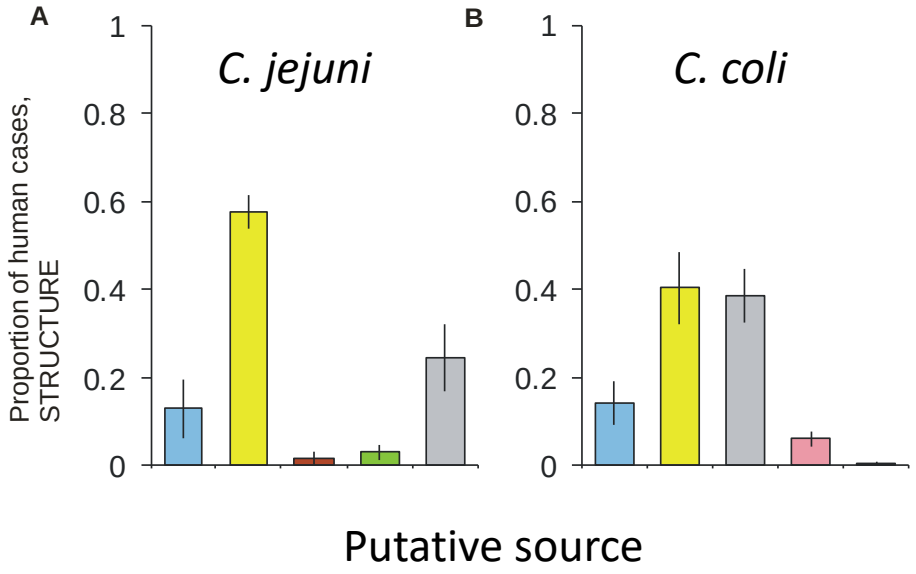
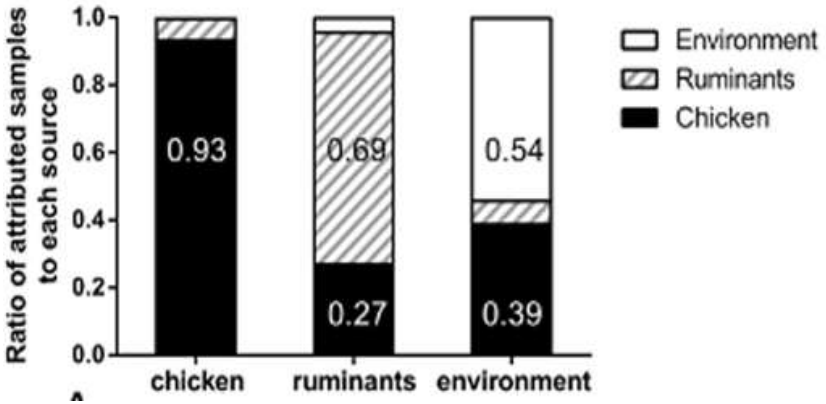
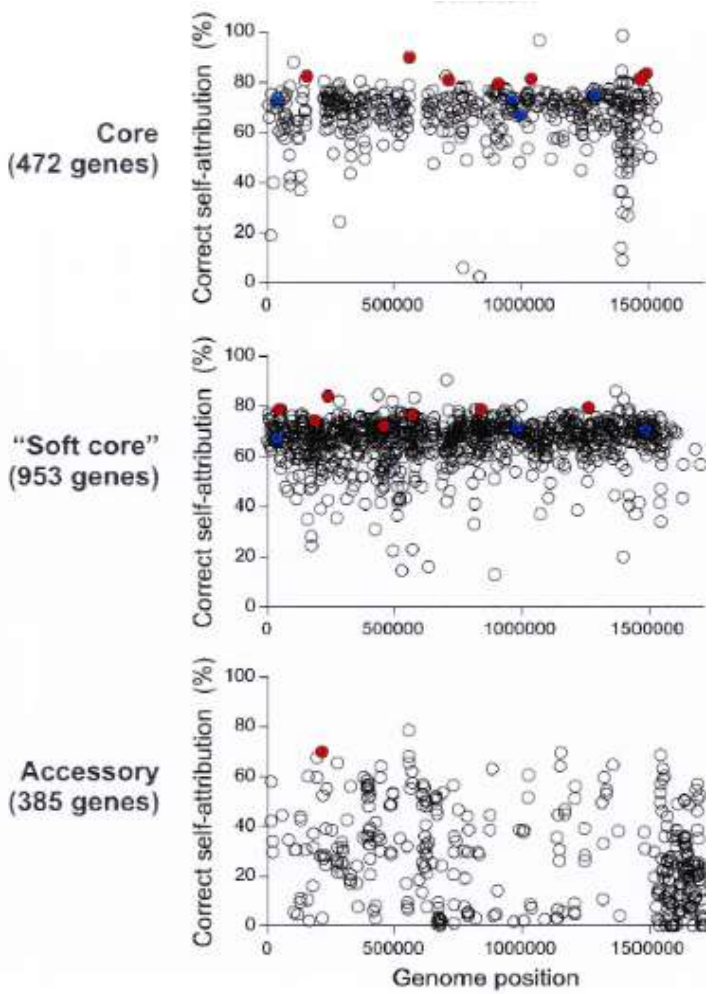


Data and models have improved

1. Model limitations can be quantified by self attribution

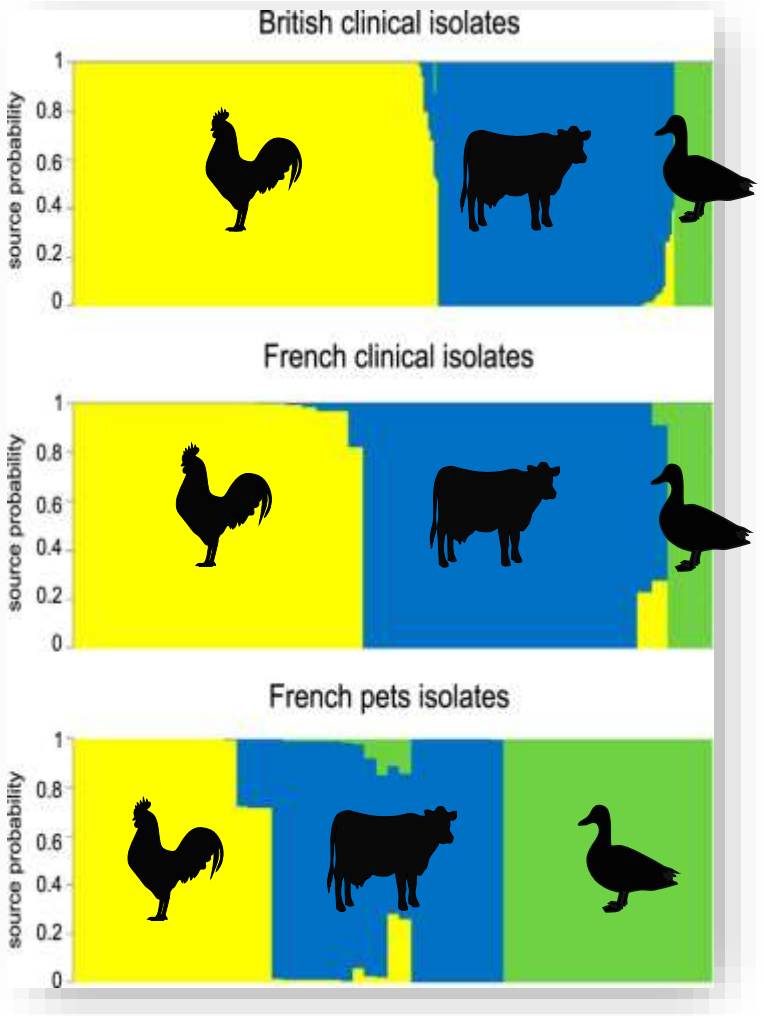


2. Genome-wide host-segregating markers



Berthenet et al. (2019) Scientific Reports 9: 8098
Thépault et al (2018) Scientific Reports 8:9305
Thepault A et al (2017) Applied and Environmental Microbiology 83(7):e03085-16

Chicken (followed by ruminants) remain the major source of human campylobacteriosis



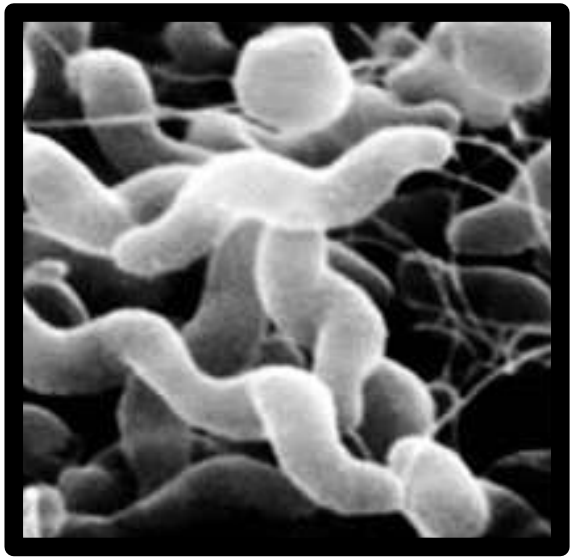
Source attribution (C. jejuni)
60 – 80 % attributed to chicken
40 – 60 % to ruminant
4 – 10 % to wild birds & environment

Biology limits:
Zoonotic transmission occurs every 1.6 years in some *C. jejuni* lineages so association signal is lost.

Berthenet et al. (2019) Scientific Reports 9: 8098
Thépault et al (2018) Scientific Reports 8:9305
Thepault et al (2017) Applied and Environmental Microbiology 83(7):e03085-16

Dearlove et al (2015) ISME Journal 10(3):721-9.

Understanding the spread of AMR *Campylobacter*



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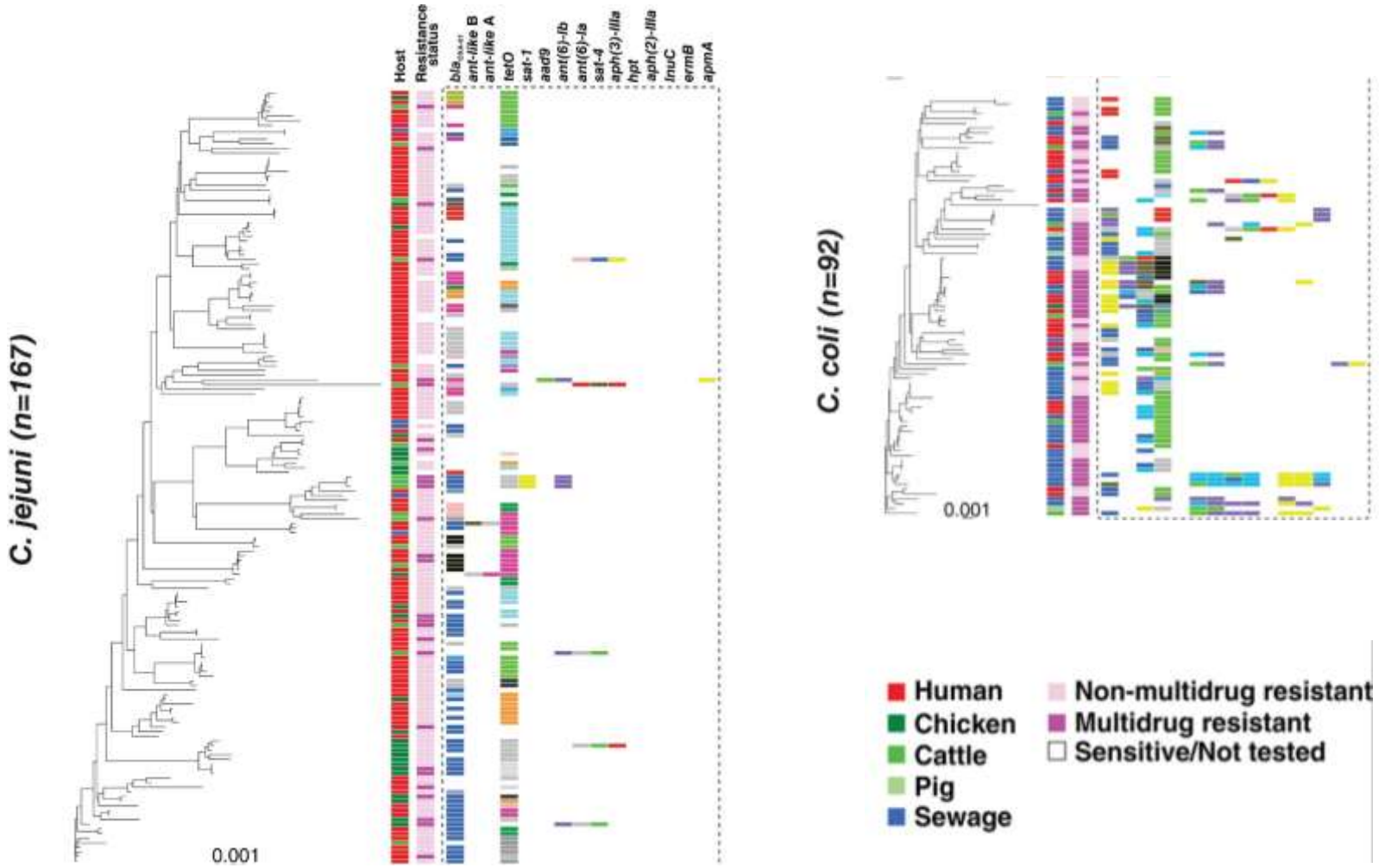
AMR *Campylobacter* from humans, animals and sewage.

		Campylobacter jejuni (*n* = 162)			*Campylobacter coli* (*n* = 91)		
	Antibiotics[a]	Animals	Humans	Sewage	Animals	Humans	Sewage
Total number of non-multidrug resistant		27/44 (61.36%)	101/115 (8.69%)	4/4 (100%)	–	15/33 (45.45%)	27/47 (57.44%)
Total number of multidrug resistant		17/44 (38.63%)	10/115 (87.82%)	–	11/11 (100%)	18/33 (54.54%)	20/47 (42.55%)
Total number of isolates		44	115	4	11	33	47

[a] Antibiotic resistance to: ciprofloxacin; tetracycline; erythromycin; streptomycin; gentamicin.

Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760
Florez-Cuadrado et al (2017) Frontiers in Microbiology 8, 2240

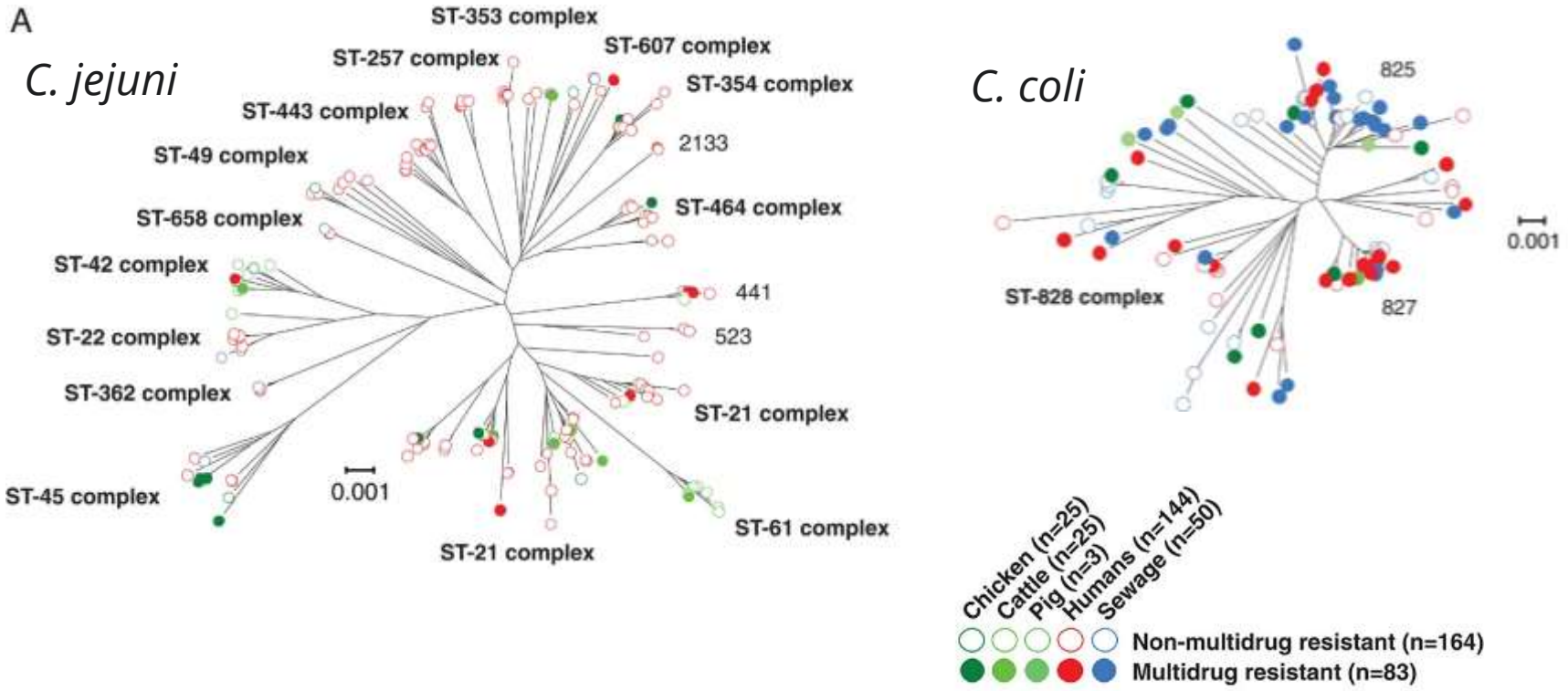
MDR is higher in *C. coli* than in *C. jejuni*



Presence/allelic diversity of 15 AMR genes, based on CARD, ResFinder and NCBI databases.

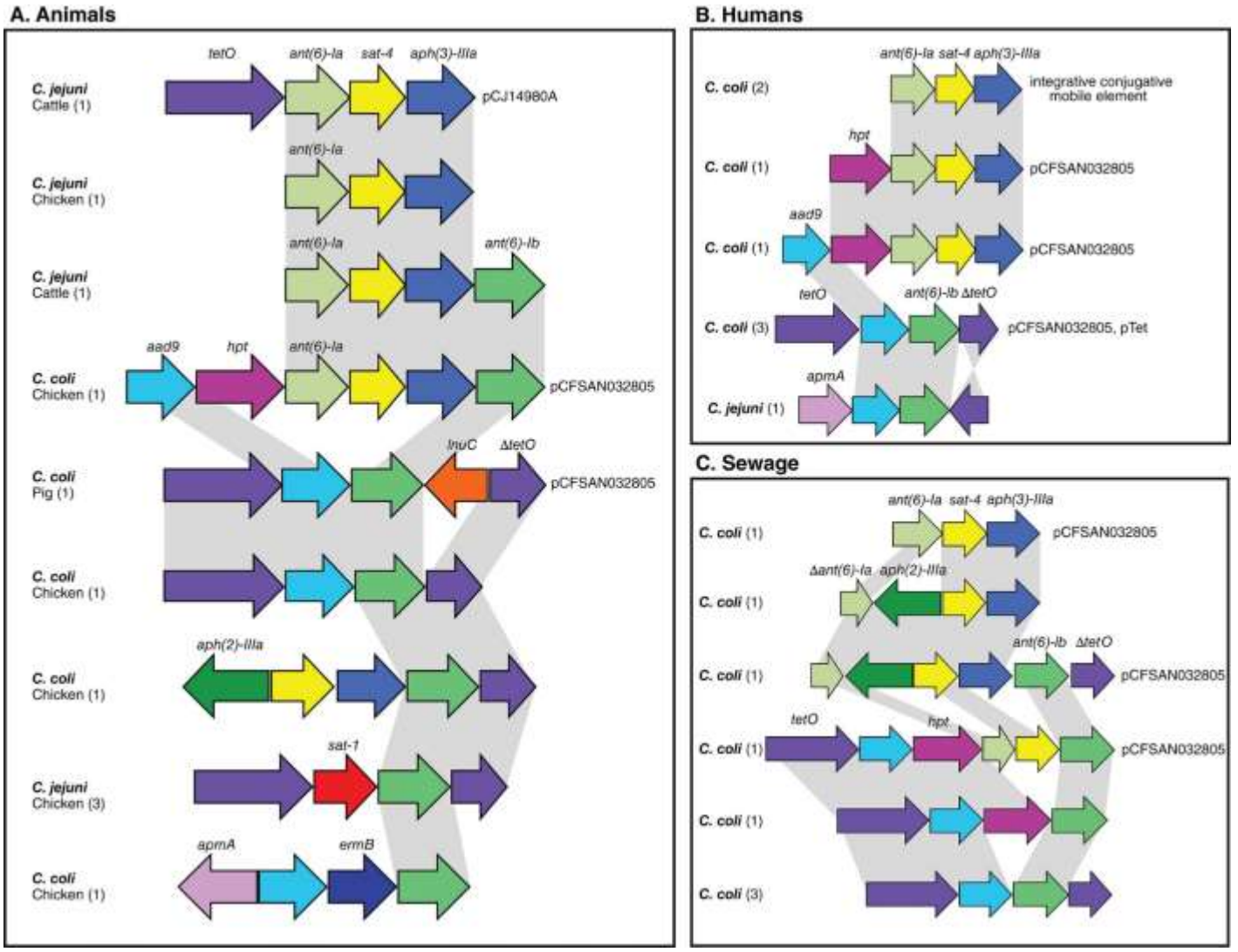
Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

AMR is distributed across structured *Campylobacter* populations – not just successful clones.



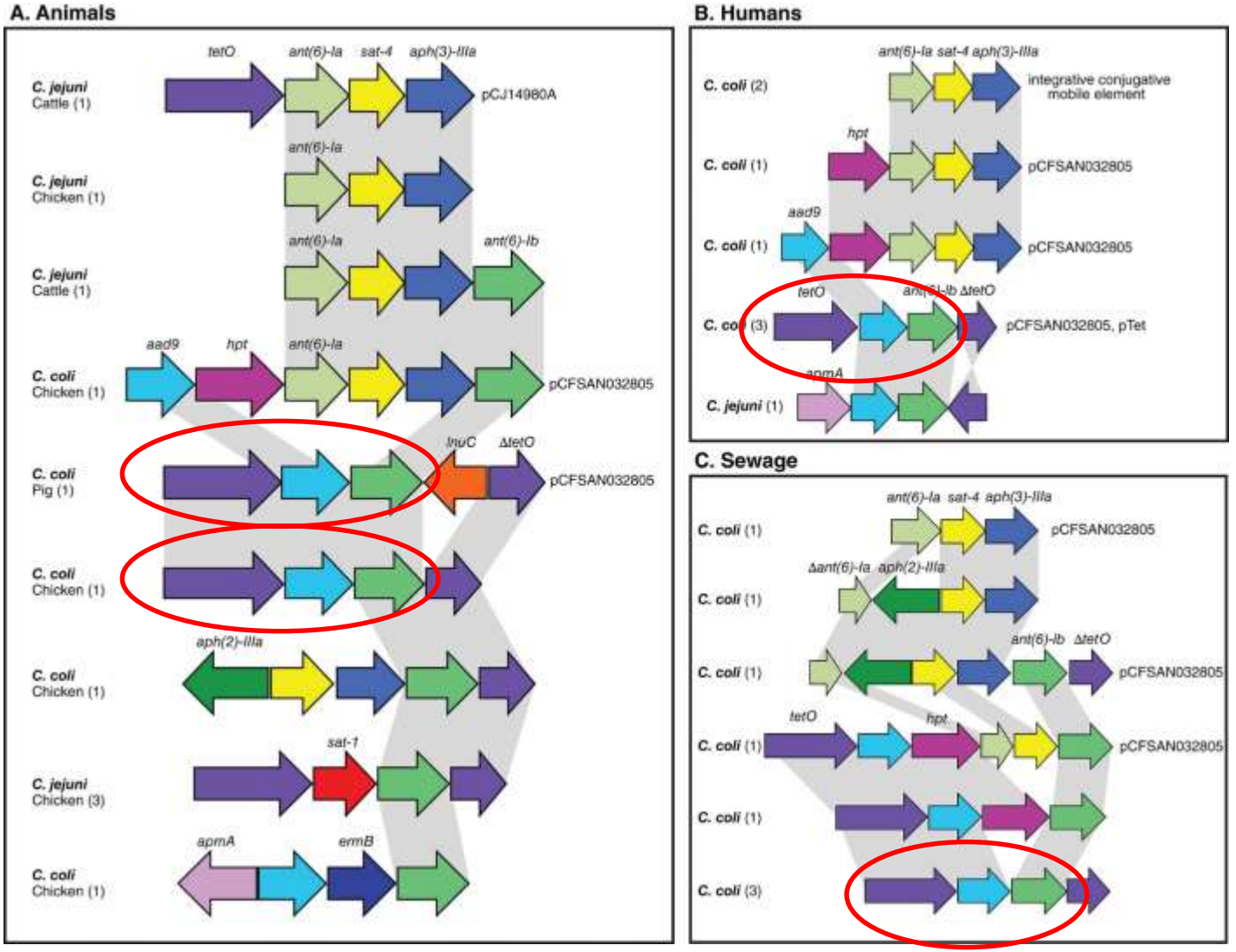
Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

AMR genes in genomic islands



Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

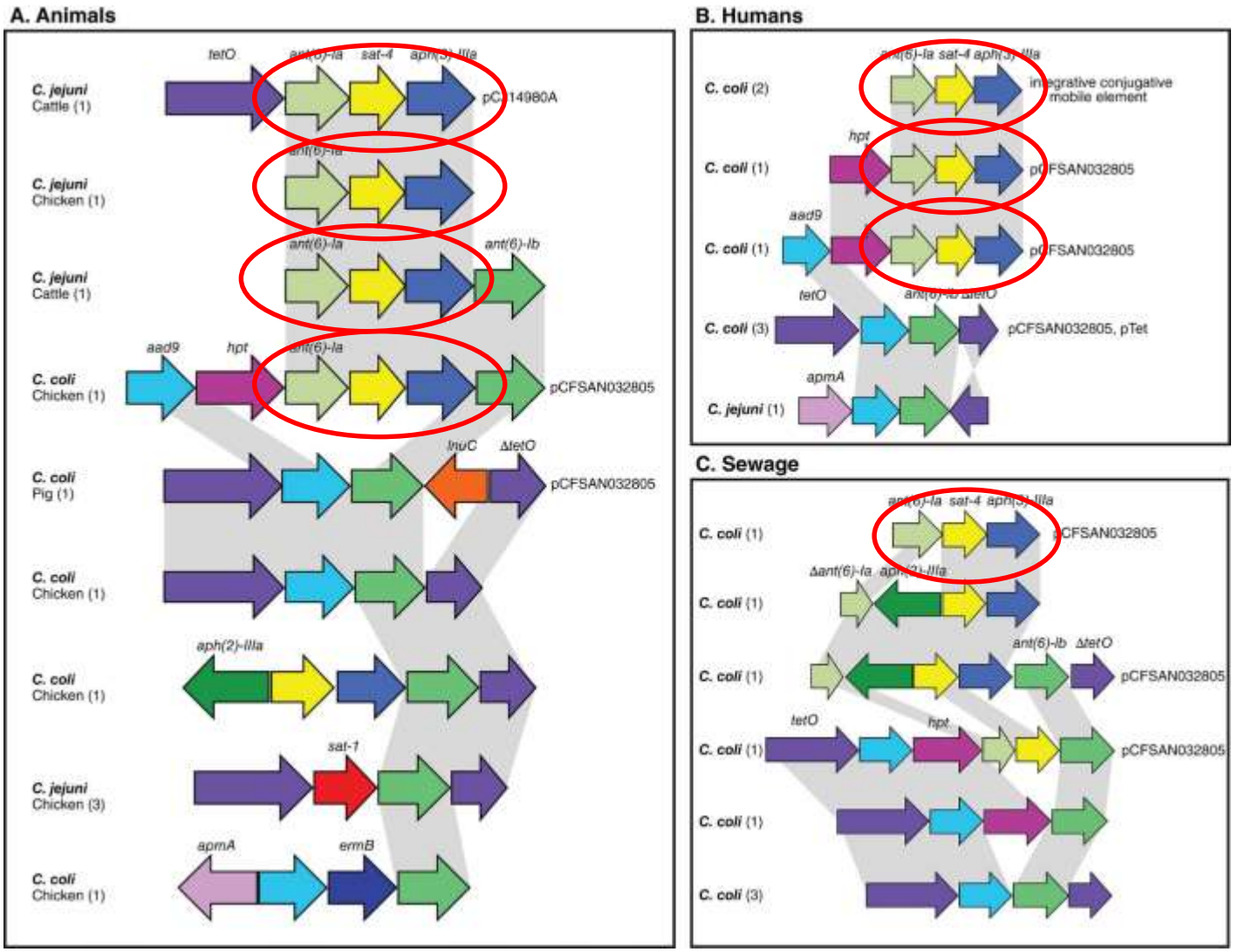
Evidence of gene pool transmission in *C. coli* from multiple sources



Co-localized *tetO, aad9, ant(6)-Ib*

Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

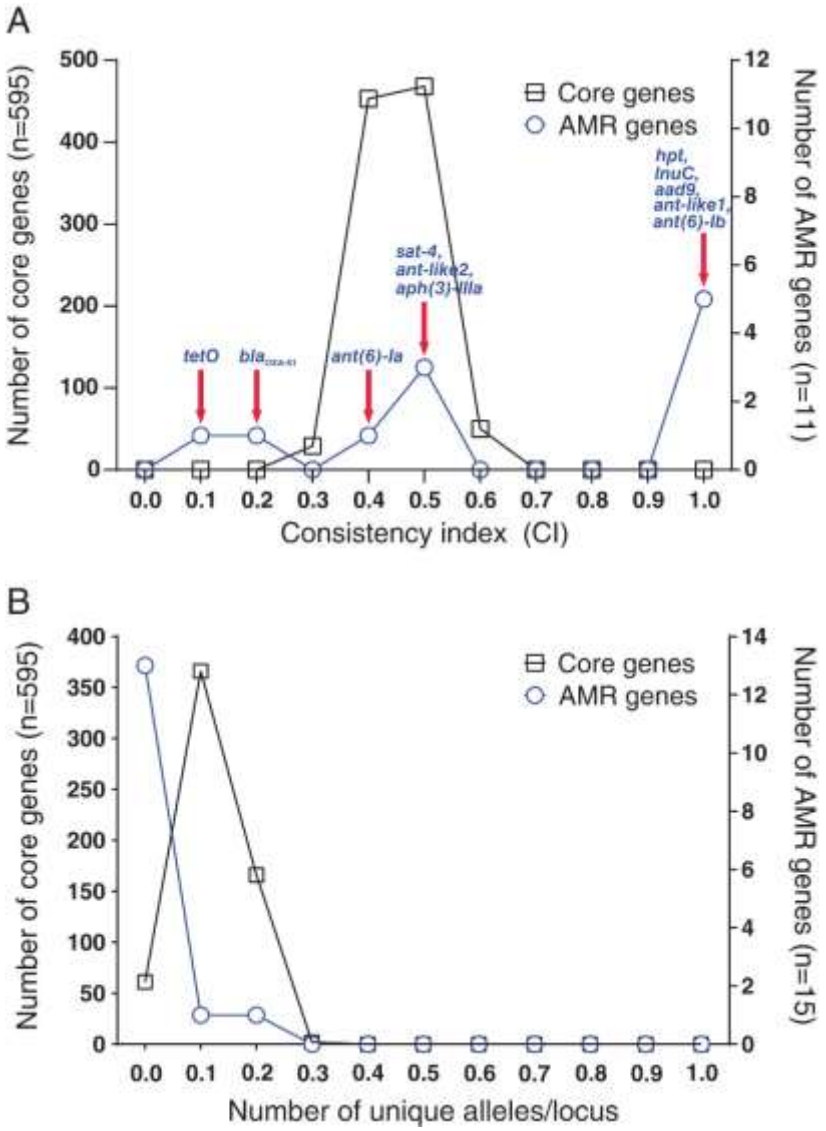
Evidence of gene pool transmission between *C. coli* and *C. jejuni*



Co-localized *ant(6)-Ia, sat-4, aph(3)-IIIa*

Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

Evidence of gene pool transmission

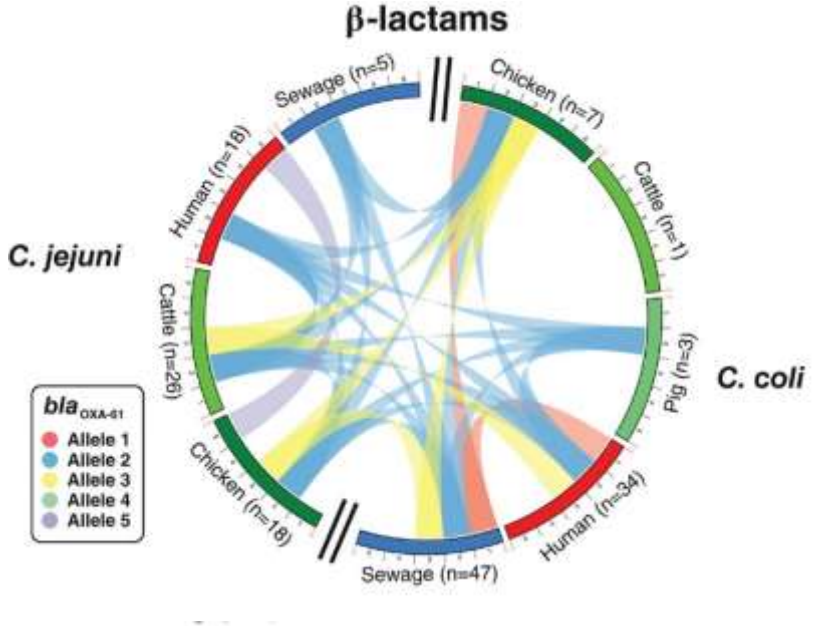


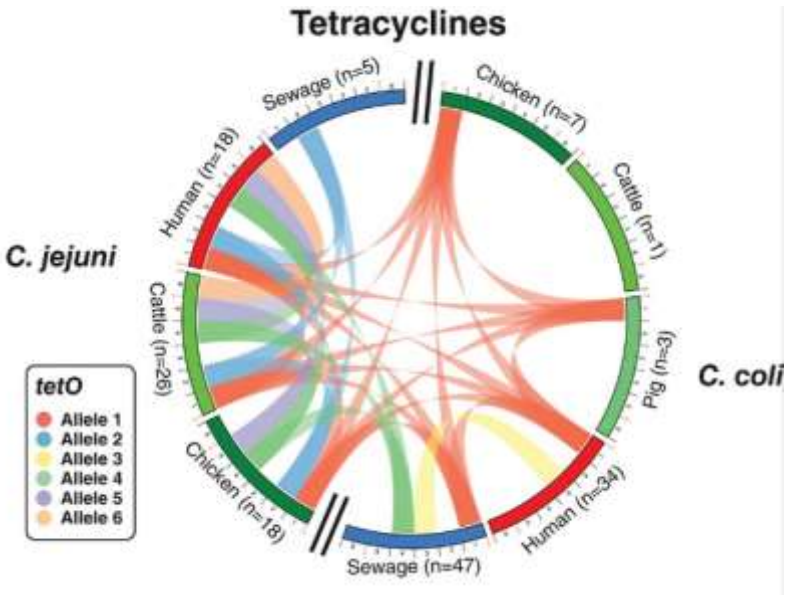
The mean consistency index (CI) was significantly higher among AMR genes (0.66) compared with core genes (0.46), and allelic variation was lower.

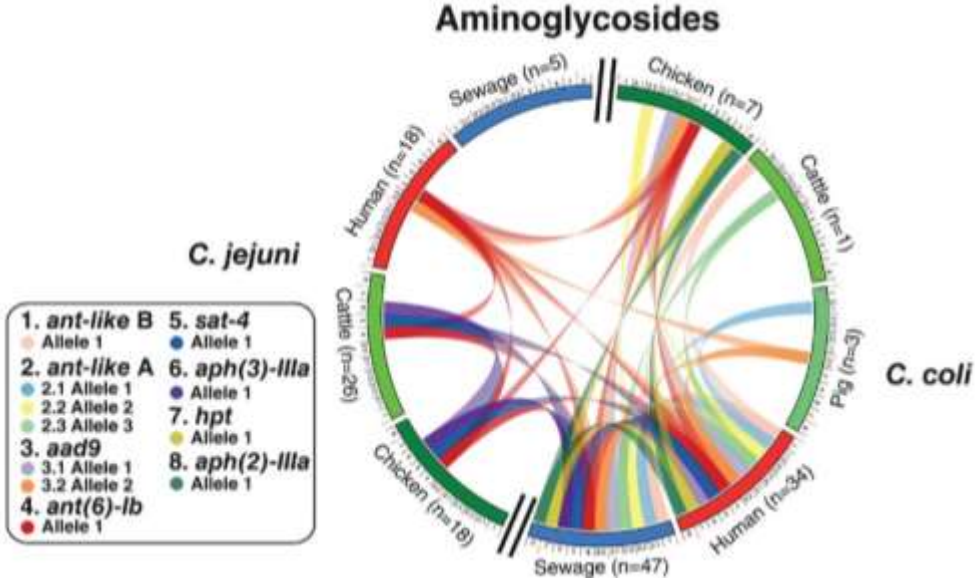
Consistent with HGT facilitating the movement of AMR genes.

Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

Allele sharing between sources and species



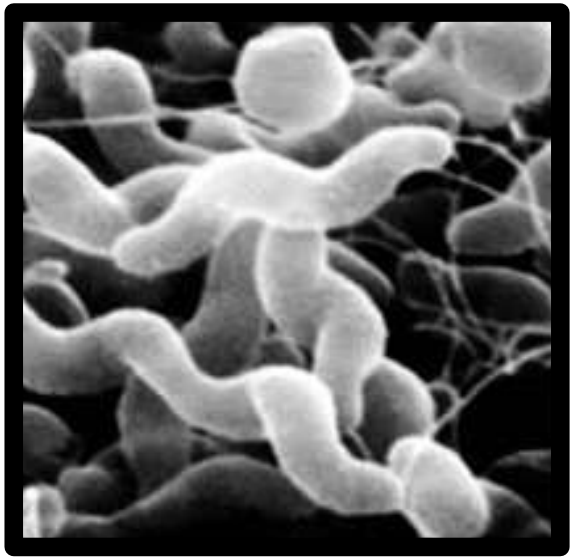




Shared alleles among β-lactam, tetracycline and aminoglycoside AMR genes (present in > 5 isolate genomes) are numbered around the perimeter.

Mourkas et al (2019) *Environmental Microbiology* doi:10.1111/1462-2920.14760

Understanding the spread of AMR *Campylobacter*



1. Genomics and host adaptation ✓
2. Clonal transmission ✓
3. Gene pool transmission ✓

Is this enough to explain the coincidence of rising AMR?

Not really – overlapping gene pools but no source sink dynamics!

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