Stunted Neonatal Gut Microbiota and Pathogen Colonisation Associated with Caesarean Births

Yan Shao

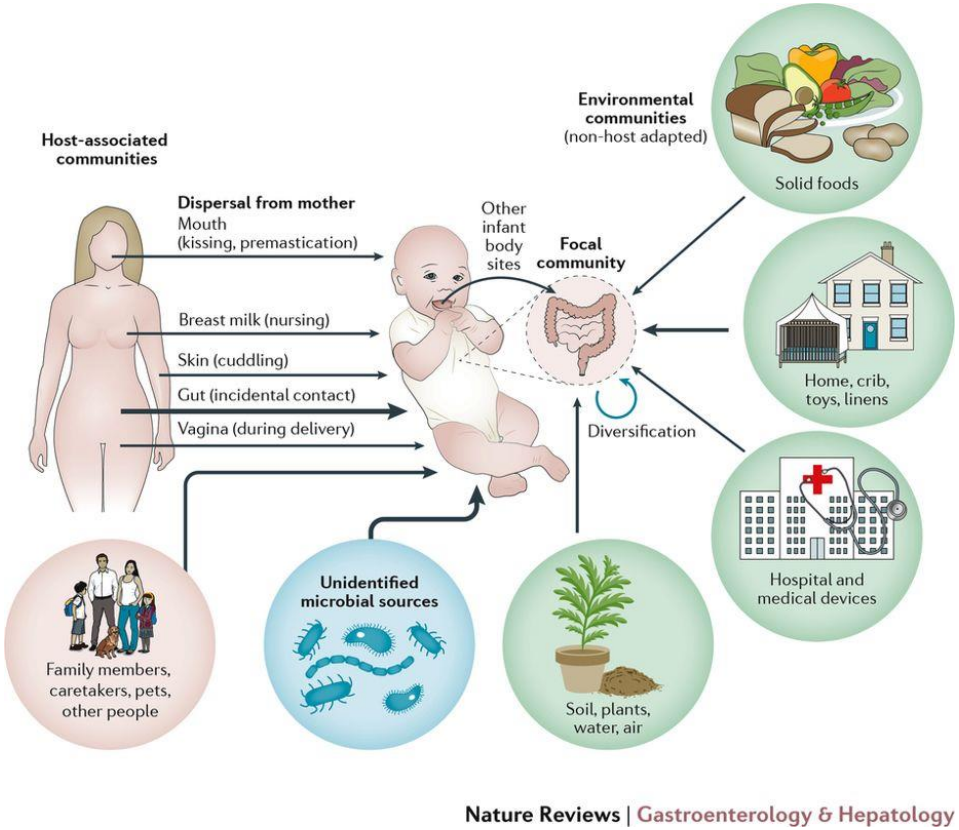
PhD Student

Host-Microbiota Interactions Lab

Wellcome Sanger Institute

Cambridge, UK

Gut Microbiota Acquisition in Very Early Life



- **Local species pool**
- **Maternal microbiota**

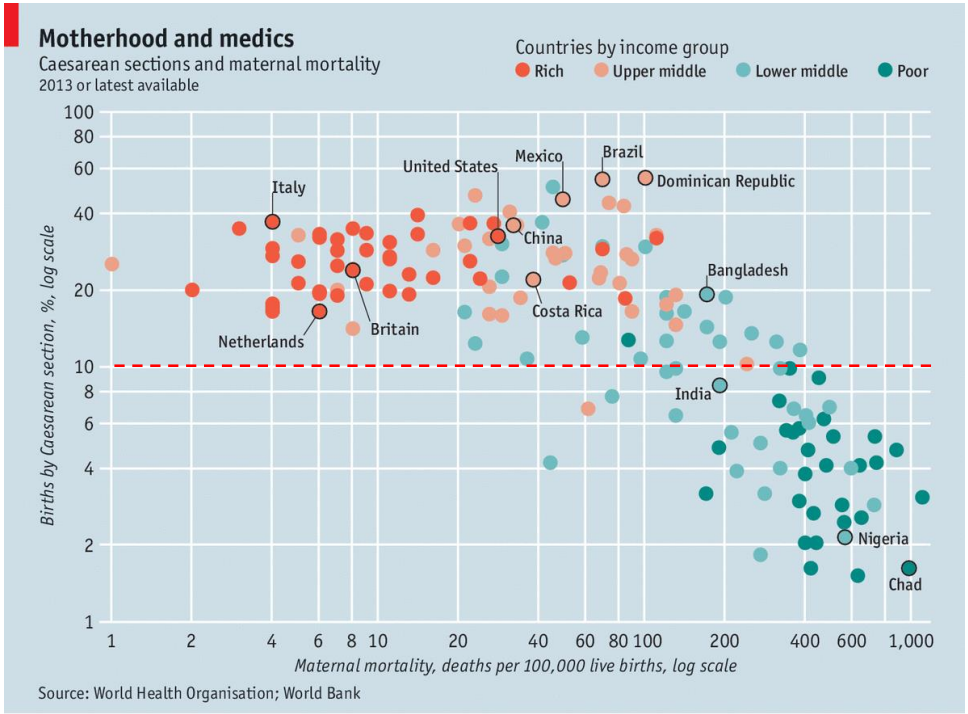
  Vaginal, faecal, skin, oral, breastmilk
- **Local environment**

  Hospital, midwives, medical device, home, pets, parents, sibling microbiota
- **Role of early life events?**

  Mode of delivery, breast/formula feeding, antibiotics, weaning

Sprockett et al, 2018

Global Trends of Elective Caesarean Sections



- Major abdominal surgery
- Maternal intrapartum antibiotics
- Elective/planned C-section frequently performed without medical indication
- Epidemiological association with autoimmune diseases (e.g. asthma)
- Hypothesis:

  Perturbed gut microbiotas of C-section babies predispose them to health issues later in life

WHO guideline on C-section rates: 10-15%,
No evidence of mortality risk reduction above this threshold

Metagenomic Sampling of the Neonatal Period

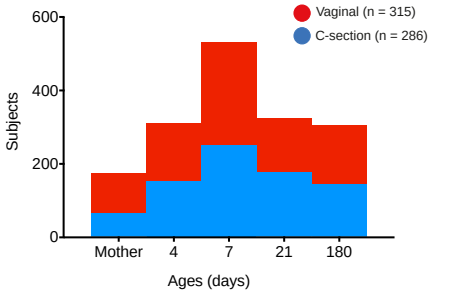
BABY BIOME STUDY

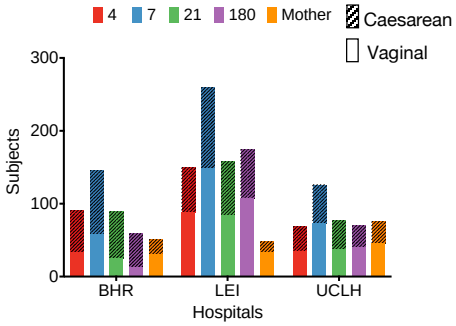
UK birth cohort (n > 2k)

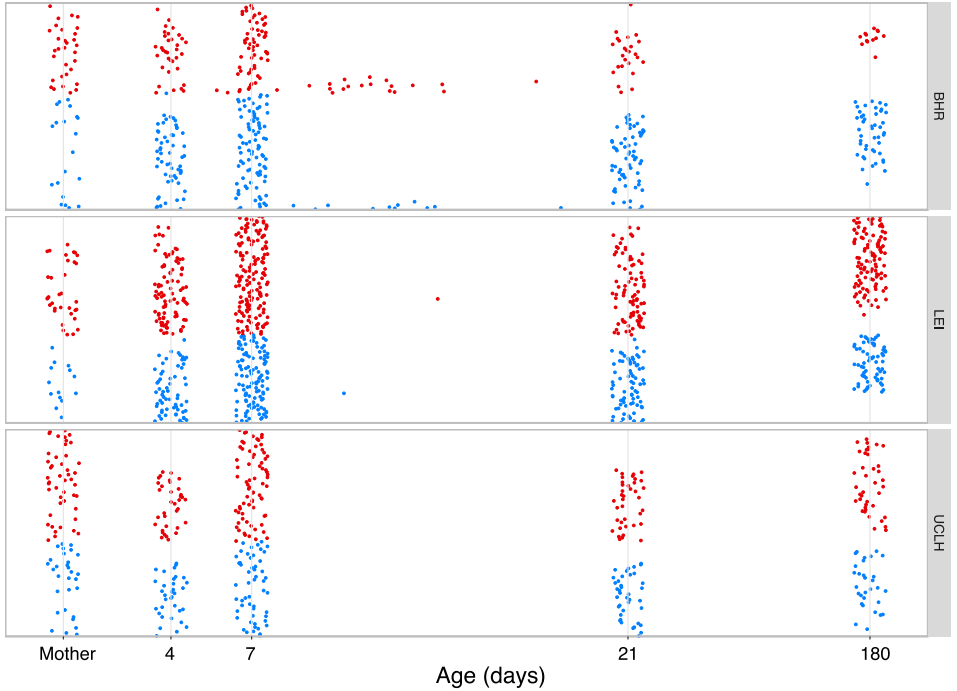
2016 - 2018

601 term babies and 176 mothers

Shotgun metagenomics of **1,683** stool samples







Barking, Havering and Redbridge University Hospitals NHS Trust

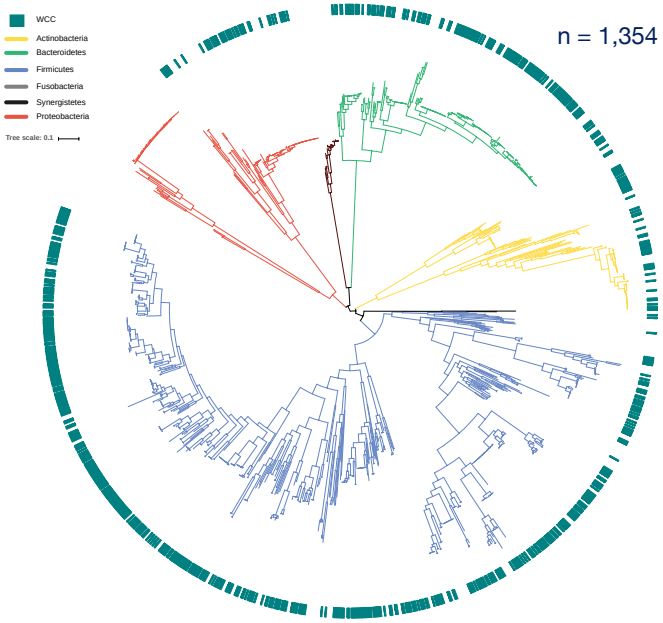
University Hospitals of Leicester NHS Trust

University College London Hospitals NHS Foundation Trust

wellcome sanger institute

High Resolution Gut Microbiome Profiling

Phylogeny of the Human Gut Microbiota



Comprehensive Database of Reference Genomes

- Lawley Lab Human Microbiota Culture Collection (~ 200 novel species)
- Quality filtered public genomes (e.g. HMP collection)

k-mer-based Read Classification (Kraken/Bracken)

- **Scalable for large-scale shotgun metagenomics**

  ~1% computing resource versus deep sequencing & *de novo* assembly

- **Improved sensitivity and taxonomic resolution**

  ~30% high recall than HMP

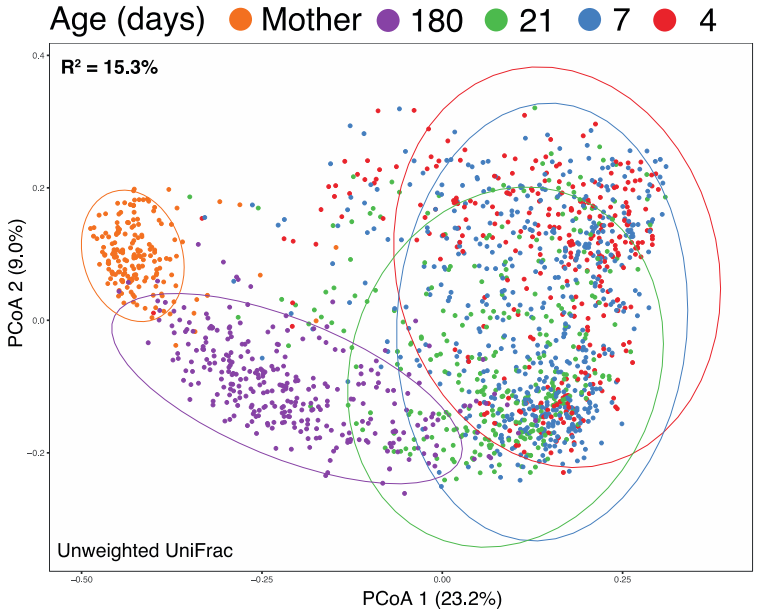
  Majority of the human gut microbiota metagenomic sequences classified at species (~80%) and strain level (~50%)

wellcome sanger institute

Forster and Kumar et al. *Nat Biotechnol, in press*
Browne and Forster et al. *Nature* (2016)

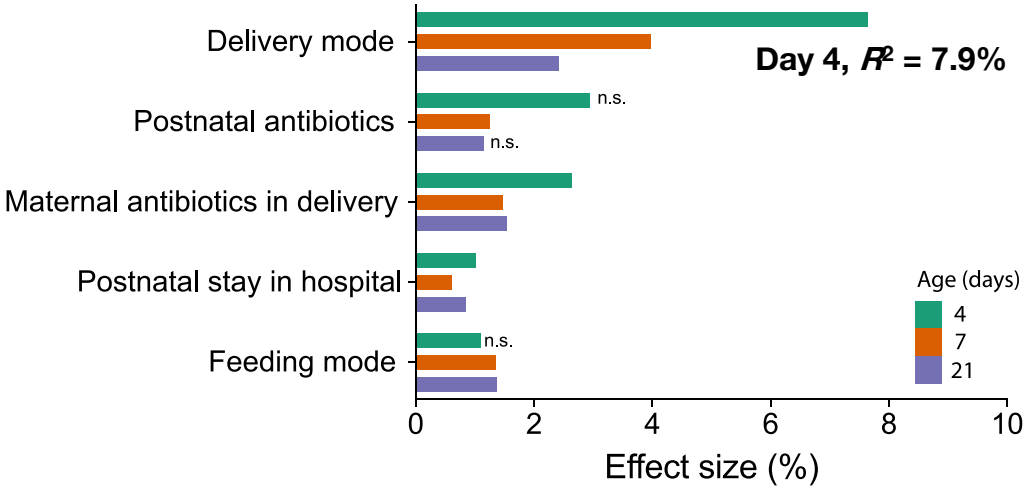
Permutational Multivariate Analysis of Variance

Age-dependent microbiome maturation



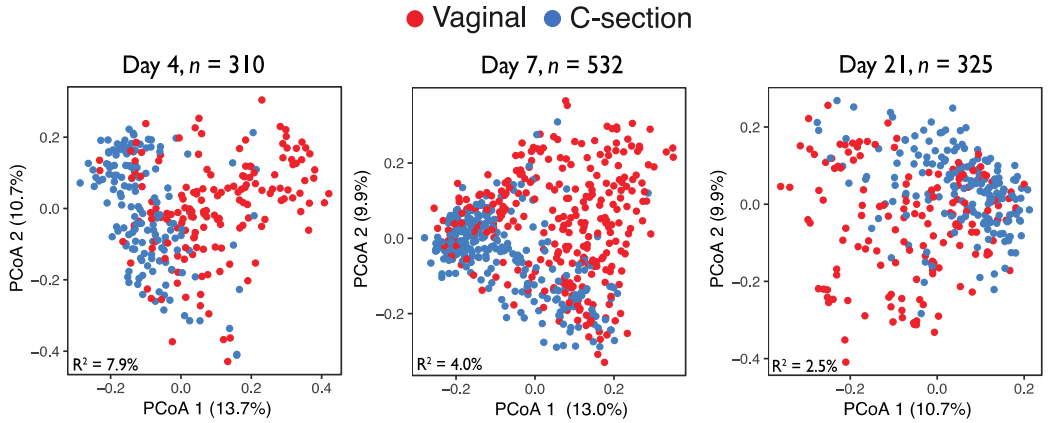
Species composition (beta diversity)

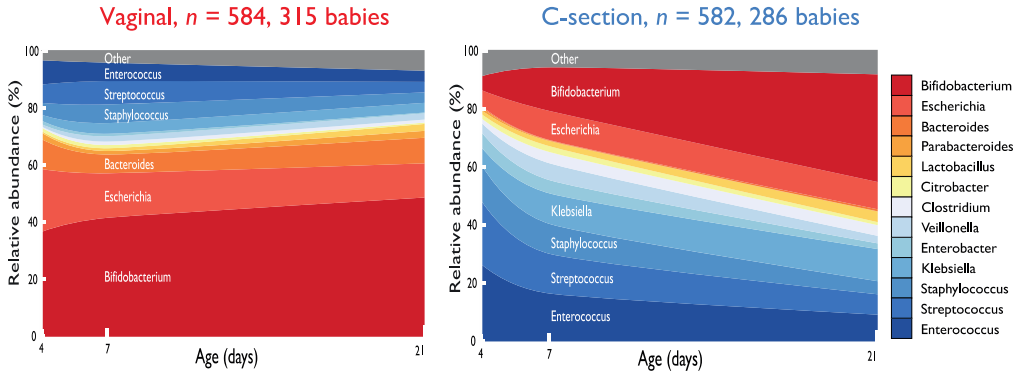
Effect size of clinical factors stratified by age



Shao et al., unpublished data

Effect of Delivery Mode on the Neonatal Gut Microbiota





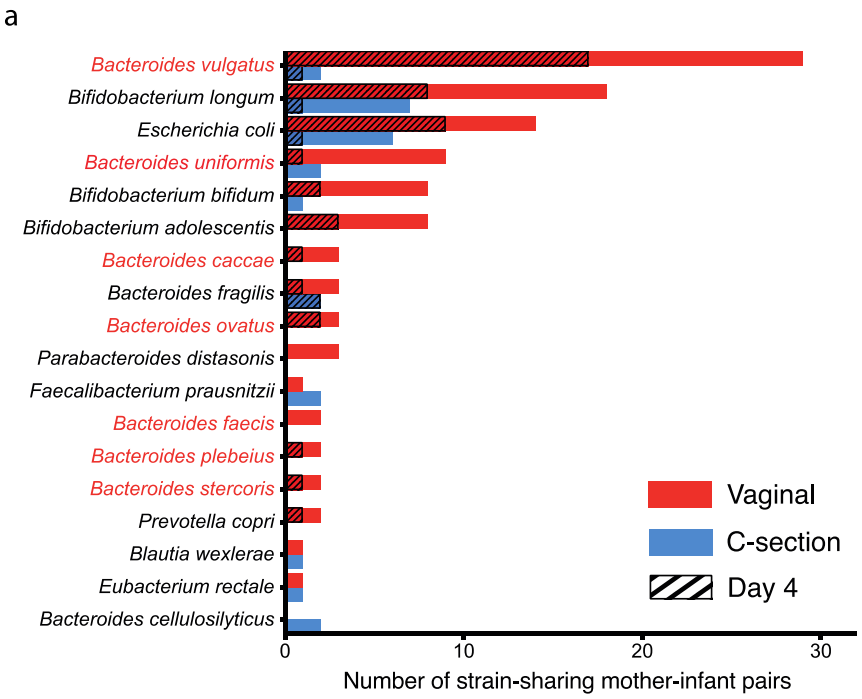
Mode of delivery:

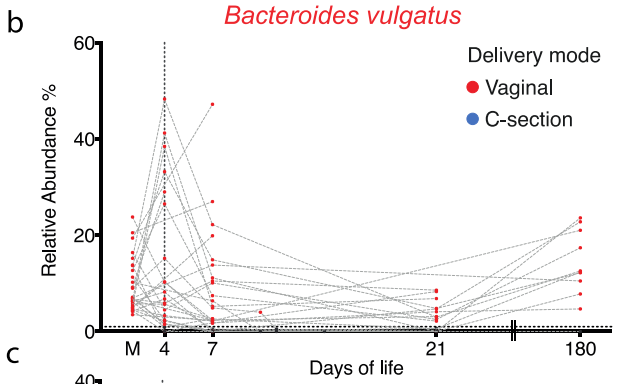
- Largest explanatory power on microbiome variation
- Effect size: 7.9% – 2.5% over the neonatal period
- Statistically significant at 6 months of age (R^2 = 1.1%)
- Vaginal microbiota-associated *Lactobacillus* spp. at very low abundance (<2%) in both groups
- Stable developmental trajectory dominated by commensal *Bifidobacterium*, *E. coli* and *Bacteroides*
- Environmental-associated bacteria ~80% on day 4
- Delayed *Bifidobacterium* spp. colonisation
  98.6% C-section newborns without *Bacteroides* spp.
  48.9% by 6 months of age

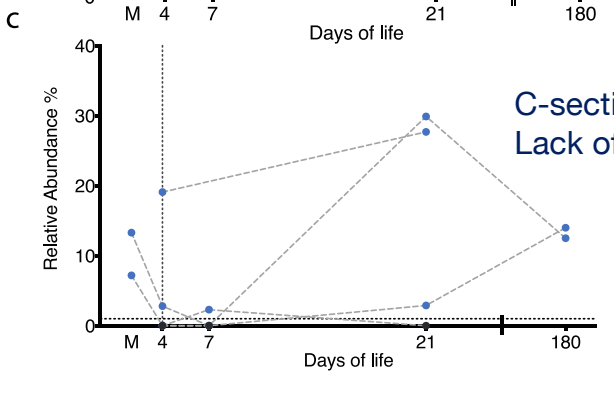
Shao et al., unpublished data

Maternal *Bacteroides* Transmission Disrupted in C-section

Strain transmission threshold: 5% sharing of unique rare SNPs within mother-baby sample pairs (*MIDAS)







C-section
Lack of late colonisation

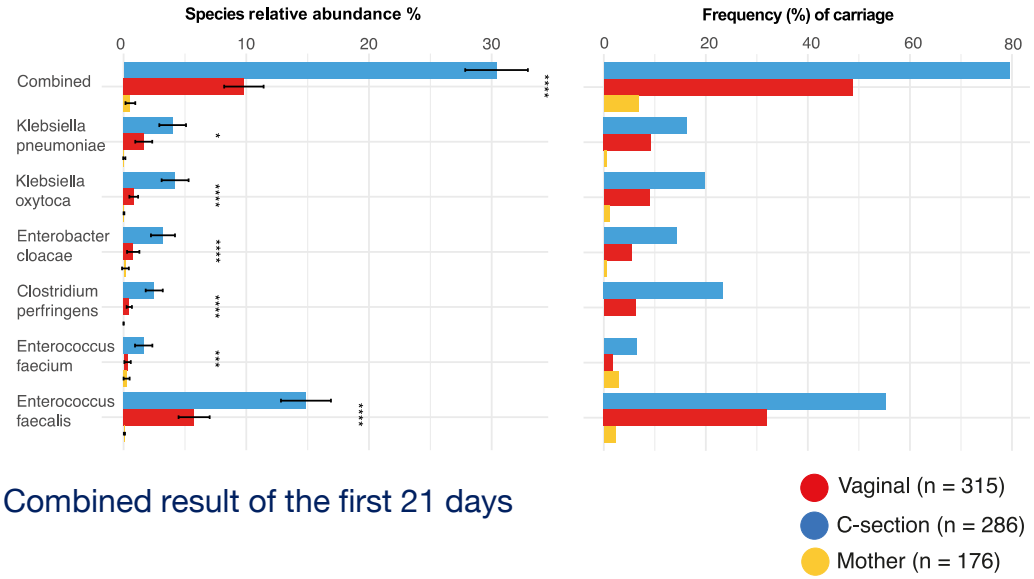
Shao et al., unpublished data

*MIDAS : Nayfach & Pollard, *Genome Res* (2016)

Opportunistic Pathogen Colonisation in C-section Babies

Differential species in C-section babies

Associated with healthcare environment
Rare, low carriage in mothers

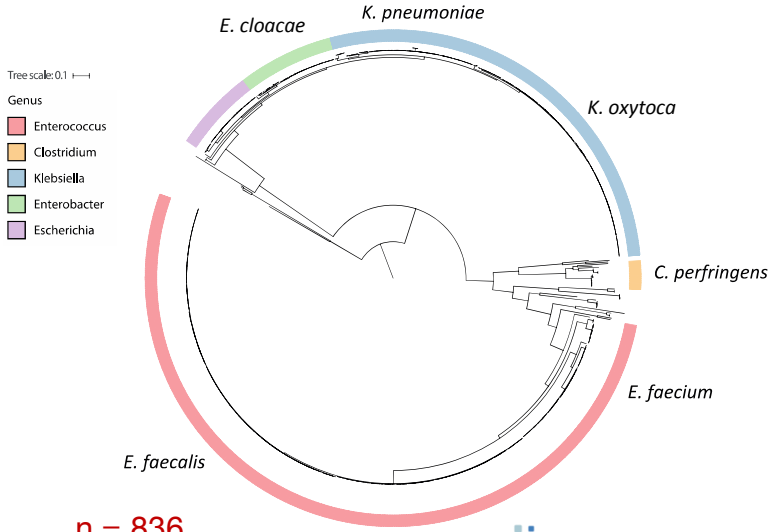


Combined result of the first 21 days

WGS of 836 pathogen isolates

Faecal biobank access

Culturing and isolation from raw stools



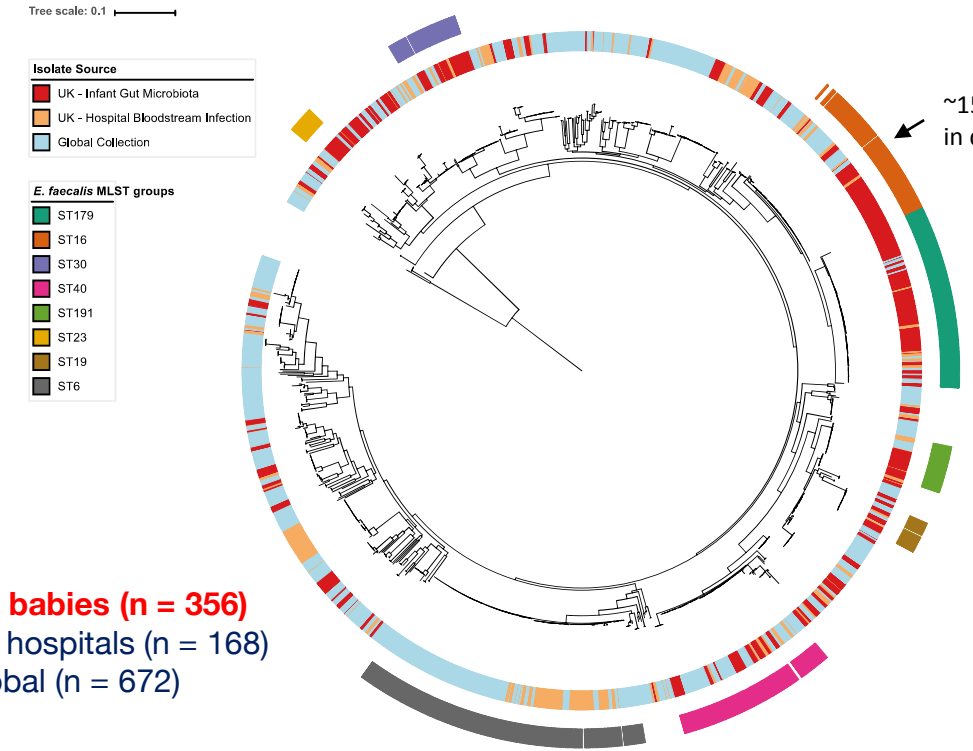
n = 836

wellcome sanger institute

Shao et al., unpublished data

Strain Diversity, Virulence and AMR of *E. faecalis*

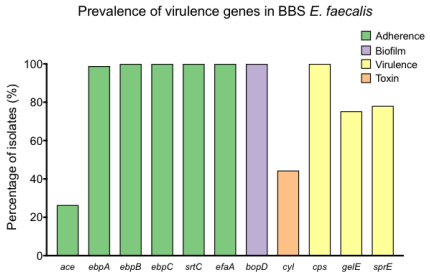
Whole-genome Phylogeny of *E. faecalis*

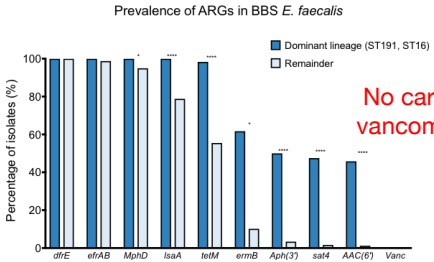


~15% of total isolates in dominant lineages

UK babies (n = 356)
UK hospitals (n = 168)
Global (n = 672)

70.5% of baby isolates carried multiple genetic determinants for hospital adaptation





No carriage of vancomycin resistance

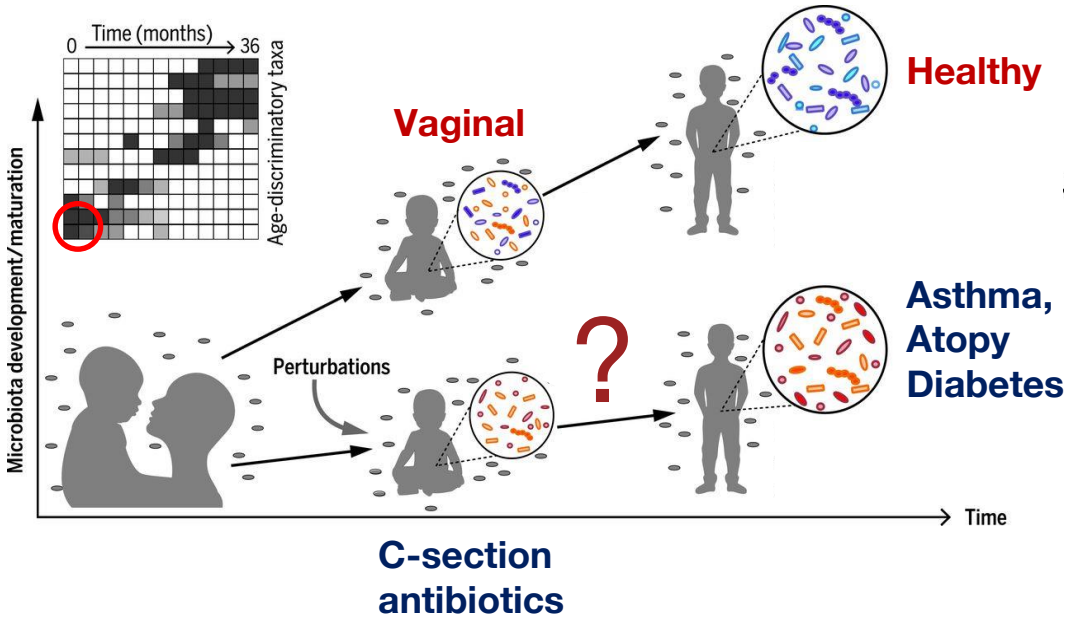
Dominant lineages: enrichment of **tetracycline** and **aminoglycoside** resistance genes

wellcome sanger institute

Shao et al., unpublished data

Early Life Microbiota Acquisition and Development

Hygiene/Missing Microbiota Hypotheses



- Missing environmental and host genetic factors unmeasured
- Stochastic colonisation process: ecological drift and priority effect

Association -- BABY BIOME STUDY **--> Causation**

- Long-term host outcome via health data linkage
- Mechanistic studies in germ-free and gnotobiotic mice

wellcome sanger institute

Adapted from Blanton et al. *Science* (2016)

Acknowledgments

Trevor Lawley

Sam Forster
Nitin Kumar
Mark Stares
Core Sequencing team
Pathogen Informatics team

BBS Recruitment

UCLH research midwives
BHRUT research midwives
UHL research midwives
NIHR Clinical Research Network
Participants and their babies

Nigel Field
Peter Brocklehurst
Alison Rodger
Evi Tsaliki
Angela Strang
Nandi Simpson

BHRUT research lab

Nadia Moreno
Samra Bibi
Henna Ali

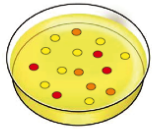
BABY BIOME STUDY

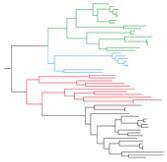
Population Metagenomics

n = 1683

Mother-infant Dyads
Neonatal Period (0-3 wks)
Longitudinal Sampling to 6 mos

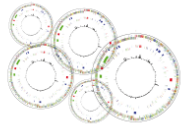
Targeted Culturing





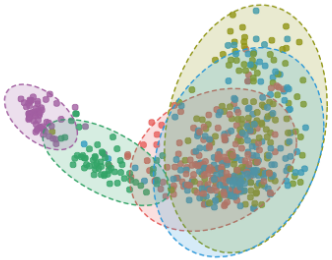
Fecal Biobank Access
Selective Media and Condition

Bacterial WGS

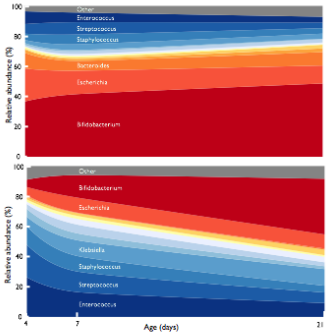


Pure Culture Collection
Expand Reference Genome DB

Colonisation dynamics in very early life

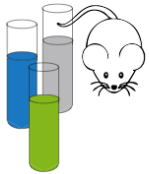


Microbiota perturbations



Pathogen phlogeny and gene carriage

Colonisation succession Pathogen resistance



wellcome sanger institute