

Infant age inversely correlates with gut carriage of resistance genes, reflecting modifications in microbial carbohydrate metabolism during early life

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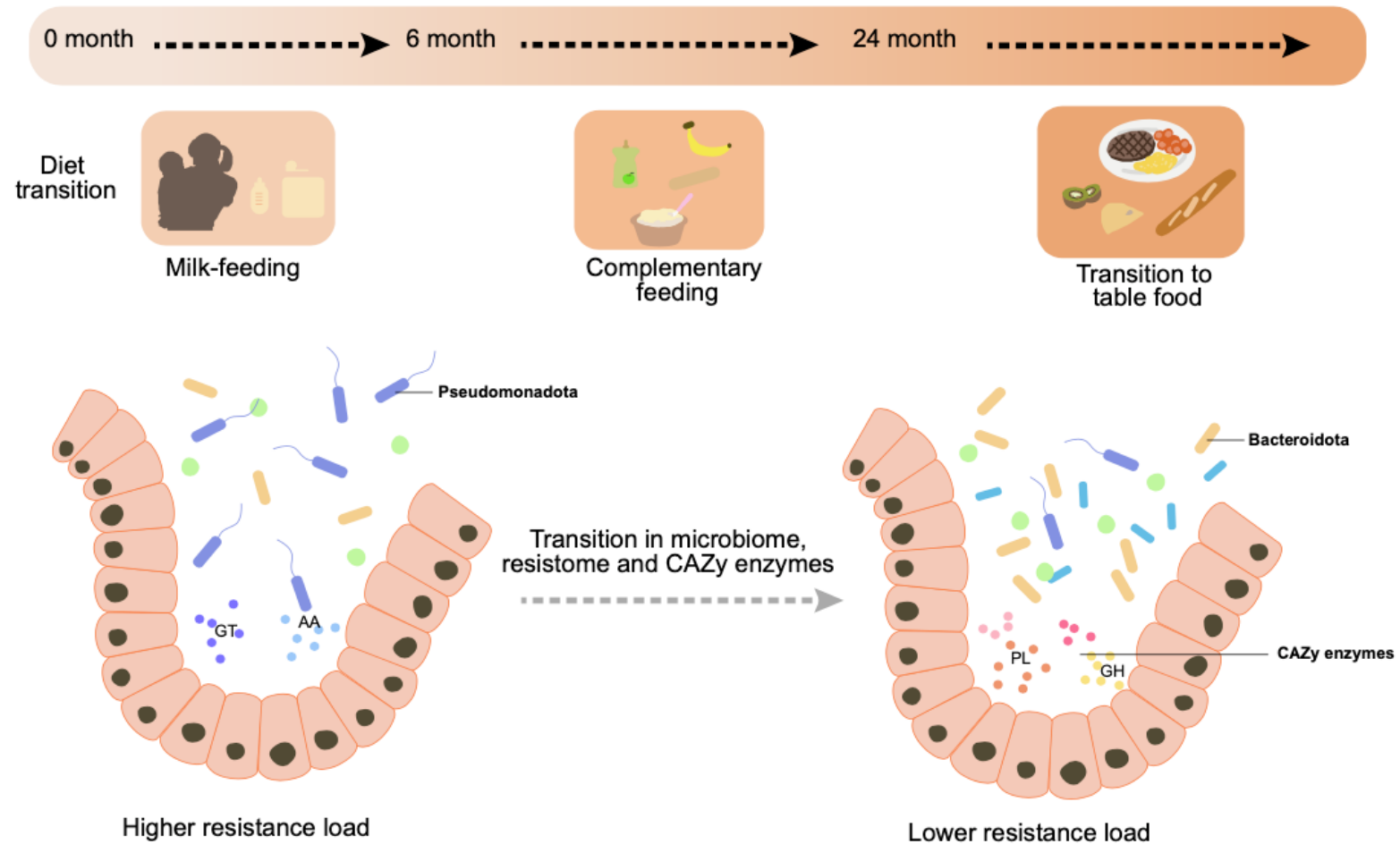
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Introduction

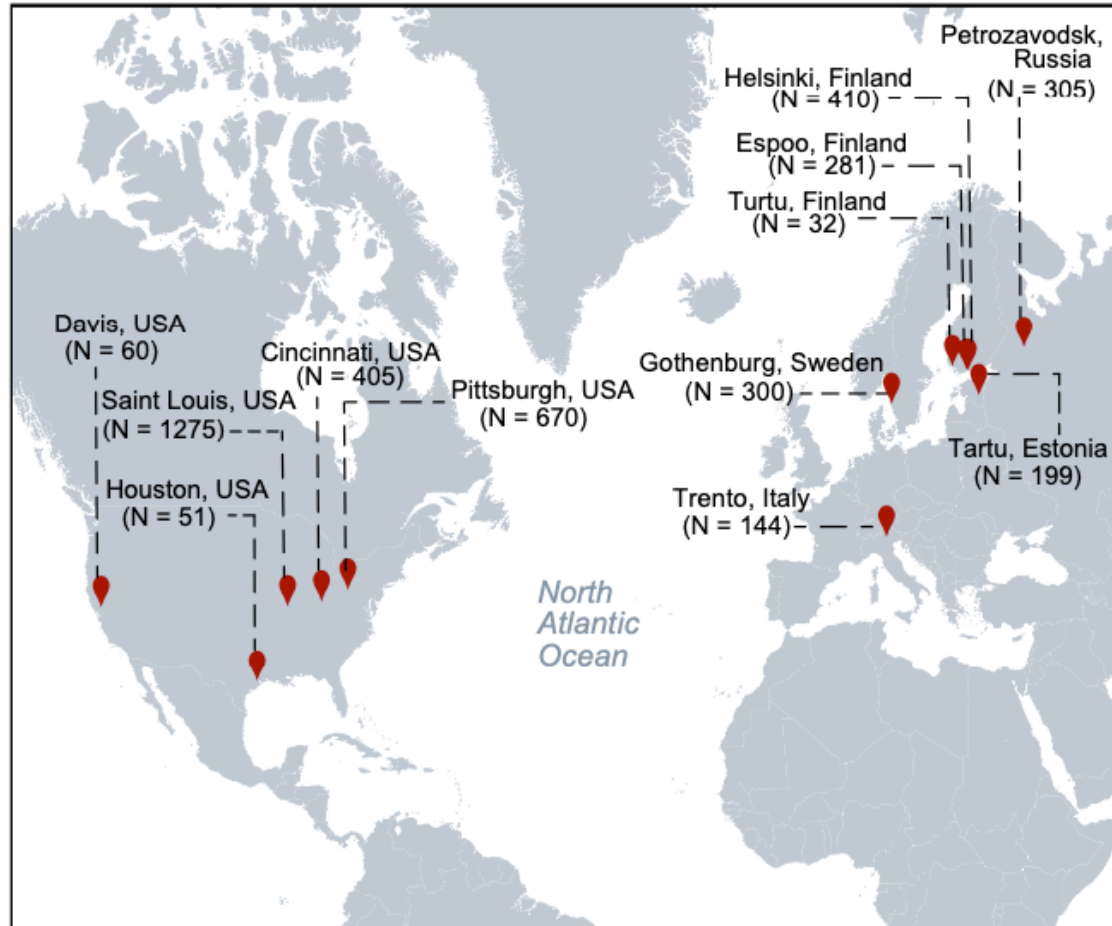


- The infant gut microbiota are recognized as reservoirs of antimicrobial resistance genes (ARGs).
- We aim to study the infant gut resistome's natural assembly, including identifying factors that influence the trajectory of resistome development using publically available metagenomes from infants and toddlers.



Results

Overview of multicohort worldwide infant gut metagenomes



- To assemble a cohort of global infant gut metagenomes, we retrieved 4132 infant and toddler - related metagenomes from 963 infants enrolled in 19 different cohorts, in 17 independent studies between 2015 and 2020.
- We applied unified quality controls and upstream analyses to all samples.



Results

The typical succession of fecal resistome during the first 14 months of life in healthy infants

- Full-term infants who were vaginally delivered without any recorded antibiotic treatment were categorized as “healthy” in our analysis.
- Consequently, 858 consecutive stool metagenomes from 272 infants during the first 14 months of life were used to capture the natural assembly of healthy infant gut microbiota.

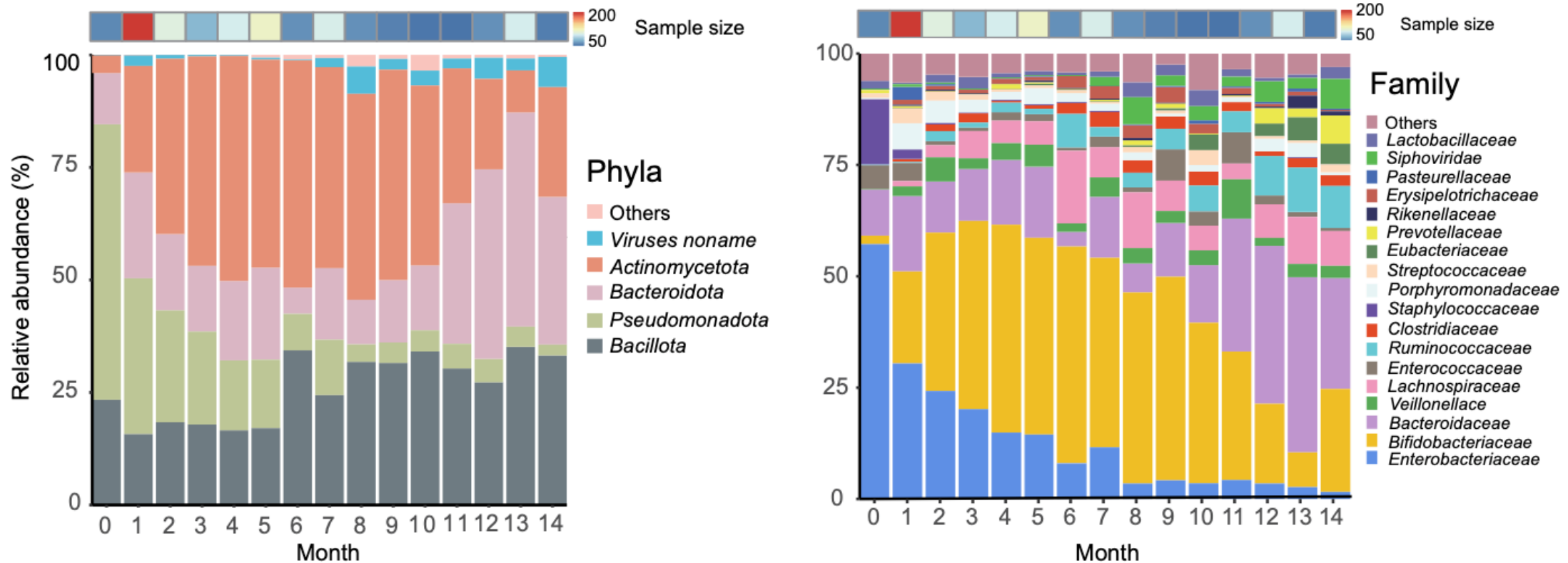


Figure. Stacked bar plots depicting the relative abundance of microbes as measured at the phyla and family level, respectively.



Results

The typical succession of fecal resistome during the first 14 months of life in healthy infants

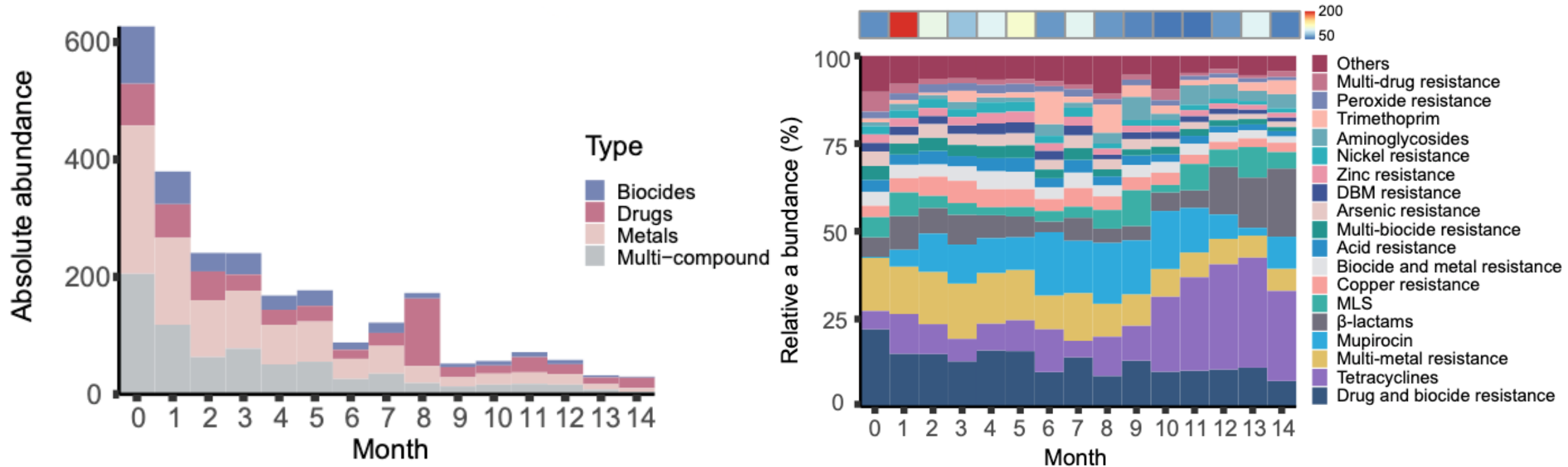


Figure. The assembly of gut resistome in healthy infants during early life.

Absolute abundance of resistance genes as measured by resistance reads per kilobase per genome equivalent (RPKG) at the type level.

Stacked bar plot depicting the relative abundance of resistance groups as measured at the class level of resistome. Resistance groups quantified with an average relative abundance <1% were aggregated into “Others.”



Results

Escherichia harbored the most resistance genes in healthy infants

- Uneven distribution of resistance genes across microbial taxa.
- By assigning a microbial taxon to the resistance gene-containing contigs, we found that *Pseudomonadota* was the dominant resistome-related phyla.
- The resistome from *Escherichia* was dominated by drug-biocide resistance (24.1%) and multimetal resistance (18.2%).

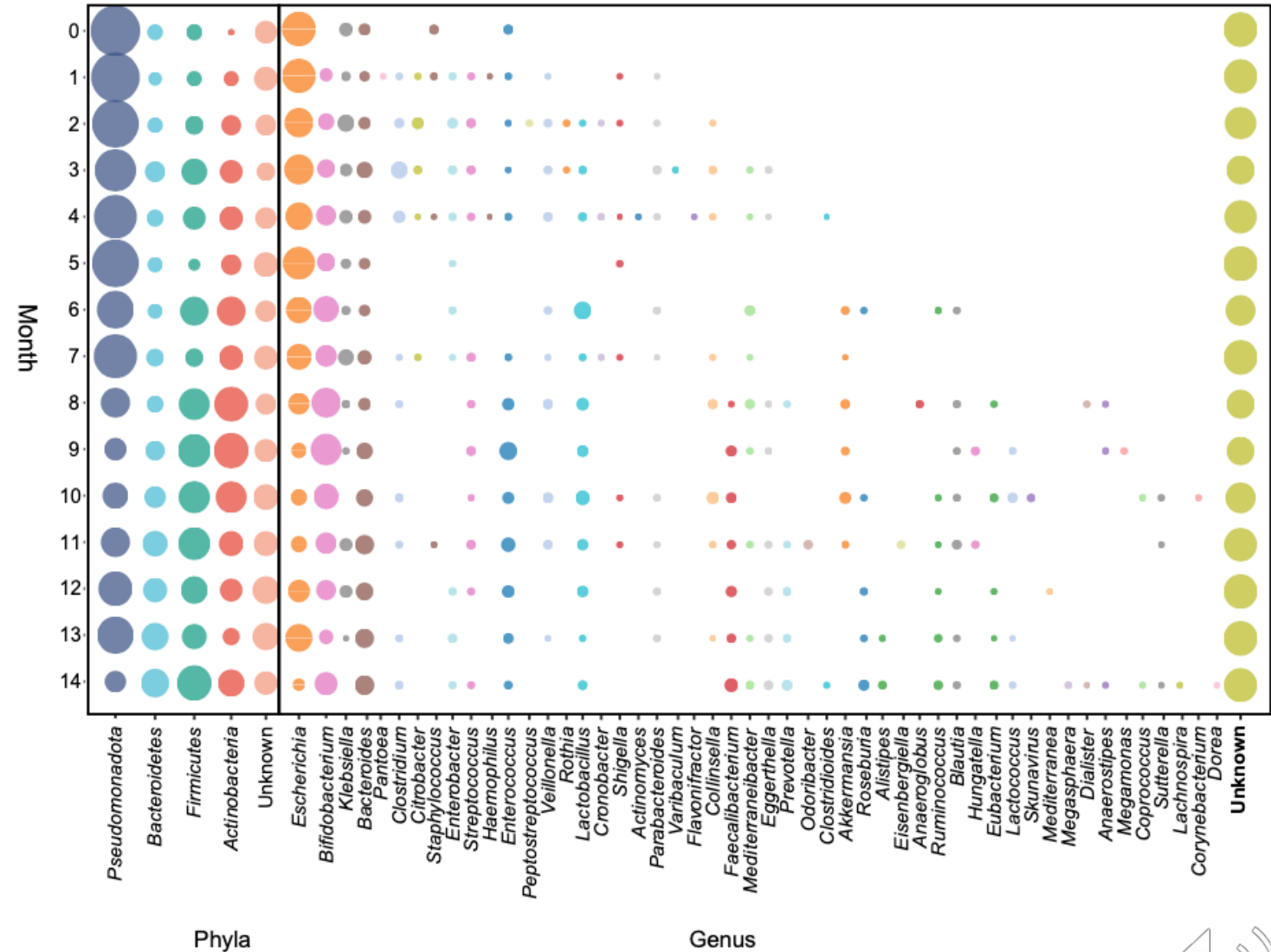
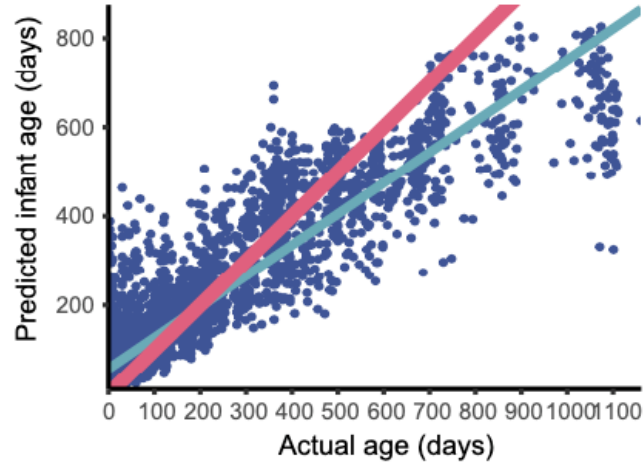


Figure. Bubble plots depicting the dynamic change of bacterial hosts of resistance genes at the phyla and genus level over time.



Results

The developing gut resistome is age-dependent during infancy



- We extended our analysis from healthy infants to all metagenomic samples to explore the factors influencing the resistome.
- The developing gut resistome was linearly related to infant biological age.
- Overall, 110 genes were grouped into six clusters with two distinct dynamic patterns: the abundance of resistance genes belonging to Clusters 1–3 (N = 53) was relatively high at the beginning and then decreased over time, while genes classified within Clusters 4–6 (N = 57) gradually increased during infancy.

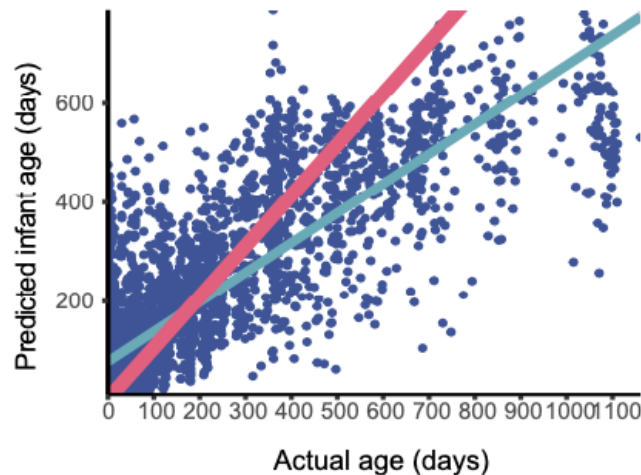


Figure. The predicted infant age (resistome age) versus actual infant age in the test set and training set in the random forest (RF) model.



Results

Infant gut resistome assembly links to shifts in microbial carbohydrate metabolism

- Half of the possible MEGID-CAZy pairs (over 5000) were significantly correlated.
- Variation in resistance abundance due to carbohydrate metabolism (40.7%) was greater than the variation due to microbial composition (36.1%).

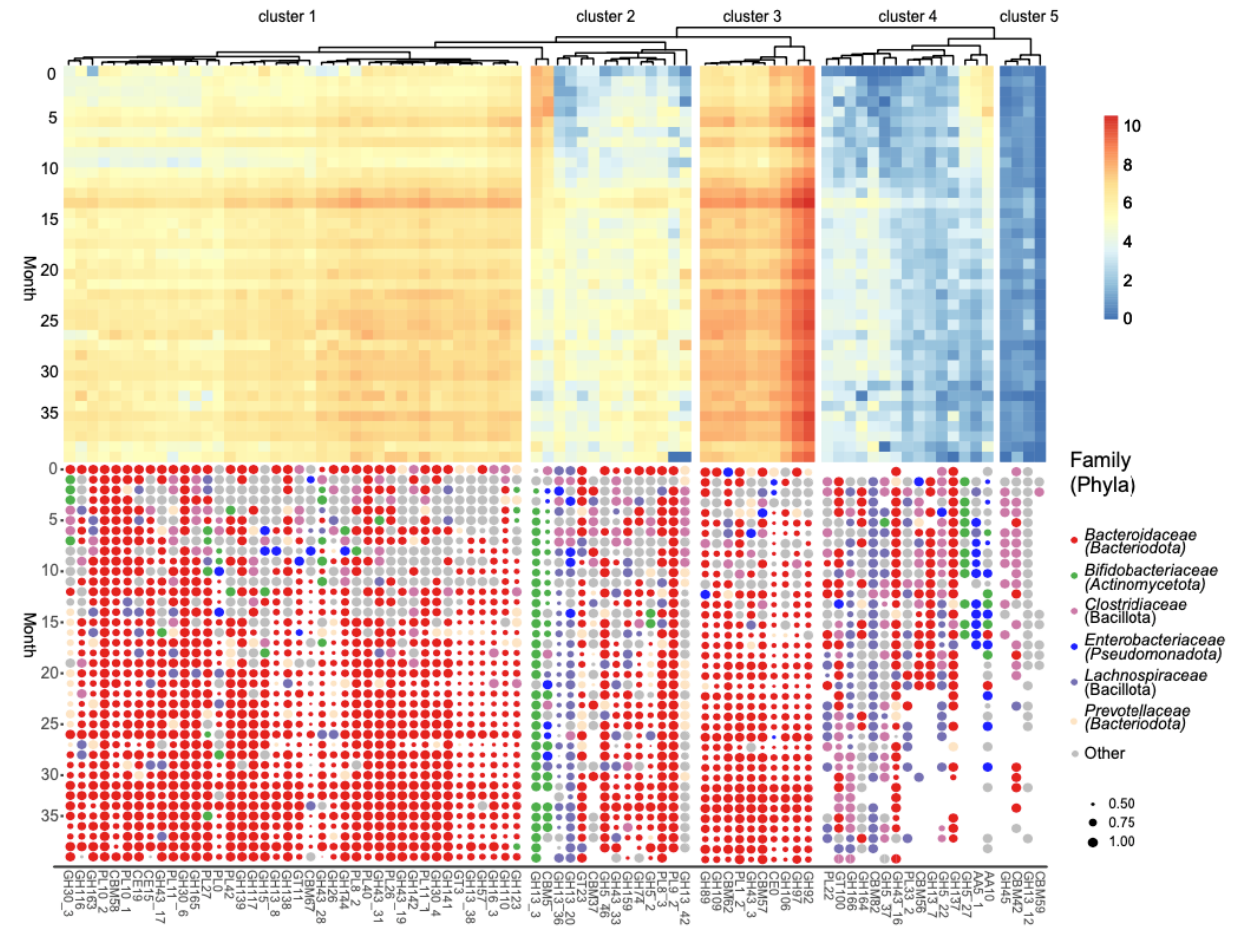


Figure. Heatmap depicting the abundance of CAZy families, which were significantly associated with infant age. The abundance values were log-transformed ($\log [\text{value} + 1, 10]$) for better visualization. The lower dot plot showed the inferred bacteria hosts producing corresponding CAZy enzymes and the sizes of dots indicated the confidence level (%) of microbial inferences. absence of a dot indicated that our inability to predict the bacterial origin or the CAZy family was not detected at a particular time.

Results

Increasing lateral gene transfer (LGT) events and transferrable resistance genes in infants' gut

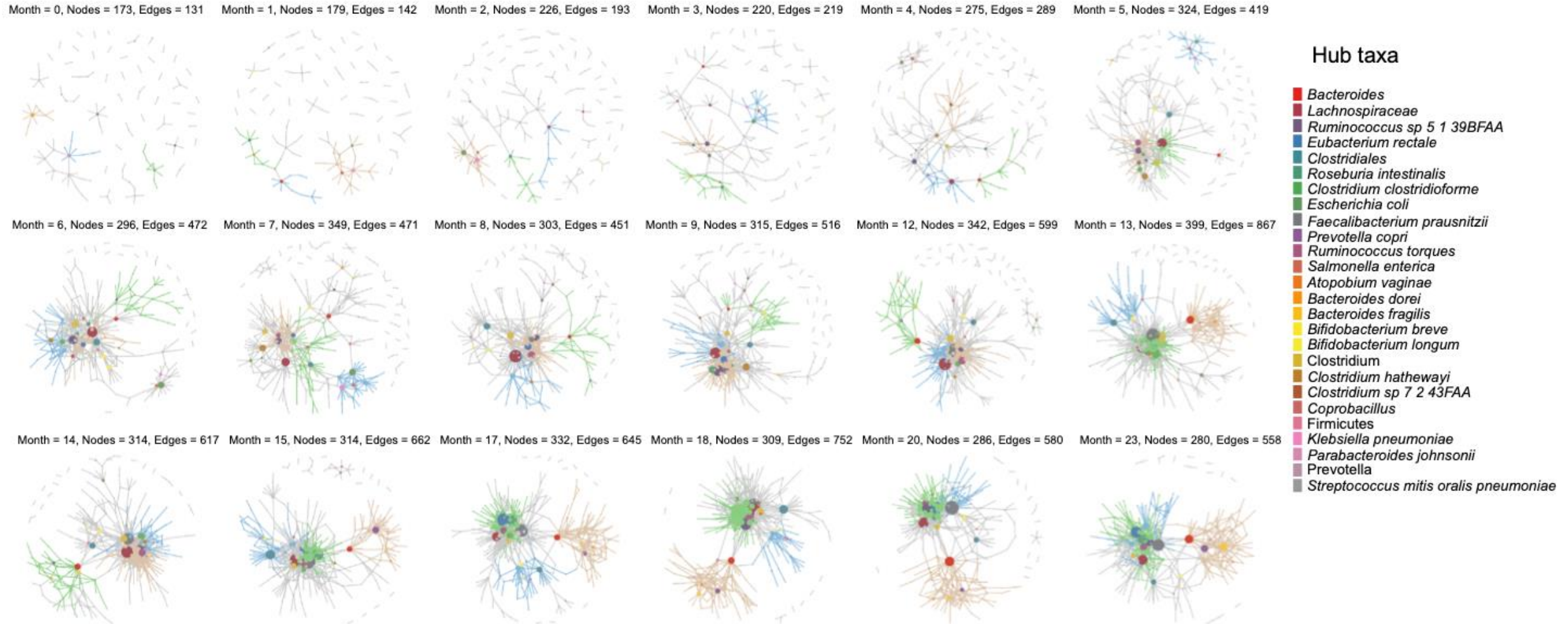


Figure. The development of infant gut mobilome. Networks illustrating predicted LGT events during early infancy.

Summary

- We first examined the natural assembly of resistome in healthy infants' guts and identified resistance genes that were significantly impacted by age.
- We inferred that the age-dependent assembly of infant resistome was a result of the shift of the gut microbiome, which was due to resistance genes being disproportionately distributed across taxa.
- Age-dependent assembly of infant resistome reflected the shift in the gut microbiome, and such modifications were often a result of dietary transitions during infancy.
- Maturation of gut resistome was driven by infants' changing carbohydrate metabolism, which demonstrated an increasing need for carbohydrate-active enzymes from *Bacteroidota* and decreasing involvements from *Pseudomonadota* during infancy.



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