



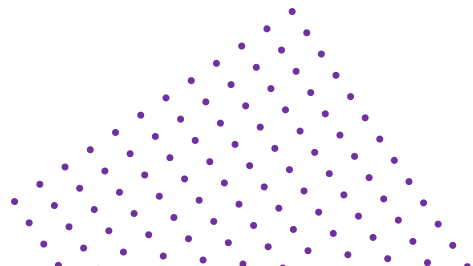
Gut Microbiota and AMR-- Unraveling the Connection Between Microbial Communities and ARGs

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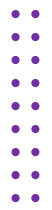


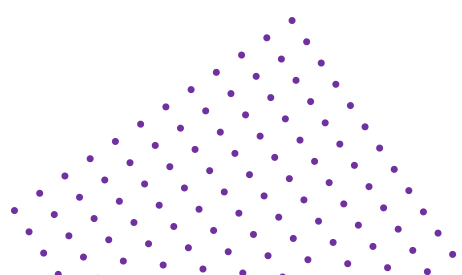
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Introduction to AMR and ARGs

History of antibiotics



In 1929, Sir Alexander Fleming's discovery of penicillin was published in *The New England Journal of Medicine* but initially ignored due to lack of support and his limited technical skills

In 1938, E.B. Chain and H.W. Florey revisited Fleming's work, recognizing its medical value and extracted penicillin

During World War II, the widespread use of antibiotics, especially penicillin, dramatically reduced bacterial infections among soldiers

In 1945, Fleming, Chain, and Florey were awarded the Nobel Prize for the successful development of penicillin

Antimicrobial Resistance (AMR)



Sir Alexander Fleming
(1881-1955)

*In his 1945 Nobel Prize lecture, Fleming himself warned of the **danger of resistance**--*

“It is not difficult to make microbes resistant to penicillin in the laboratory..... The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

AMR—One of The Top Global Public Health & Development Threats



Key facts:

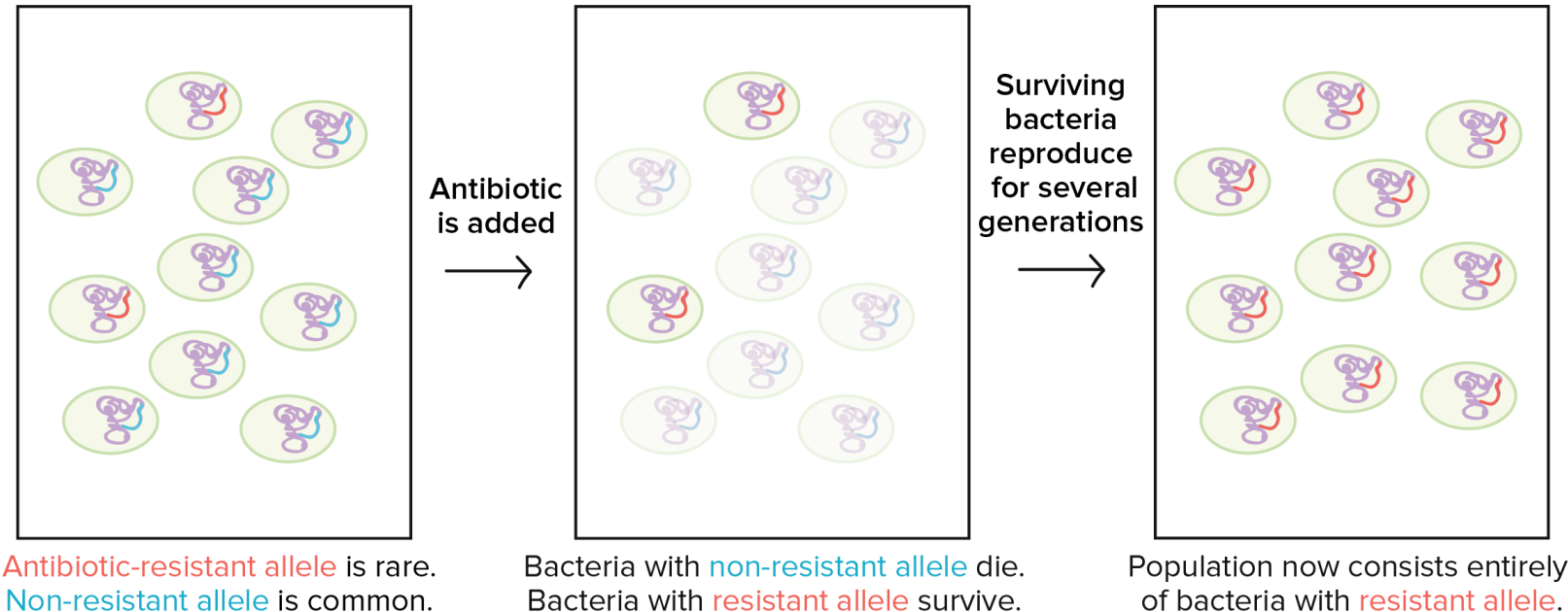
- It is estimated that bacterial AMR was directly responsible for **1.27 million** global deaths in 2019 and contributed to **4.95 million** deaths [1]
- The World Bank estimates that AMR could result in **US\$ 1 trillion** additional healthcare costs by 2050, and **US\$ 1 trillion to US\$ 3.4 trillion** GDP losses per year by 2030 [2].
- The misuse and overuse of antimicrobials in humans, animals and plants are the main drivers in the development of drug-resistant pathogens
- AMR puts many of the gains of modern medicine at risk
 - Makes infections harder to treat
 - Makes other medical procedures and treatments riskier

<https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>

[1] Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet; 399(10325): P629-655

[2] <https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future>

Antibiotic Resistance Genes--the key factor in Antimicrobial Resistance

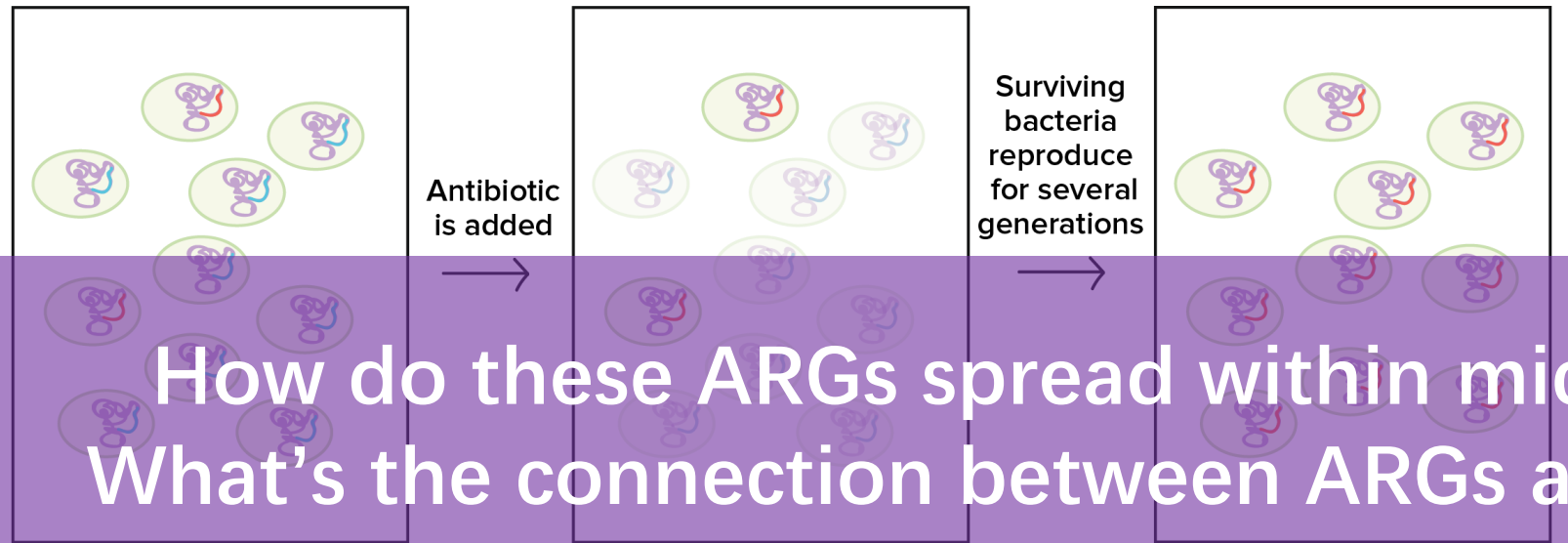


- The presence of antibiotics killed-off non-resistant bacteria while **selected** those resistant ones

- Over time, the resistant genes proliferate creating entire strains of **resistant super bacteria**



Antibiotic Resistance Genes--the key factor in Antimicrobial Resistance



- The presence of antibiotics killed-off non-resistant bacteria while **selected** those resistant ones

How do these ARGs spread within microbial communities?
What's the connection between ARGs and human microbiota?

Antibiotic-resistant allele is rare.
Non-resistant allele is common.

Bacteria with non-resistant allele die.
Bacteria with resistant allele survive.

Population now consists entirely
of bacteria with resistant allele.

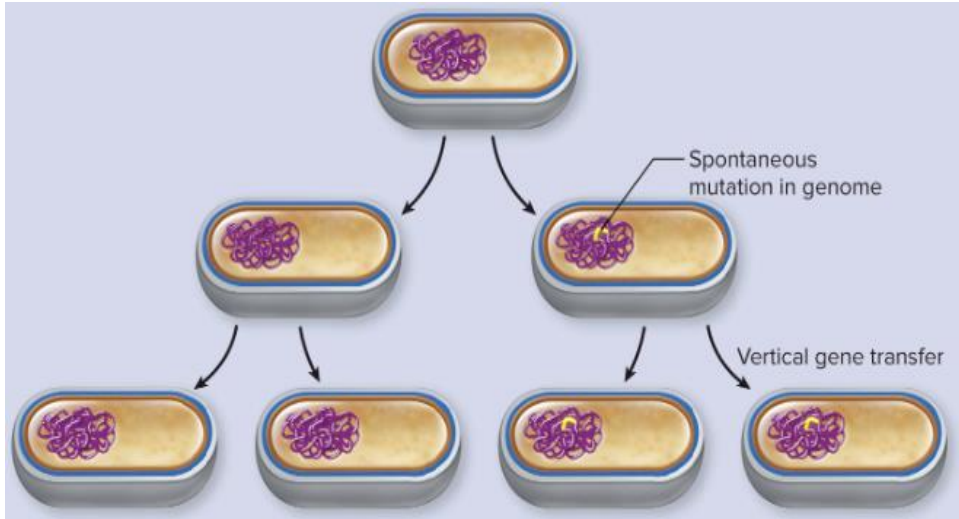
- Over time, the resistant genes proliferate creating entire strains of **resistant super bacteria**



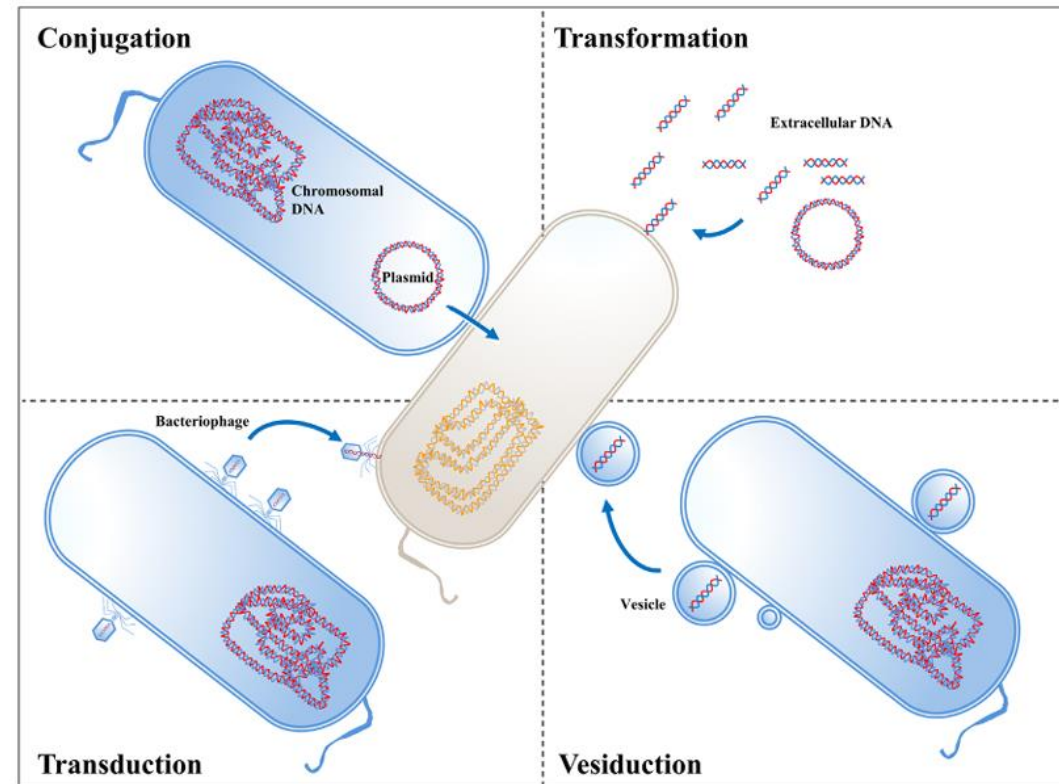
Gut microbiota as the reservoir of ARGs

Spread of ARGs between bacteria

Vertical Gene Transfer (VGT)



Horizontal Gene Transfer (HGT)



E. coli as the reservoir of ARGs

Cell Host & Microbe

CellPress

Article

The infant gut resistome associates with *E. coli*, environmental exposures, gut microbiome maturity, and asthma-associated bacterial composition

Xuanji Li,¹ Jakob Stokholm,² Asker Brejnrod,³ Gisle Alberg Vestergaard,⁴ Jakob Russel,¹ Urvish Trivedi,¹ Jonathan Thorsen,² Shashank Gupta,¹ Mathis Hjort Hjelmsø,² Shiraz A. Shah,² Morten Arendt Rasmussen,² Hans Bisgaard,² and Søren Johannes Sørensen^{1,5,*}

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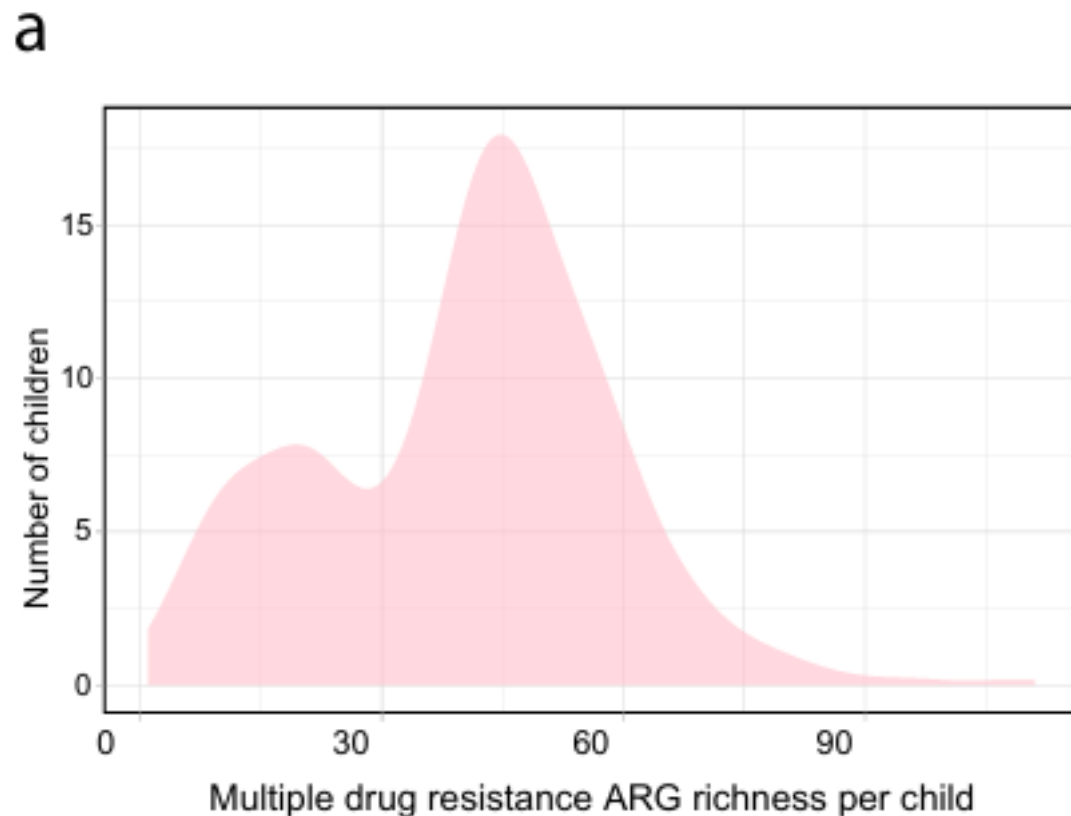
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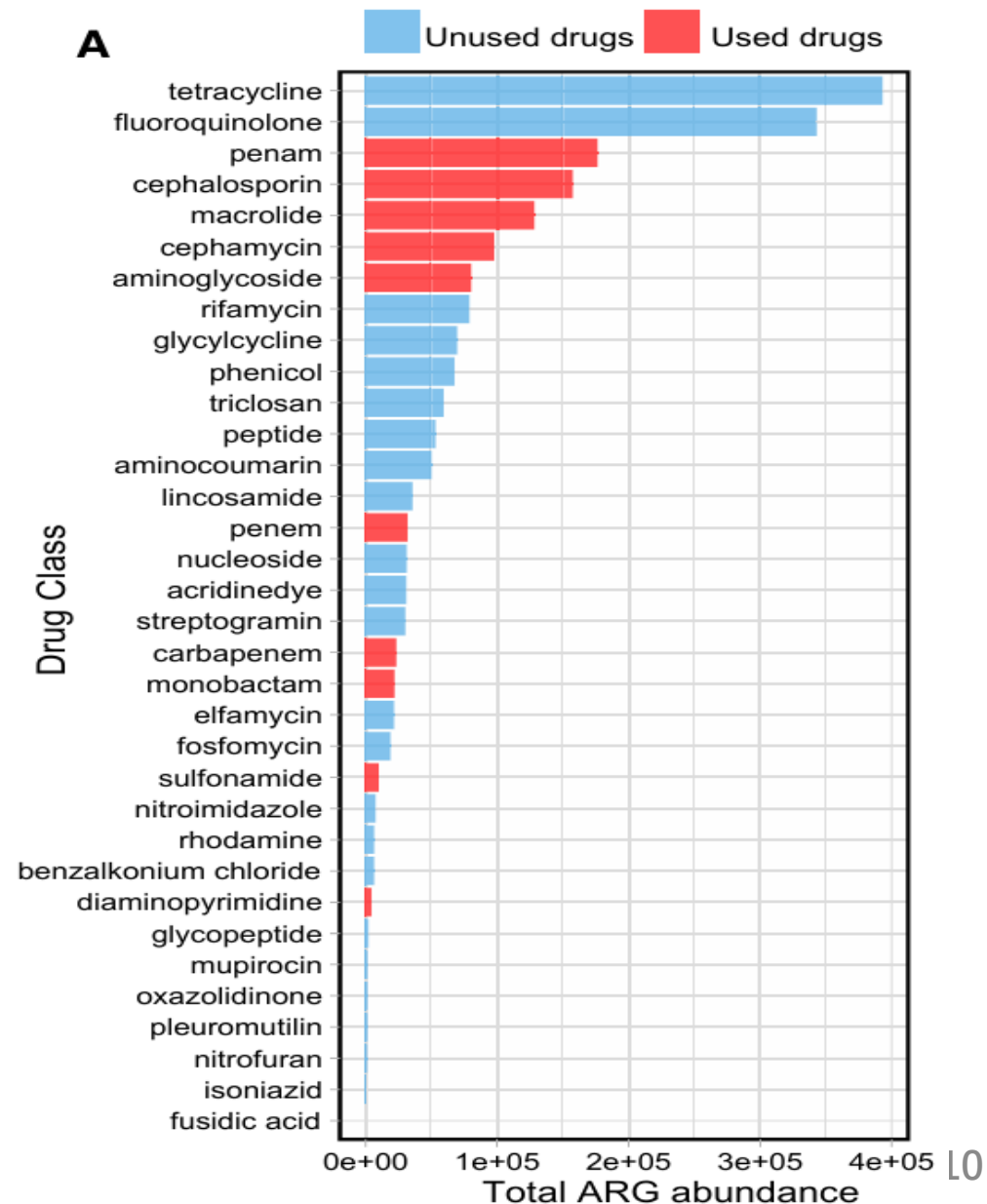
<https://doi.org/10.1016/j.chom.2021.03.017>

Study Objective: stool samples from 662 healthy children at 1 year of age

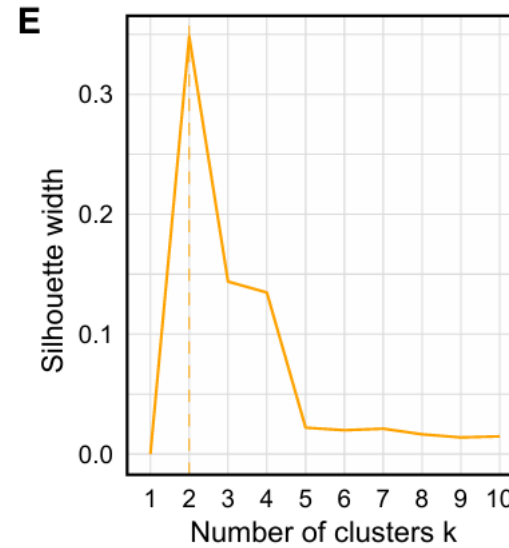
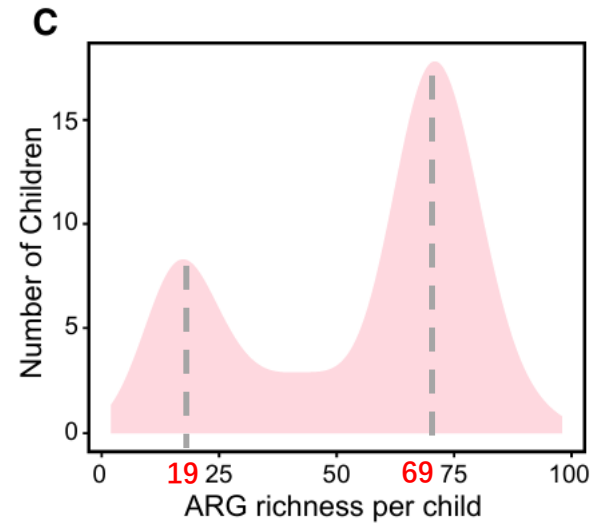
ARGs are prevalent in the gut of children



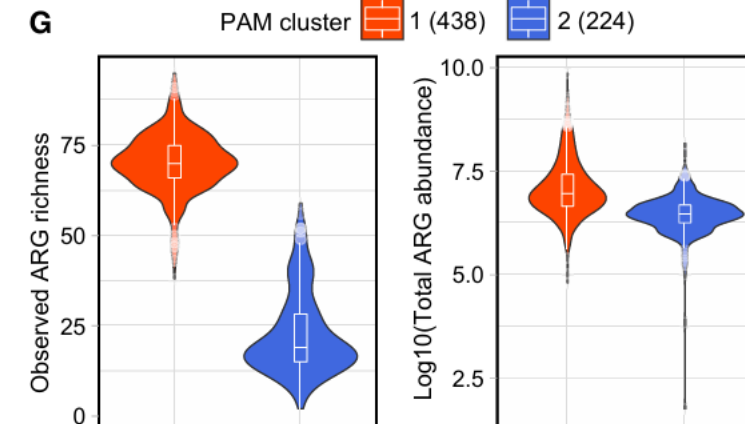
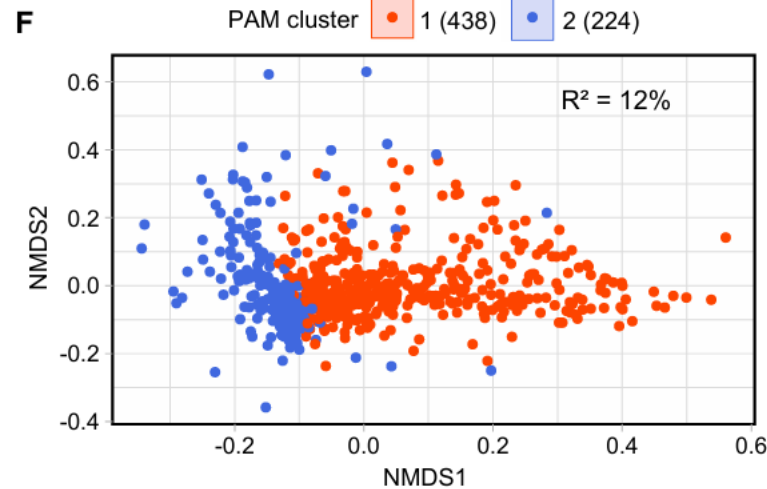
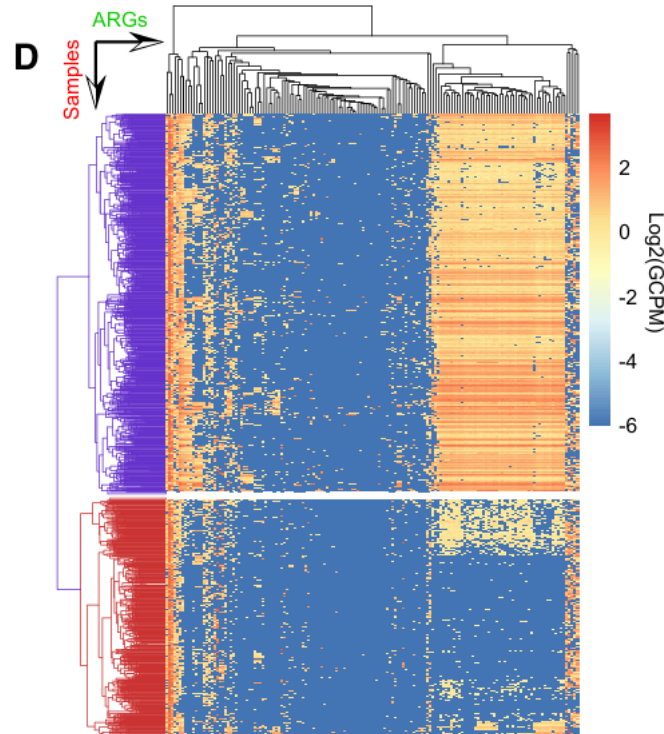
All children had at least one type of multiple drug resistance ARG in their gut



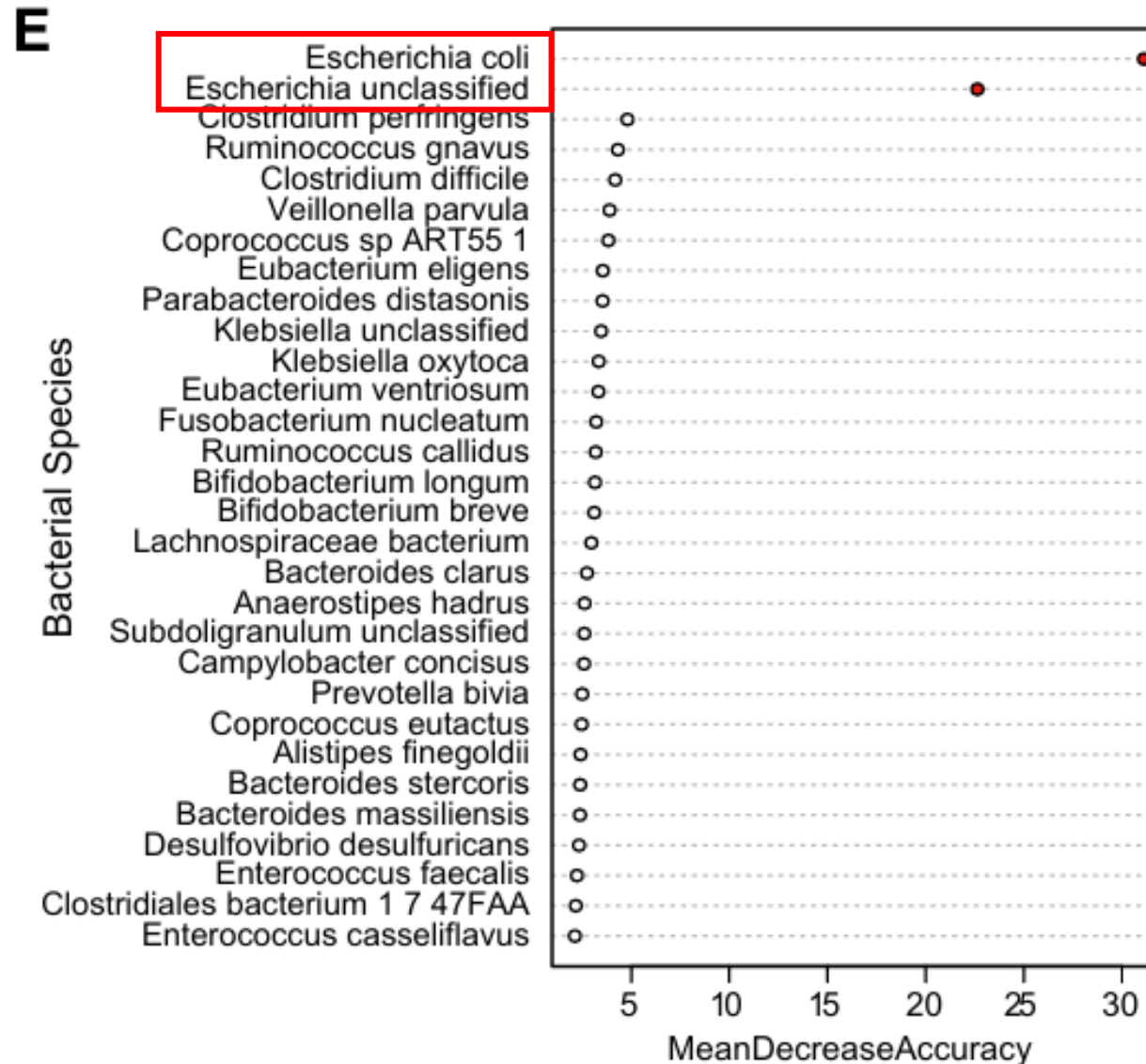
The distribution of ARGs are bimodal



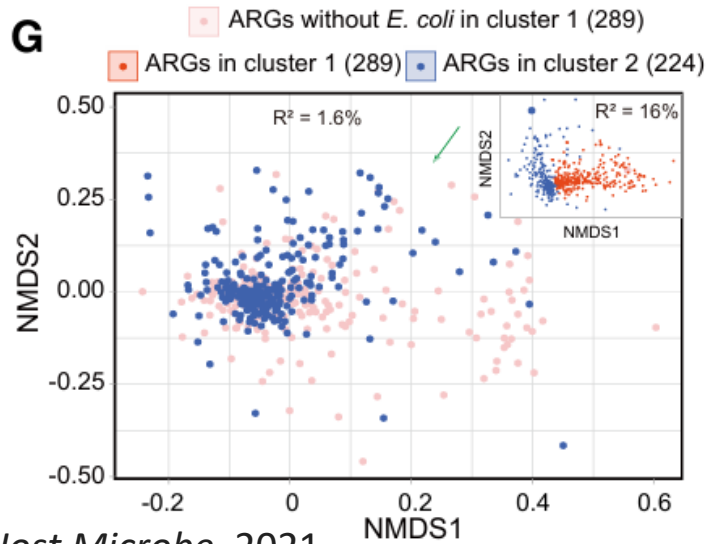
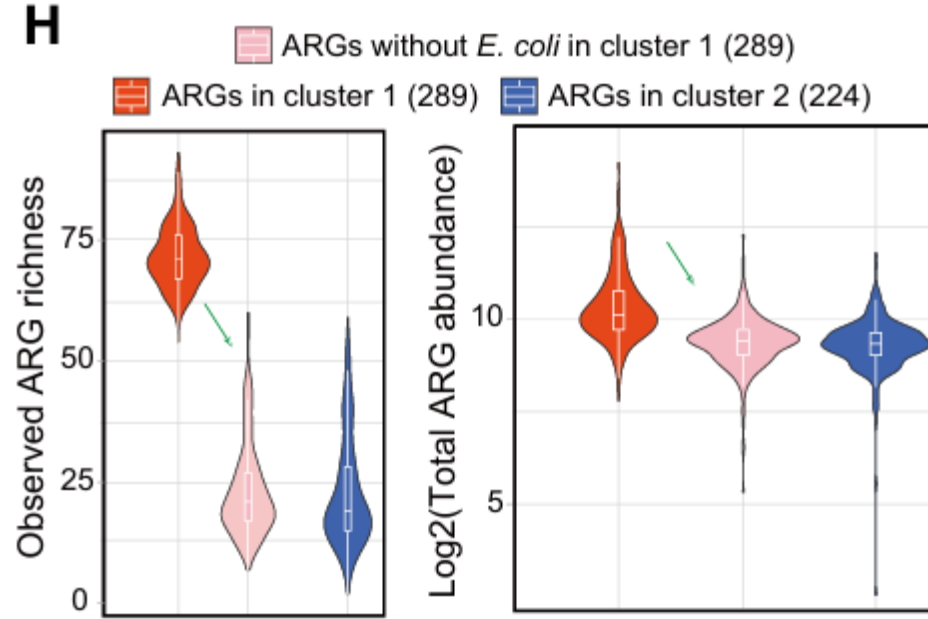
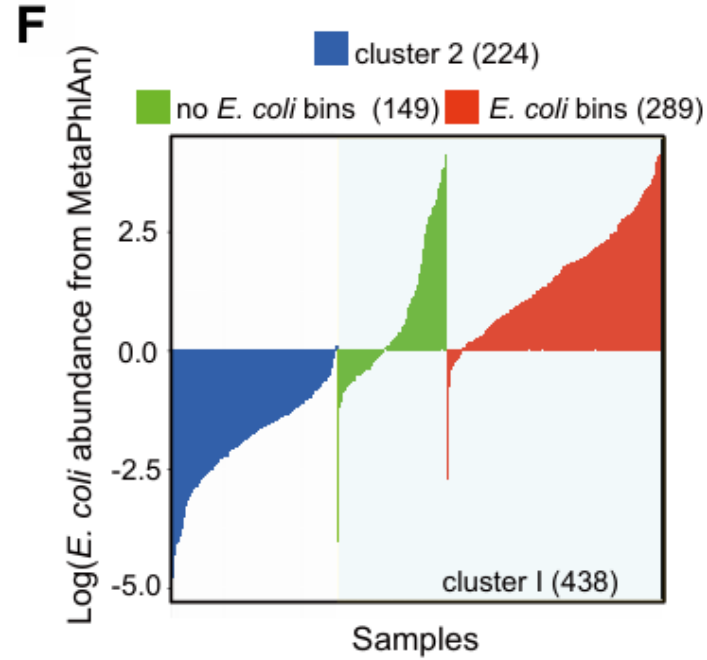
Silhouette Score: A higher score indicates better clustering quality in data analysis.



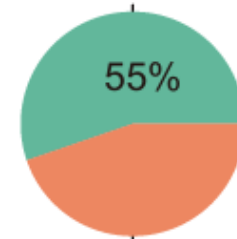
E.coli plays a dominant role in shaping the division between the two clusters



E. coli plays a dominant role in shaping the division between the two clusters

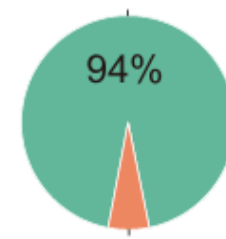


I ARGs in *E. coli* in cluster 1 (289)



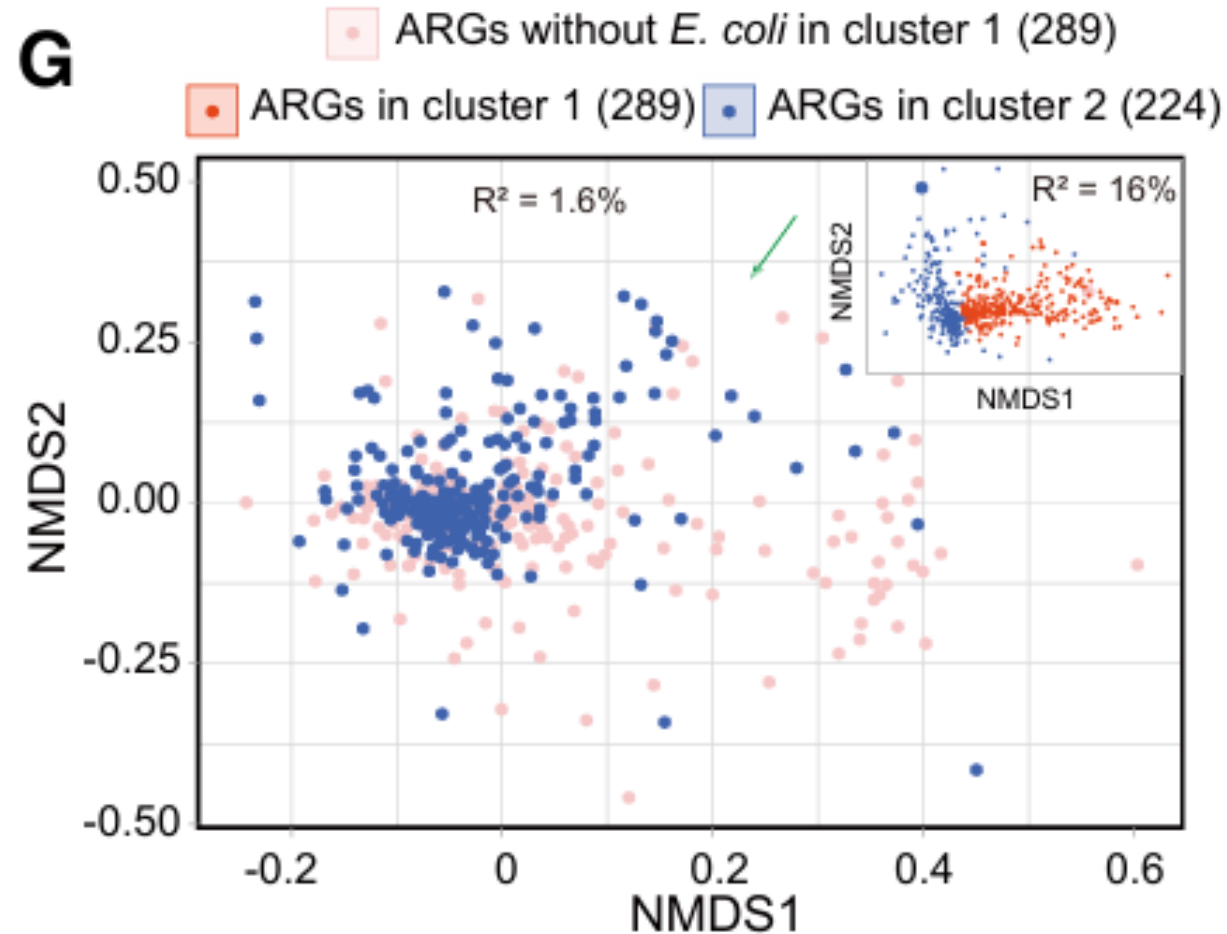
ARGs without *E. coli* in cluster 1 (289)

J 58 differentially abundant ARGs in *E. coli* (289)

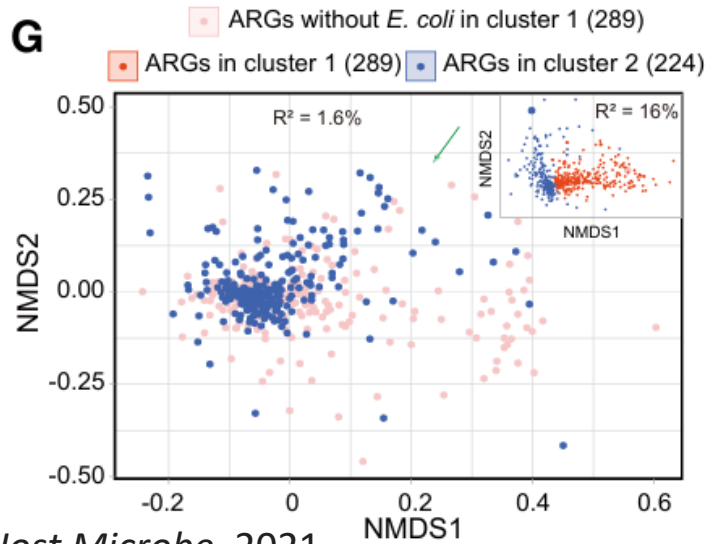
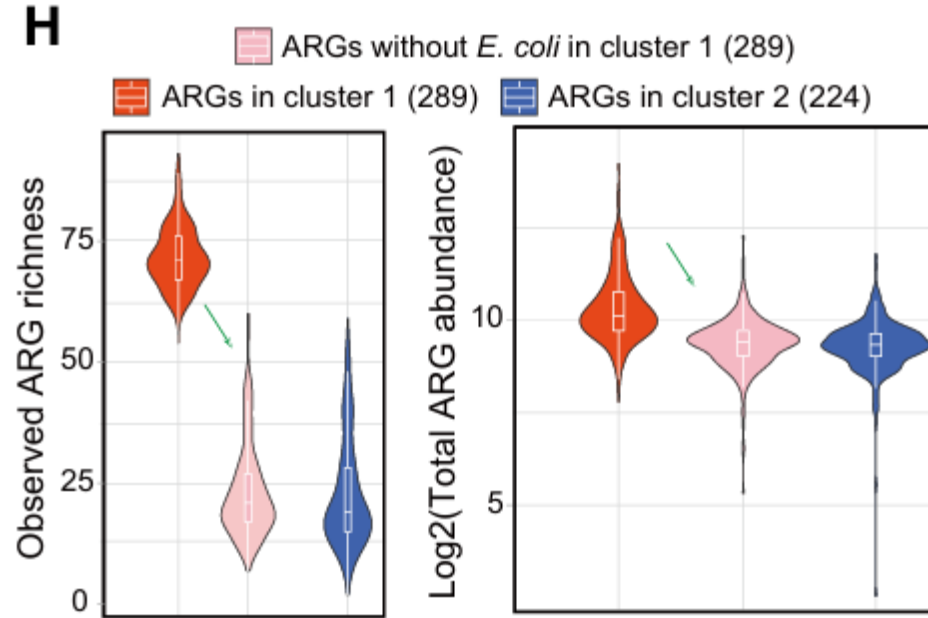
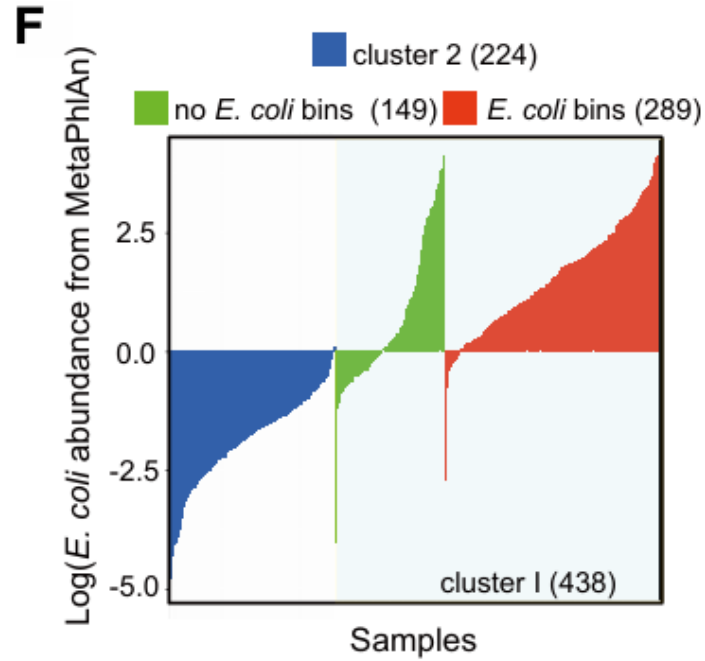


58 differentially abundant ARGs in other bacteria (289)

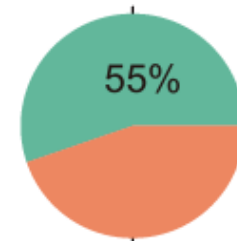
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E. coli plays a dominant role in shaping the division between the two clusters

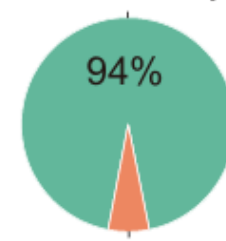


I ARGs in *E. coli* in cluster 1 (289)



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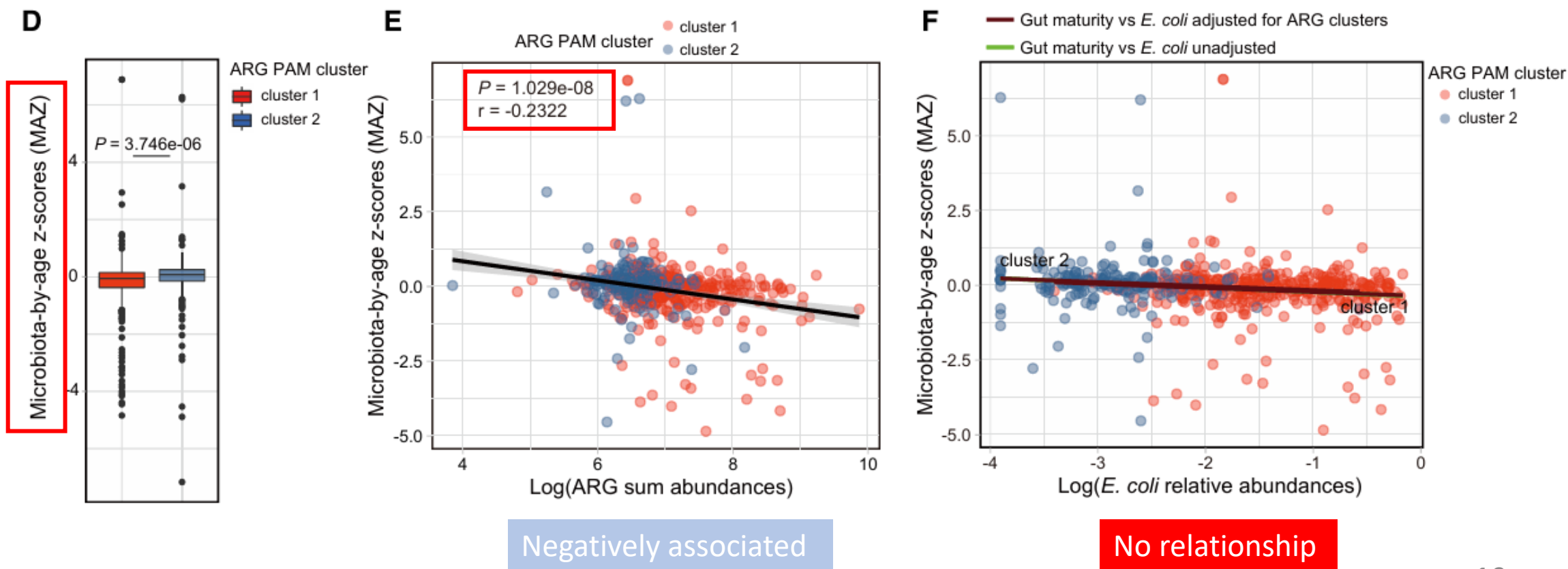


58 differentially abundant ARGs in other bacteria (289)

Impact of ARGs on gut microbiome maturity

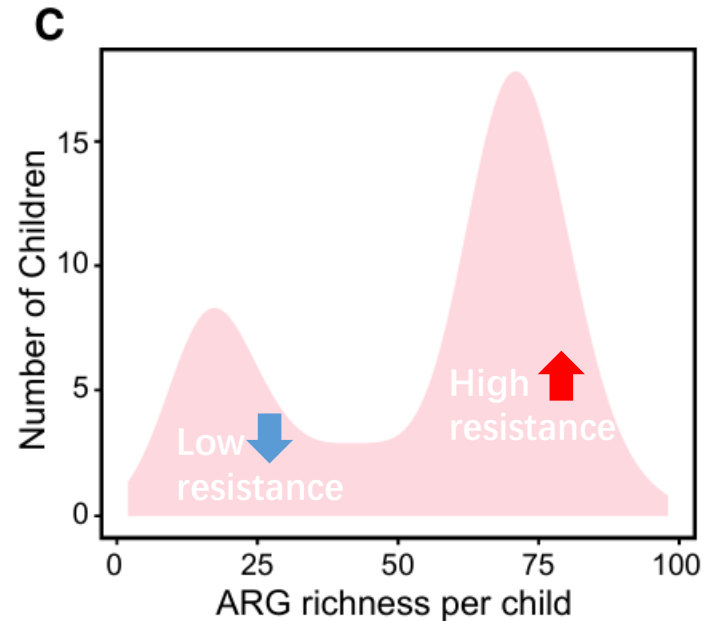
***E. coli* was the sole factor underlying the association between gut microbiome immaturity and the two ARG clusters**

MAZ score: machine-learning based model



Summary

- Distribution of infant gut resistome is bimodal, mainly driven by *E. coli*
- *E. coli* is an extremely important reservoir of ARGs.
- Low maturity of microbiome is associated with high *E. coli* abundance / high ARG load



Low *E. coli* abundance
High gut microbiome maturity

High *E. coli* abundance
Low gut microbiome maturity

<https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture>

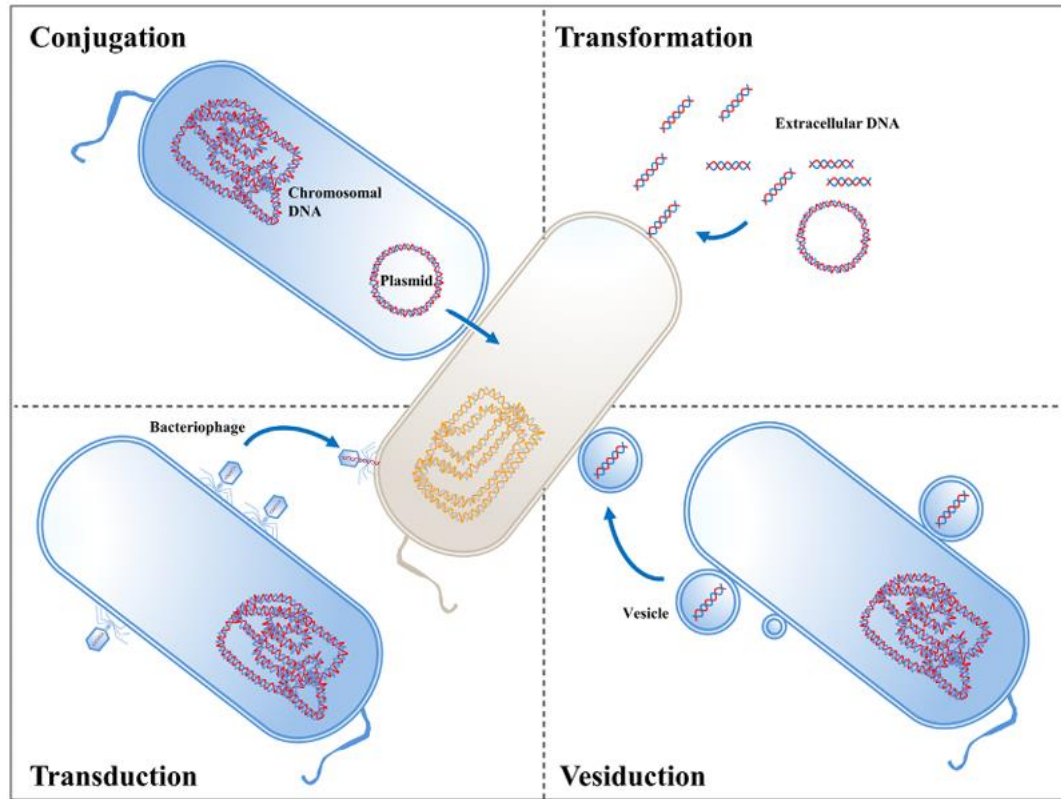
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Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. Erratum in: *Lancet*. 2022 Oct 1;400(10358):1102. doi: 10.1016/S0140-6736(21)02653-2. PMID: 35065702; PMCID: PMC8841637.

<https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future>

Jiang Q, Feng M, Ye C, Yu X. Effects and relevant mechanisms of non-antibiotic factors on the horizontal transfer of antibiotic resistance genes in water environments: A review. *Sci Total Environ*. 2022 Feb 1;806(Pt 3):150568. doi: 10.1016/j.scitotenv.2021.150568. Epub 2021 Sep 24. PMID: 34627113.

Li X, Stokholm J, Brejnrod A, Vestergaard GA, Russel J, Trivedi U, Thorsen J, Gupta S, Hjelmsø MH, Shah SA, Rasmussen MA, Bisgaard H, Sørensen SJ. The infant gut resistome associates with *E. coli*, environmental exposures, gut microbiome maturity, and asthma-associated bacterial composition. *Cell Host Microbe*. 2021 Jun 9;29(6):975-987.e4. doi: 10.1016/j.chom.2021.03.017. Epub 2021 Apr 21. PMID: 33887206.



Conjugation: the process of transferring ARGs from a donor cell to a recipient cell through direct cell-to-cell contact via mobile genetic elements (MGEs), such as plasmids, integrons, and transposons

Transformation: the uptake of extracellular plasmid or chromosomal DNA by a “competent” recipient cell, and its stable integration into the bacterial genome and functional expression of antibiotic resistance

Transduction: occurs when bacteriophages infect a donor cell, whose ARG-containing DNA is packaged into the capsid of bacteriophages; subsequently, the genome of bacteriophages released from the lytic donor cell is transferred to a recipient cell along with the infection by bacteriophages

Vesiduction: described as that membrane vesicles secreted from the surface of a donor cell transport ARG-containing DNA into the cytoplasm of a recipient cell by fusing with its cytomembrane

Other factors influencing load of ARGs?

