
FOURTEENTH INTERNATIONAL
ROTAVIRUS SYMPOSIUM
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The role of tryptophan metabolites and AhR signaling in rotavirus infection

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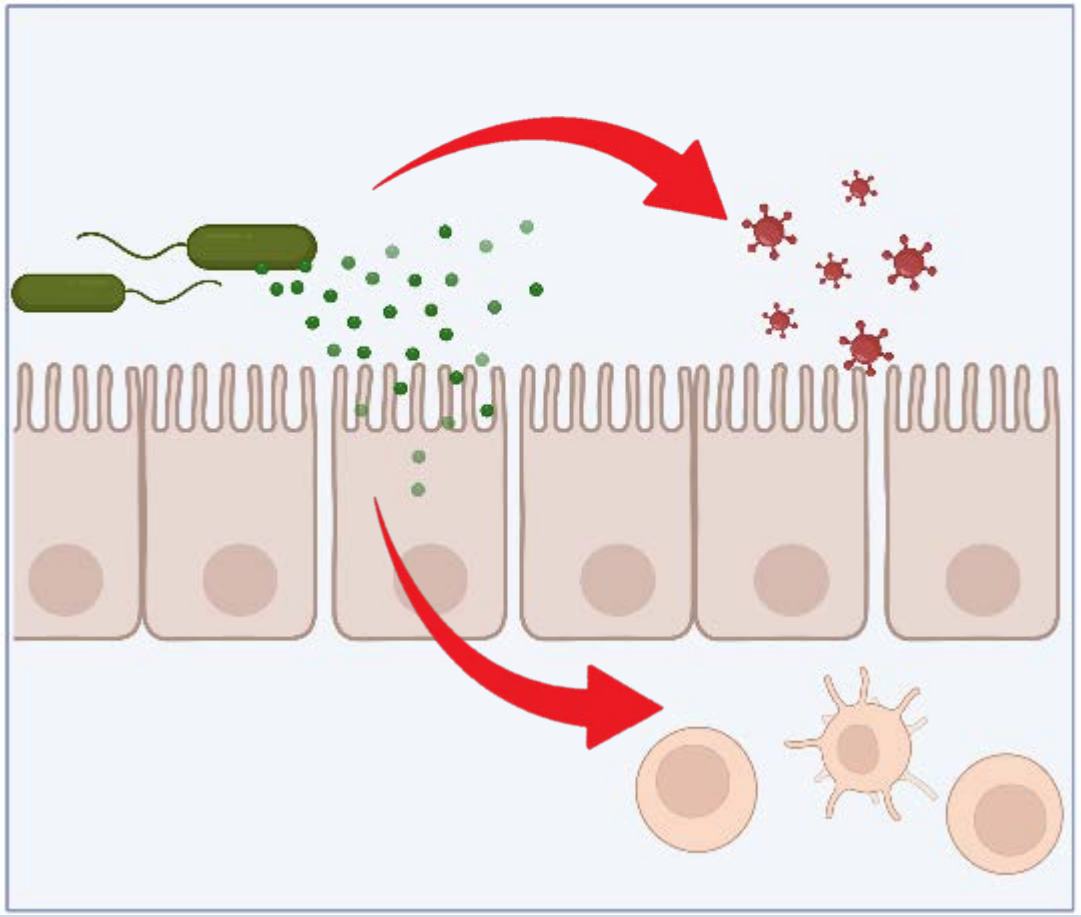
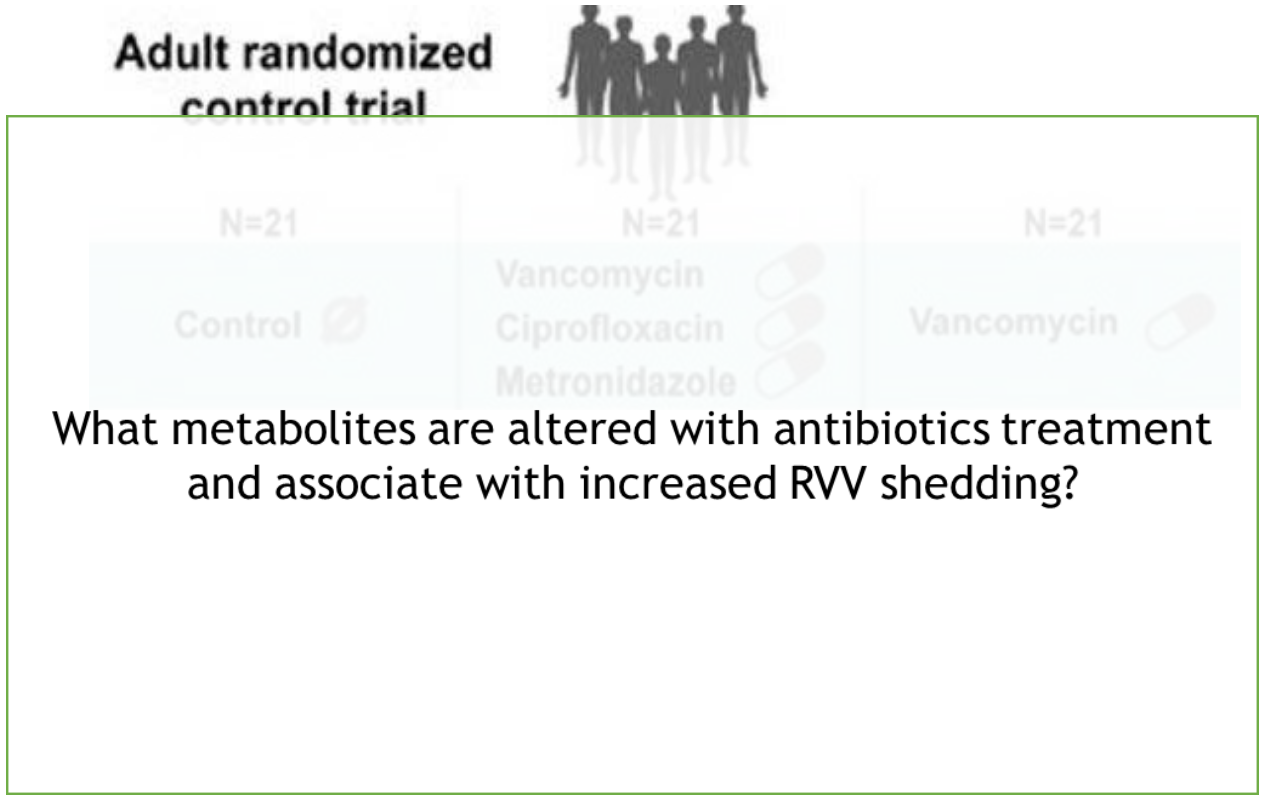
Bali, Indonesia

Microbial metabolites are critical mediators of interkingdom interaction during enteric virus infections



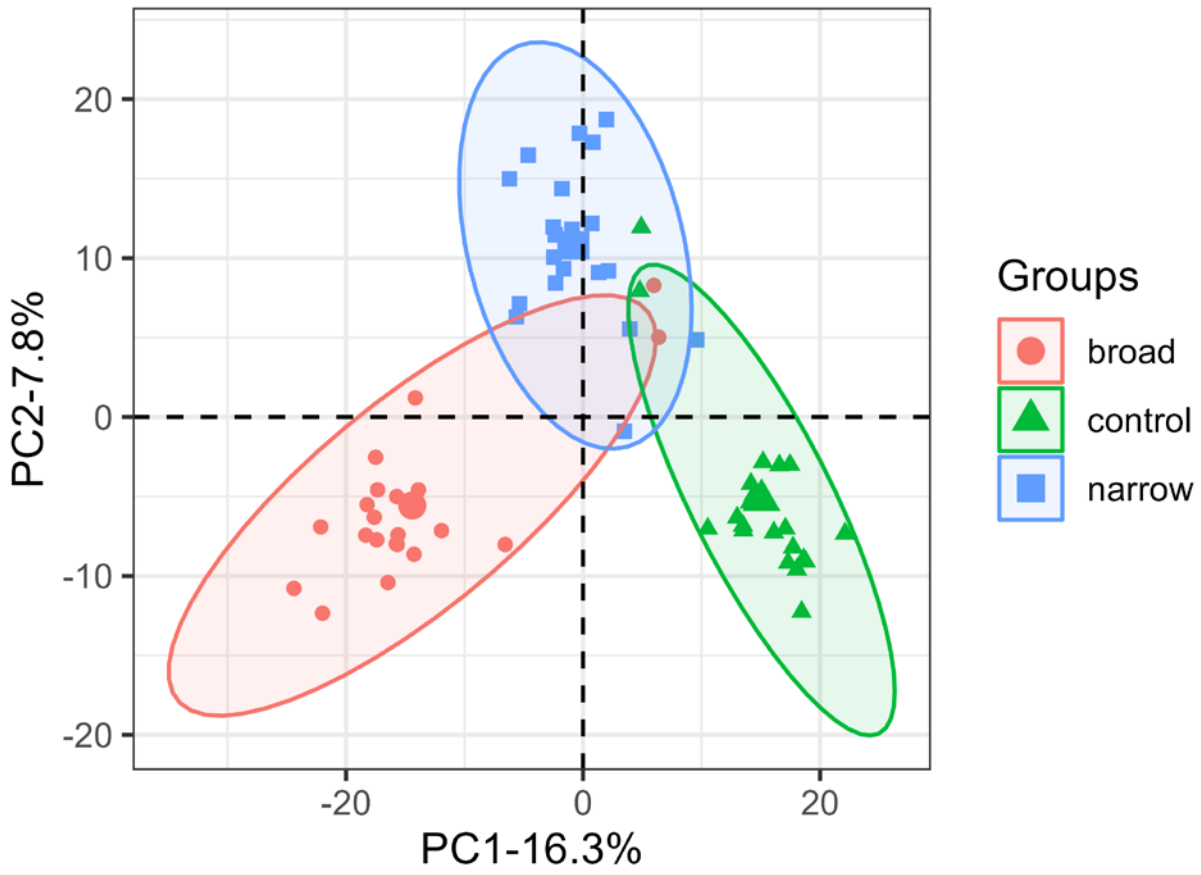
Background study: Antibiotic modulation of gut microbiota alters response to rotavirus vaccination



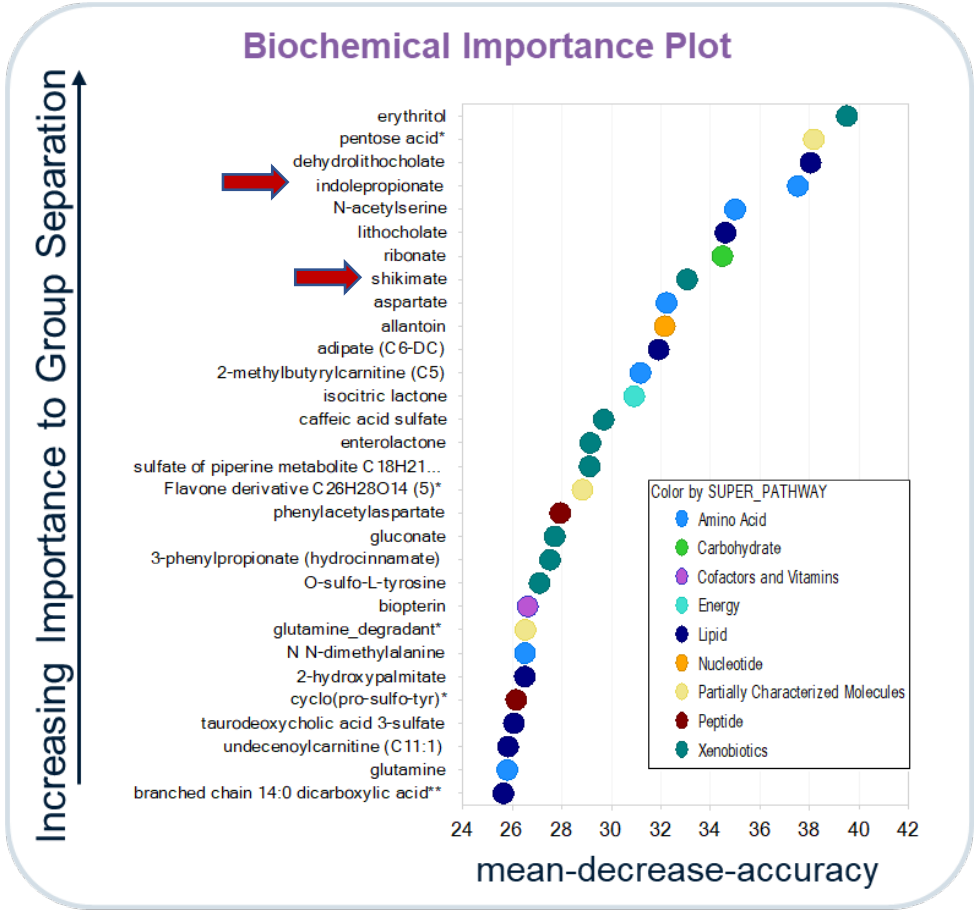
Harris, et al. *Cell Host & Microbe* (2018); Kim, et al. *Cell host & microbe* (2021).

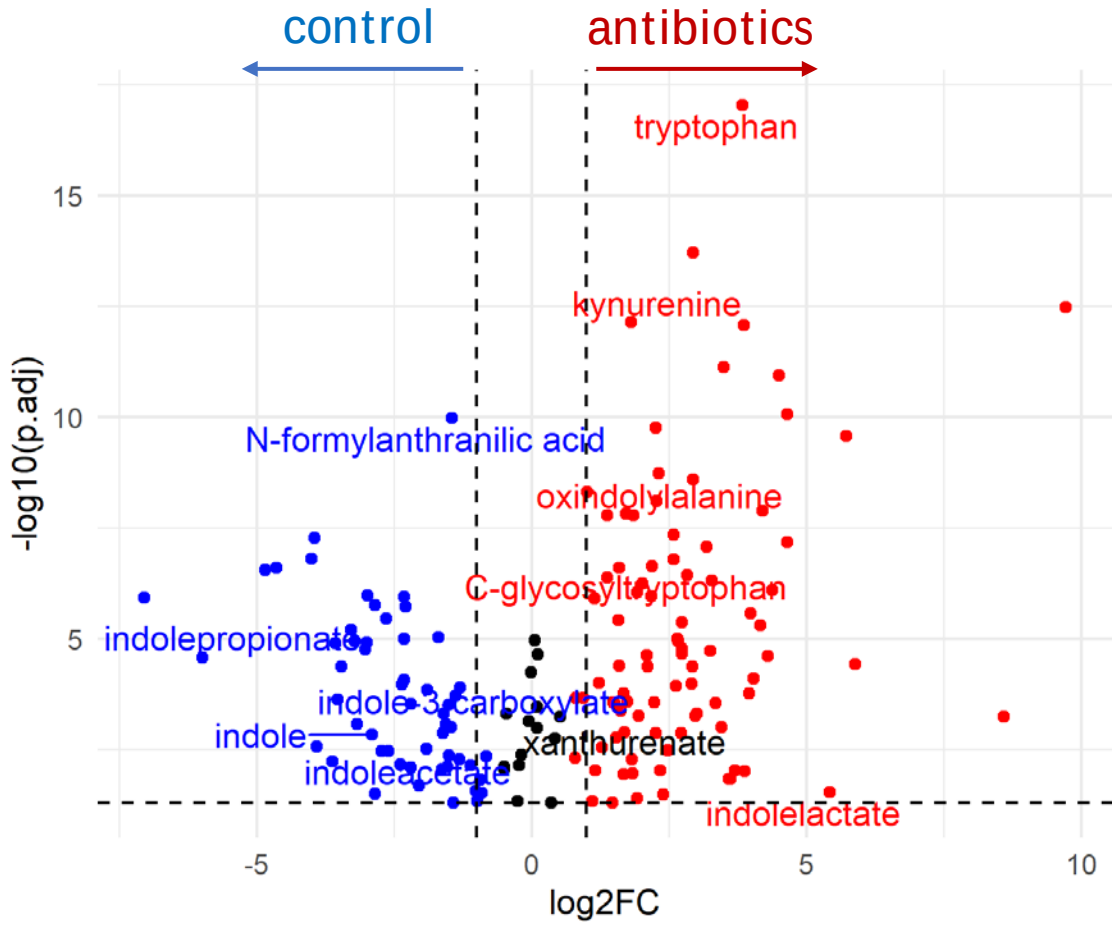
Pipeline of metabolomics analysis

Antibiotics treatment significantly altered metabolite composition

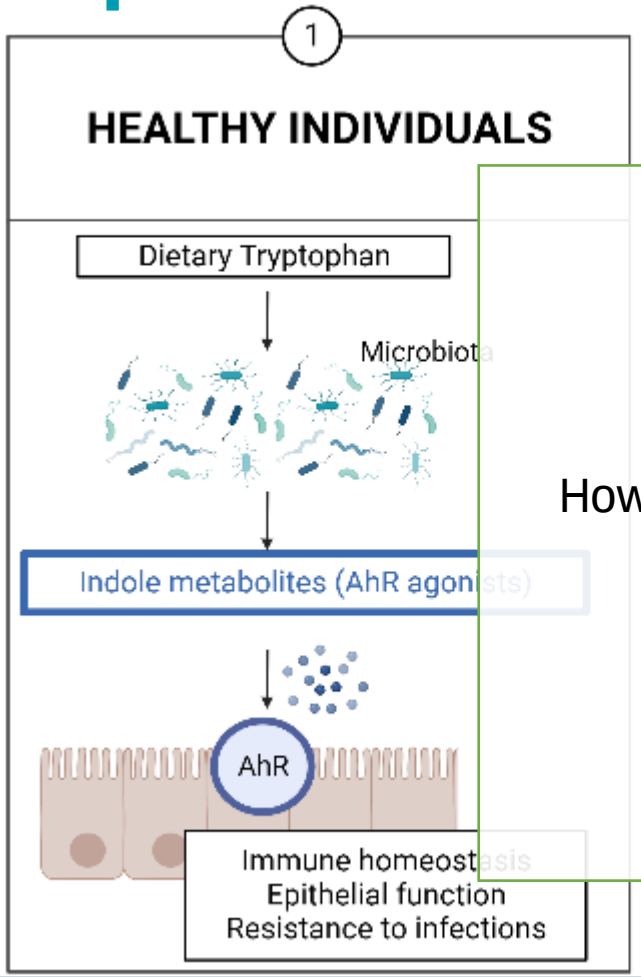


Differentially abundant metabolites





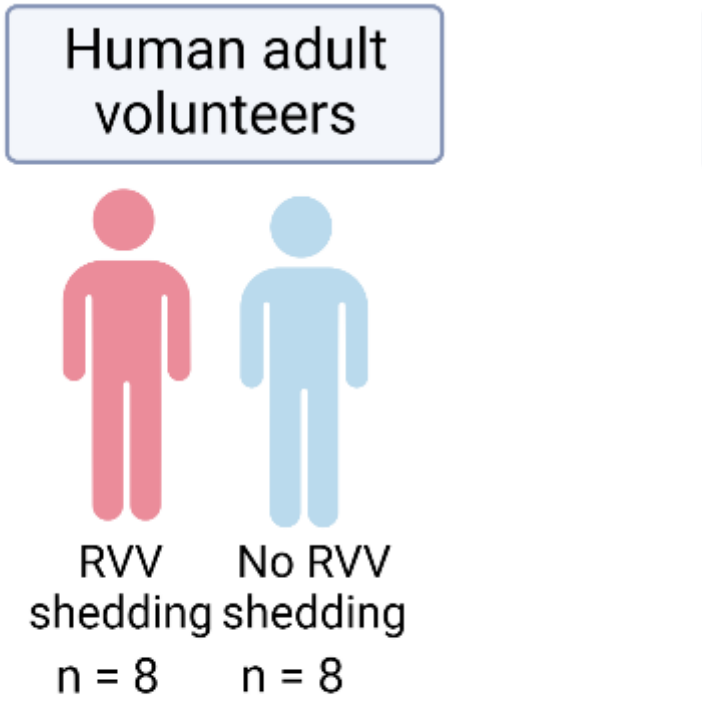
Tryptophan metabolism & AhR signaling in health and disease



How is the tryptophan metabolism and AhR activation altered during a Rotavirus infection?

Roager and Licht. Nature communications (2018); Agus, et al. Cell host & microbe (2018)

Methods

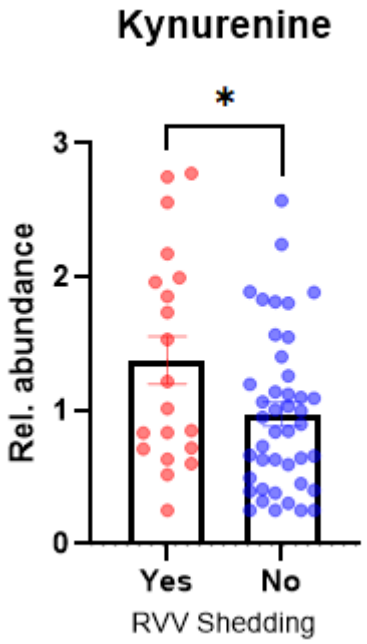


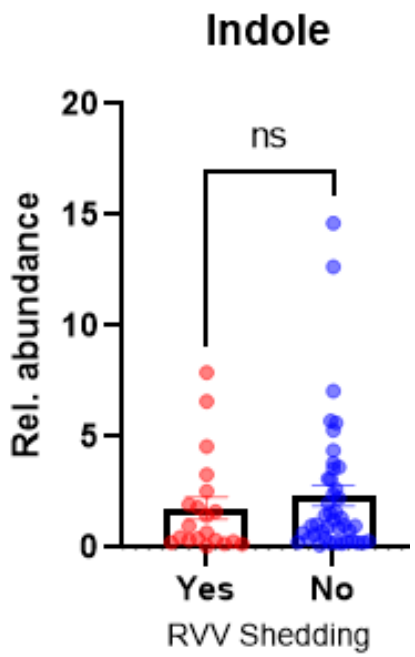
- Abundance of Trp metabolites
- Functional AHR activation

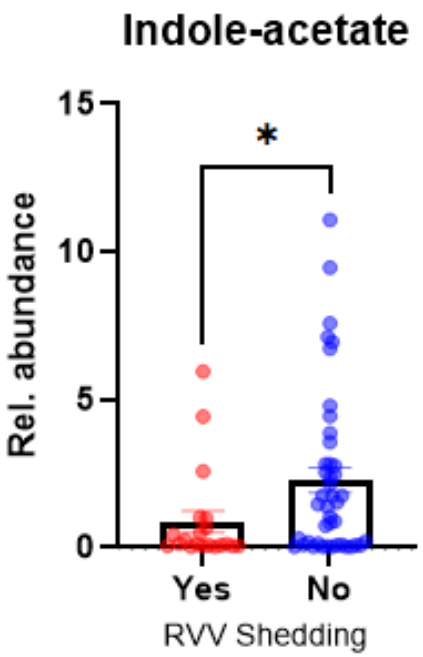
Adult volunteers: Kynurenine and indole metabolites abundance

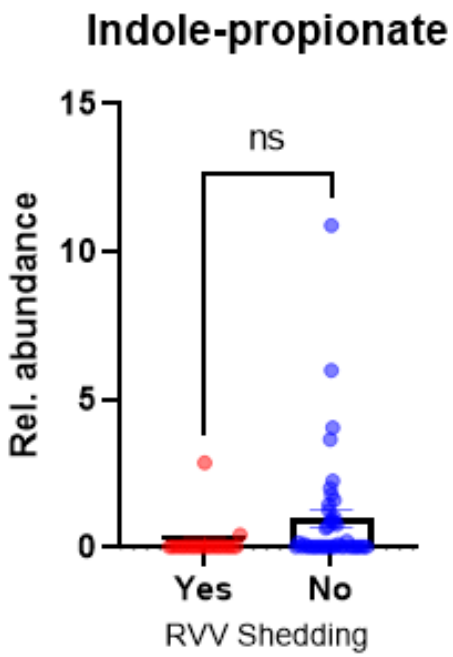
Kynurenine pathway

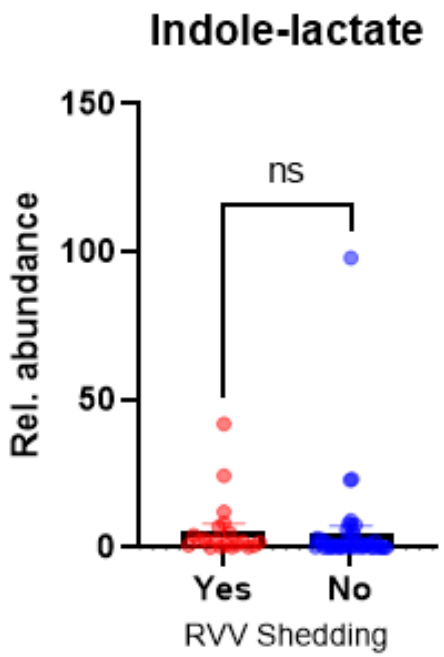
Indole pathway



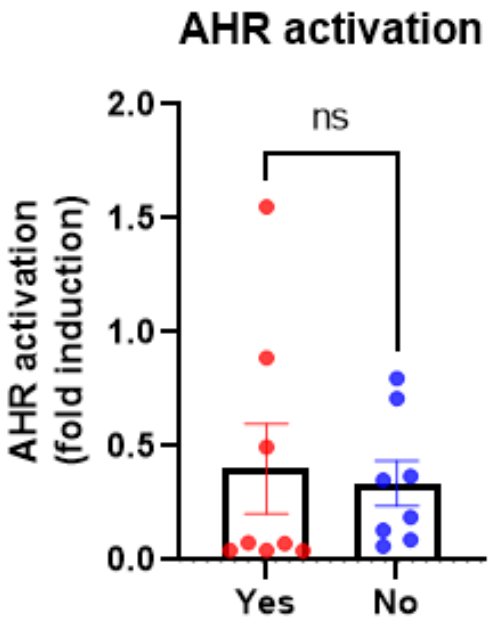




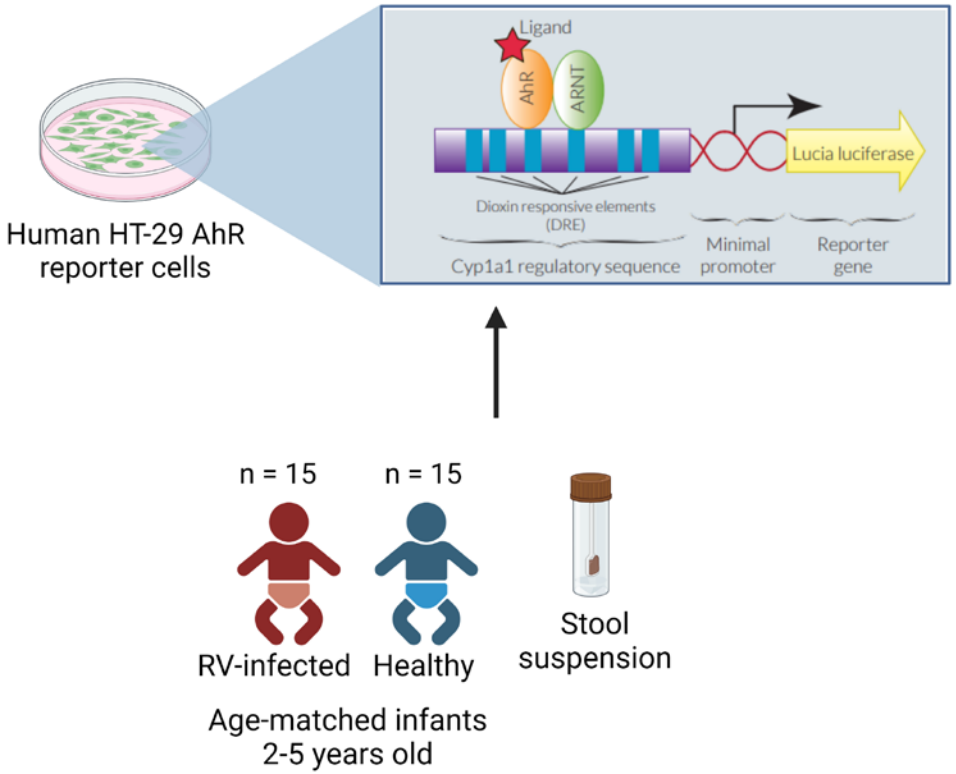


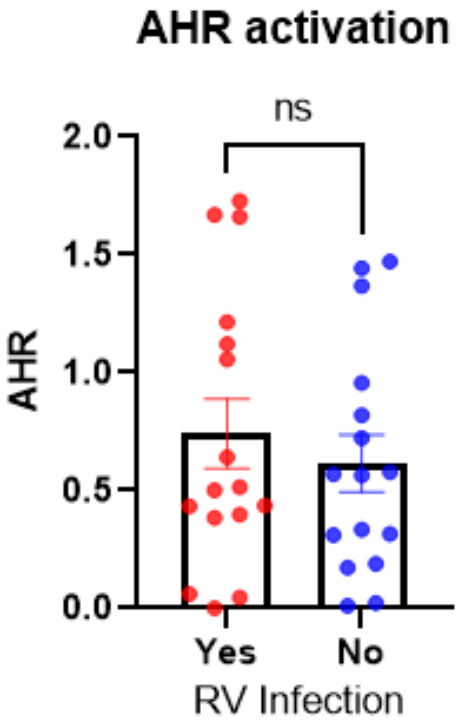


Adult volunteers: Functional AHR activation

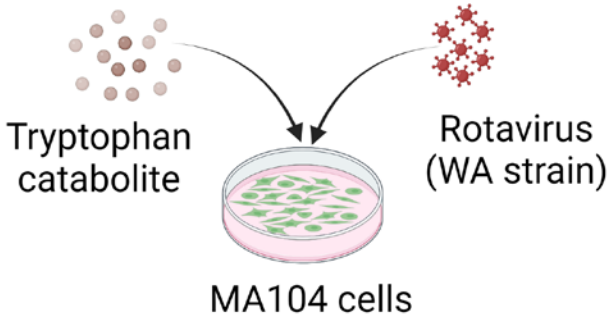


Infant cohorts: Functional AHR activation

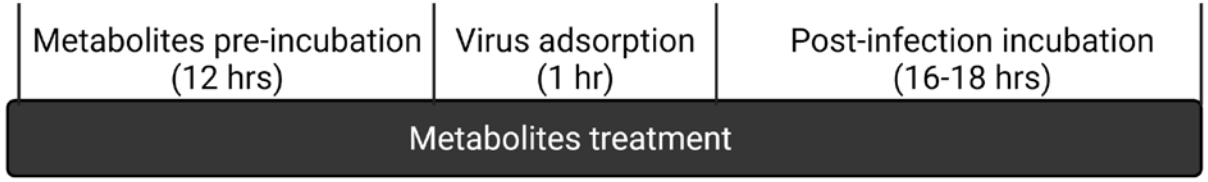


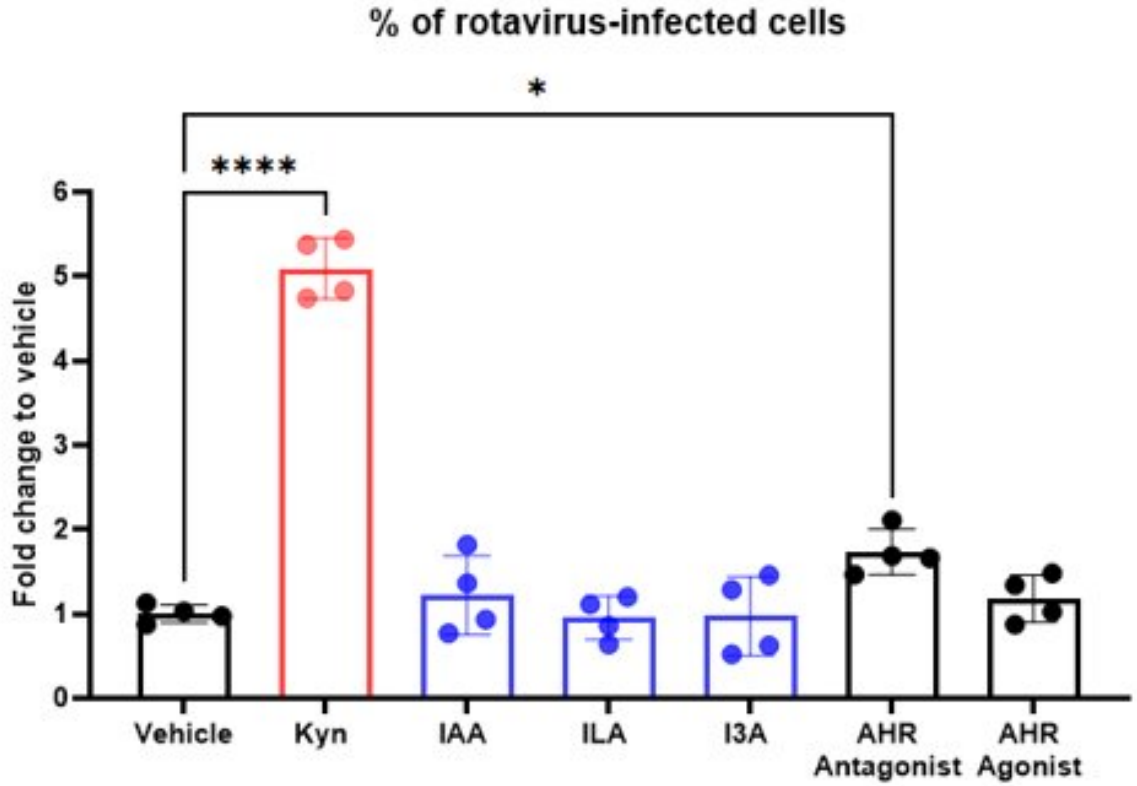


Proof of principle: *In vitro* infectivity assay



- Kynurenine
- Microbiota-derived indole:
  - Indole-acetic acid (IAA)
  - Indole lactic acid (ILA)
  - Indole-3-aldehyde (I3A)
- AHR agonist (FICZ)
- AHR antagonist (CH223191)

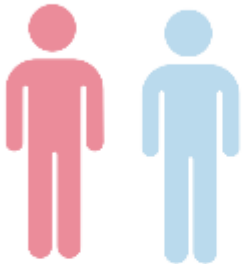




From 2 independent experiments

Summary

Human adult volunteers



RVV shedding | No RVV shedding

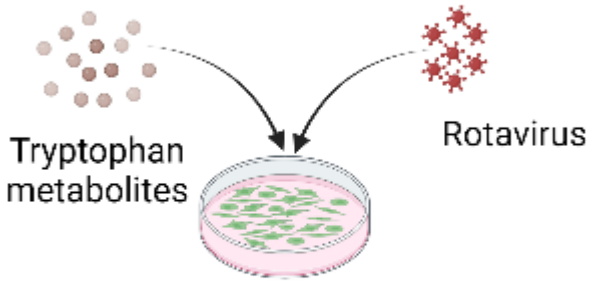
- ↑ Kynurenine, ↓ microbial-derived indoles
- No significant difference in functional AHR activation

Age-matched infants 2-5 years old

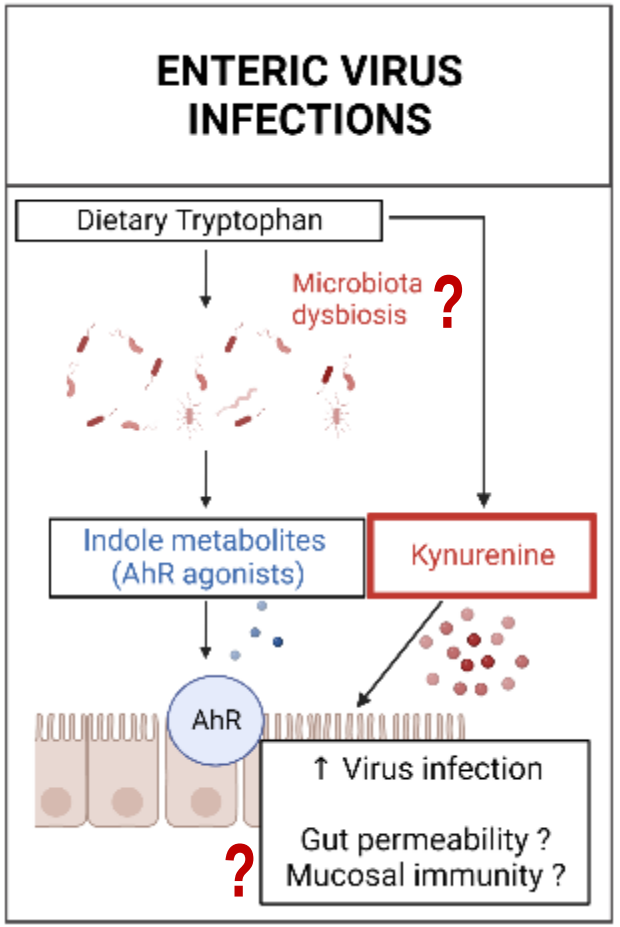
RV-infected | Healthy

- No significant difference in functional AHR activation

In vitro infectivity assay



- ↑ RV infection with kynurenine pre-treatment



Take home message

Disruptions in gut microbiota composition can lead to alterations in metabolite composition that have the potential to alter enteric virus infection

Microbiota-associated metabolites can be leveraged for novel treatment strategies to enhance live-attenuated RV vaccine infectivity and as anti-virals.

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