

# Single Dose Azithromycin to Prevent Cholera in Children

Study Team Leads

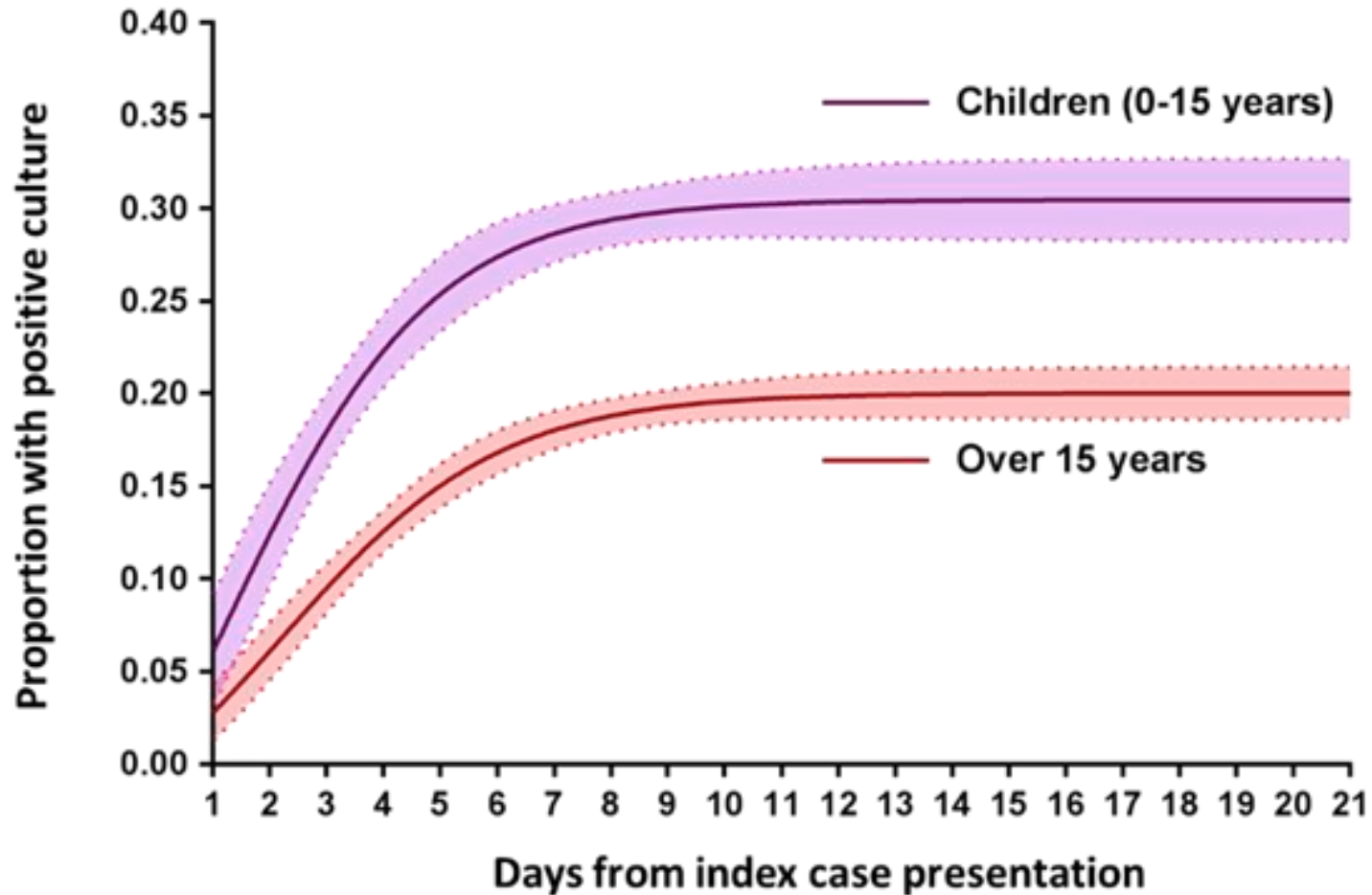
icddr,b: Dr. Fahima Chowdhury

MGH: Dr. Jason Harris

UW: Dr. Ana Weil

**Figure 1: Risk of *V. cholerae* infection in contacts\***

\*Nelson-Aalen Cumulative Hazard Estimates



# Can azithromycin prevent cholera in children?

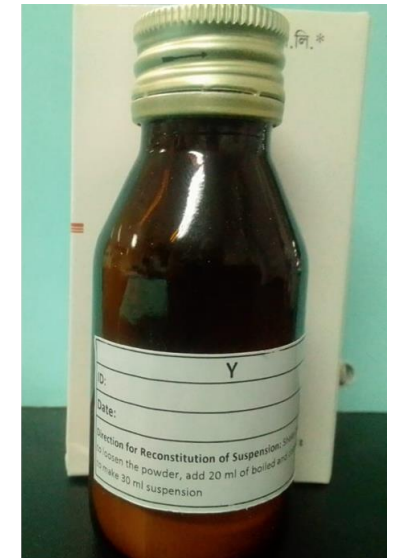
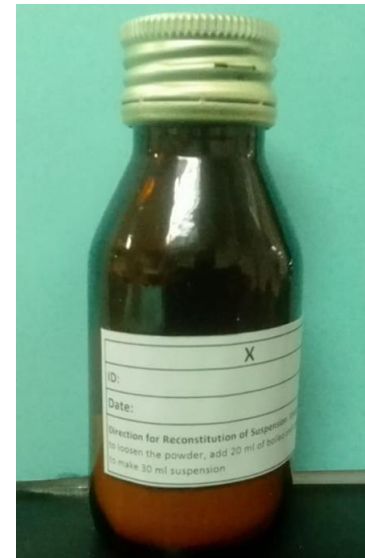
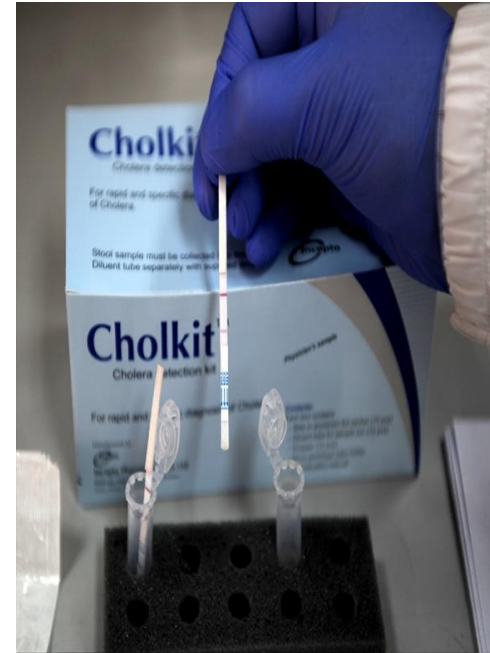
- Antibiotics are used in some settings for close contacts of patients with cholera with unclear benefit
- 1966 RCT followed 655 household contacts of patients with cholera in Bangladesh and found that a five-day course of tetracycline reduced infections from 12.6% to 0.3% over a 10-day period. However, tetracycline has an elimination half-life ( $T_{1/2}$ ) of less than six hours, and single-dose tetracycline only reduced infection to 8%
- Data on household chemoprophylaxis is also limited in epidemics. One study demonstrated 8% to 4.5% reduction in hospitalizations among household contacts (Khan MU. J Trop Med Hyg. 1982 Feb;85(1):27-9)
- Tetracycline also can induce plasmid mediated resistance.
- No similar trials have been done with azithromycin  $T_{1/2} = 55-72$

# Aims

- Aim 1. Determine whether single-dose azithromycin reduces the risk of *V. cholerae* infection.
- Aim 2. Determine whether single-dose azithromycin reduces the duration and quantity of *V. cholerae* shedding.
- Aim 3. Determine how single-dose azithromycin impacts the use of other antibiotics.
- Aim 4. Determine the effect of single-dose azithromycin on the acquisition and persistence of antibiotic resistance.

# Approach

- Double-blind cluster randomized trial comparing azithromycin and placebo
- All children 1-15 in 400 households with rapid test + index case
- Within 12 hours of index + to get baseline swab receive either placebo or azithro.
- 7 days of daily followup with daily rectal swabs
- Late follow up at 1 and 6 months to see if persistent resistance





# CAZ study map showing the geographical location of the enrolled cholera index cases and their HH contacts

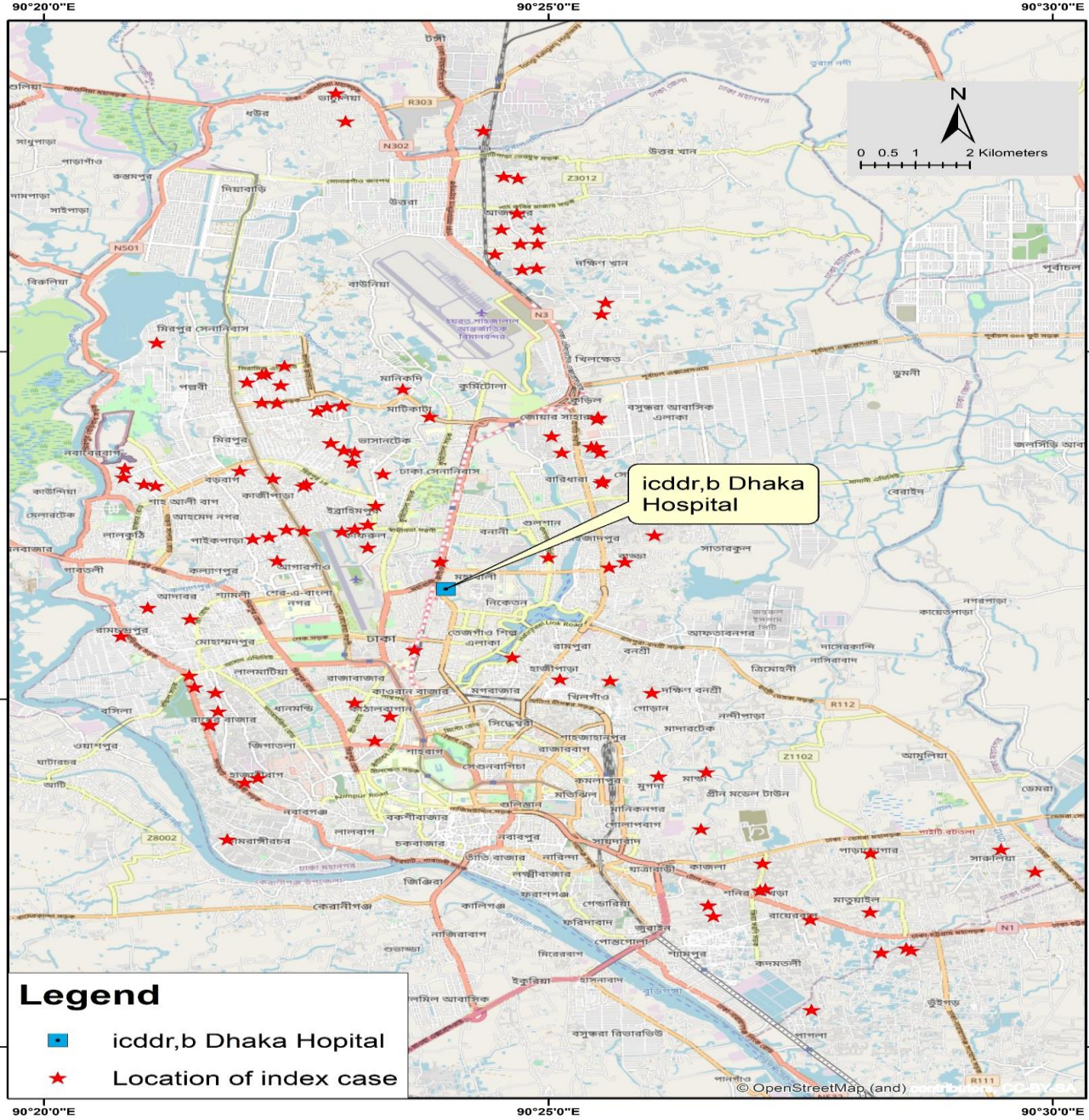
**Initiation of the study:** 31st October 2021

**Enrollment status:** Till 17th June 2023

**Total Screened:** 486

**Index cholera cases:** 122

**HH contacts:** 202 (20 culture positive so far)





# Antibiotic equity and avoiding a post-antibiotic era

- Prioritize the use of diagnostic testing
- Prioritize the prevention and treatment of serious illness in children and the most vulnerable
- Understand the impact of antibiotic use on AMR





## Samples Collected

## Outcomes



Rectal swab 1 (culture)

*V. cholerae* O1 culture, Days 1-7 (**Aim 1**)



Rectal swab 2 (molecular)

qPCR for *V. cholerae*, Days 1-7 (**Aim 2**)  
AMR-metagenomics, All time points (**Aim 4**)



Stool

All rectal swab outcomes, and:  
Antibiotic metabolite testing (LC/MS), Day 4 (**Aim 3**)  
Enhanced AMR-metagenomics, Day 4, 1- and 6-months (**Aim 4**)\*

\*Baseline enhanced AMR from rectal swab only. If insufficient biomass select ARM genes of interest will be chosen based on findings.

# Enrolment

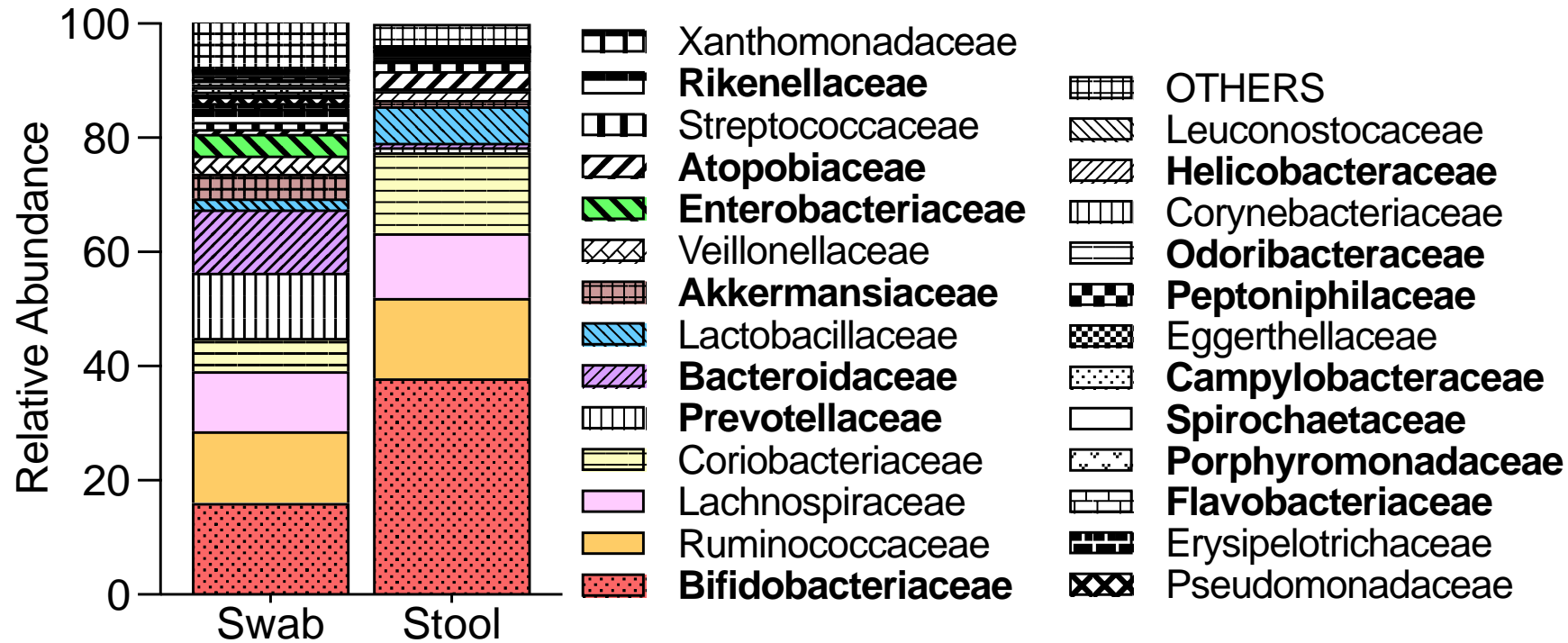
- Inclusion criteria

- Shared cooking facilities for the prior three days with an RDT positive index case
- Age 1 to 15 years
- A parent or guardian available to provide informed consent
- Intention to remain enrolled in the study for 6 months

- Exclusion criteria

- Participation in any other drug, device, or vaccine trial at present or within the past 30 days
- Known or suspected hypersensitivity to azithromycin or other macrolide antibiotics

# Family-level Abundance

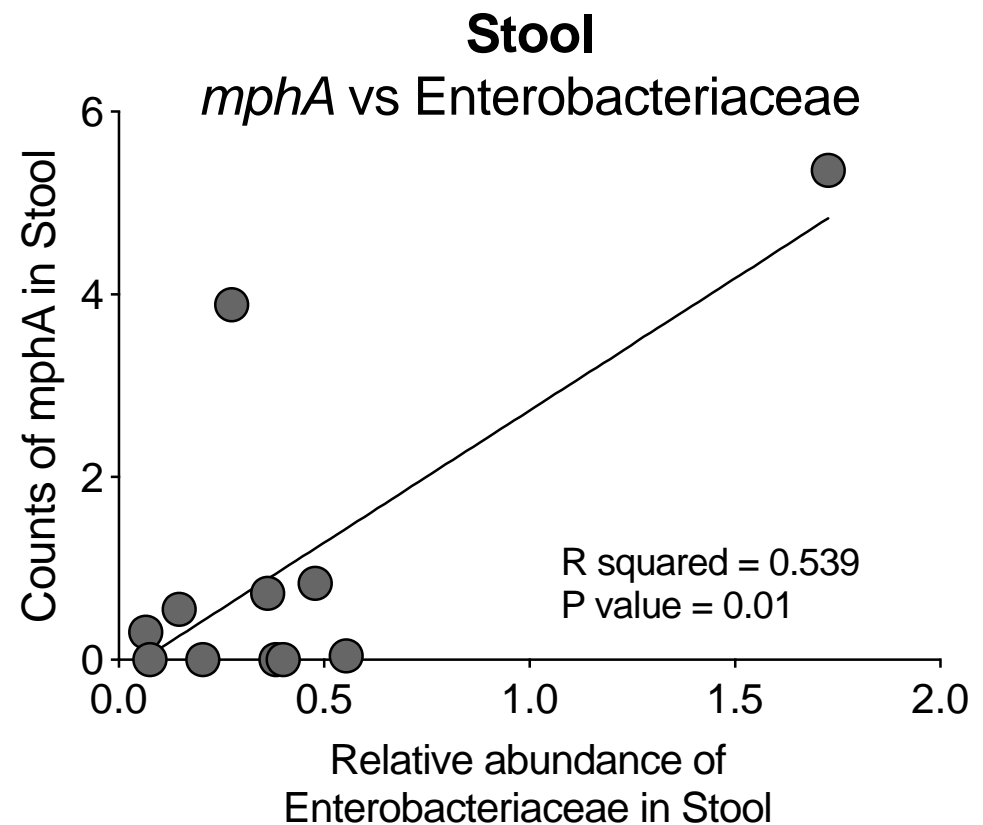
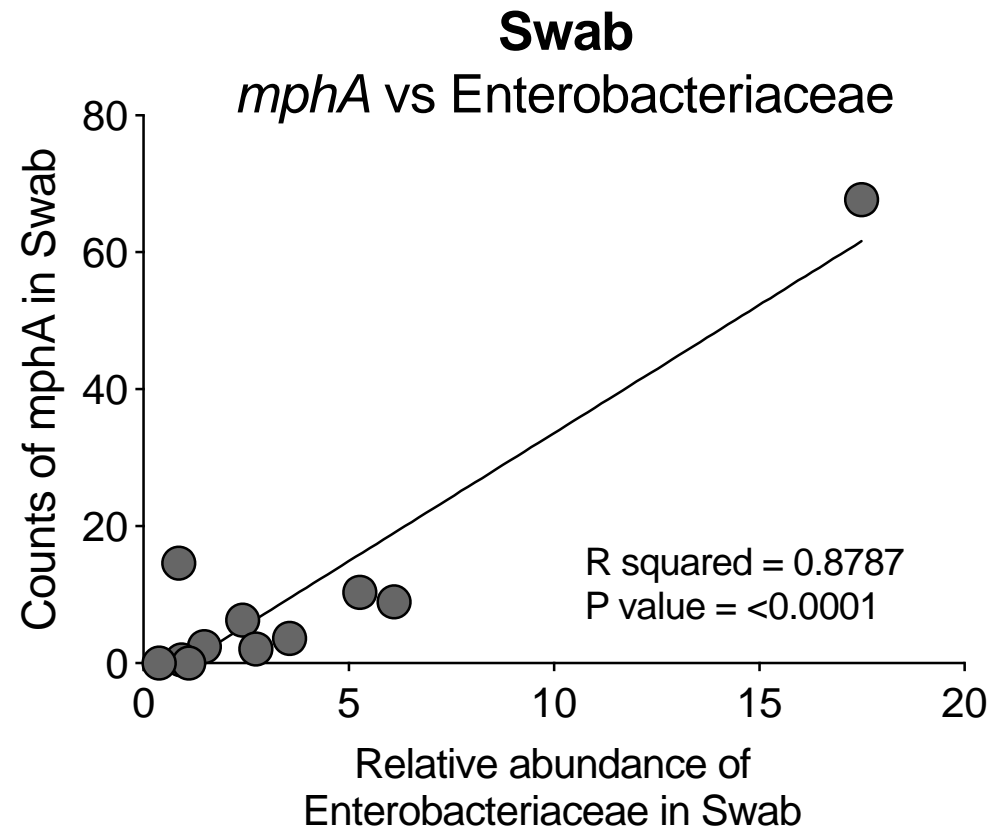


- Family assignments using Kraken2 (k-mer mapping to lowest common ancestor)

Family level abundance of rectal swabs and stool samples (pooled average)

- Only families with >1% abundance in at least 1 sample are shown
- Bolded** families are statistically different by non-parametric paired T test with multiple comparisons  
Multiple Wilcoxon test, q-values less than 0.01

# *mphA* correlation with Enterobacteriaceae abundance



- Simple Linear regression, goodness of fit  $R^2$  values