Long-term impact of an urban sanitation intervention on child health in low-income neighborhoods of Maputo city, Mozambique: a cross-sectional follow-up five years post-intervention in the Maputo Sanitation (MapSan) trial

Data Analysis Plan

Version 2.1

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Objectives

We have previously conducted a controlled before-and-after trial (Maputo Sanitation trial) to evaluate the impact of an onsite urban sanitation intervention on the prevalence of bacterial and protozoan infection (primary outcome), soil-transmitted helminth (STH) re-infection, and seven-day period prevalence of diarrhea among children living in informal neighborhoods of Maputo city, Mozambique (clinicaltrials.gov: NCT02362932).[1–3] We will conduct a cross-sectional survey of Maputo Sanitation (MapSan) trial compounds (clusters of households sharing sanitation and outdoor living space) at least 60-months post-intervention to evaluate the impact of the sanitation intervention on child health outcomes, specifically in children born after implementation of the sanitation intervention.

Hypotheses

H1. The risk of stool-based enteric pathogen detection among children 29 days – 60 months old is reduced for children born into households that previously received the sanitation intervention.

H2. Children born into households that previously received the sanitation intervention experience delayed exposure to enteric pathogens relative to comparably aged children from non-intervention households, reflected in a greater reduction in the risk of enteric pathogen detection among younger age groups and attenuated reduction in risk among older children.

Study Design

We will revisit both the intervention and control compounds from the MapSan trial to cross-sectionally assess enteric pathogen detection, growth, and seven-day period prevalence of diarrhea in the children born into the study compounds after the sanitation intervention was delivered in 2015-2016.

Inclusion and Exclusion Criteria

We will attempt to enroll all eligible children in each compound that previously participated in the MapSan trial, including any eligible children from the same household. Participant inclusion criteria include:

1. Child aged 29 days – 60 months old
2. Born and residing in a MapSan trial intervention or control compound; in intervention compounds, child must have been born following the delivery of the sanitation intervention
3. Has continuously resided in the MapSan trial compound for the preceding 6 months
4. Has a parent or guardian who is able to understand and complete the written informed consent process and allow their child to participate

Children will be excluded if they have any caregiver-indicated medical condition or disability that precludes participation in the study.

We anticipate some of the control compounds may have independently upgraded their sanitation facilities to conditions comparable to the intervention. Children living in control compounds with independently upgraded latrines will still be enrolled, but will be excluded from the main analyses of the intervention effects. Instead, these children will be included in a set of secondary analyses using the full cohort to explore the impacts of independent upgrades on estimates of the intervention effect when considered either as control or intervention sites. Control compounds with sanitation facilities observed to possess cleanable, intact hardscape slabs; pour-flush or water-sealed toilets; a functional ventilation pipe; and a permanent superstructure with sturdy walls and a secure door that ensure privacy during use will be considered as having independently upgraded to conditions comparable to the intervention. We

will also assess the current conditions of intervention facilities, but will not exclude or otherwise adjust for either upgraded or degraded sanitation facilities in intervention compounds in order to evaluate the long-term impacts of the intervention following extended use.

Data Analysis

Outcomes

Outcome Ascertainment

Stool-based detection of enteric pathogens will be performed for children who aged 29 days – 60 months who were born into and continue to reside in MapSan study compounds.[4] Reverse-transcription quantitative polymerase chain reaction (RT-qPCR) will be conducted by custom TaqMan Array Card (TAC) to simultaneously quantify genetic targets corresponding to 13 bacterial pathogens (*Aeromonas* spp.; *Campylobacter jejuni*/*coli*; *Escherichia coli* O157; *Clostridioides difficile*; enteroaggregative *E. coli* (EAEC); Shiga toxin-producing *E. coli* (STEC); enteropathogenic *E. coli* (EPEC); enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC)/*Shigella* spp.; *Helicobacter pylori*; *Plesiomonas shigelloides*; *Salmonella enterica*; *Vibrio cholerae*), 4 protozoan parasites (*Cryptosporidium* spp.; *Cyclospora cayetanensis*; *Entamoeba histolytica; Giardia* spp.), 5 soil transmitted helminths (*Ascaris lumbricoides*; *Ancylostoma duodenale*; *Necator americanus*; *Strongyloides stercolaris*; *Trichuris trichiura*), and 5 enteric viruses (adenovirus 40/41; astrovirus; norovirus GI/GII; rotavirus, sapovirus). Additionally, child weight and recumbent length (child age < 24 months) or standing height (24 – 60 months) will be assessed according to standard World Health Organization (WHO) protocols and transformed to age-adjusted z-scores using WHO reference populations to obtain height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) z-scores, with stunting defined as HAZ < -2, underweight as WAZ < -2, and wasting as WHZ < -2.[5,6] Caregiver

surveys will be administered to ascertain child diarrheal disease, defined as the passage of three or more loose or watery stools in a 24-hour period, or any bloody stool, in the past 7 days.[7–9]

Primary Outcome

The primary outcome is the weighted-mean enteric pathogen prevalence across 13 bacterial pathogens, 4 protozoan parasites, and 5 soil transmitted helminths assessed in child stool using the custom TAC. As in the original MapSan study, we exclude enteric viruses from the primary outcome due to the potential for person-to-person transmission, which is unlikely to be impacted by the intervention.[1,3] Children living in control compounds that have independently upgraded their sanitation facilities will be excluded from the primary outcome analysis. Stool-based detection of all 22 primary outcome enteric pathogens will be analyzed simultaneously under an individual participant data (IPD) random effects meta-analysis framework and the group mean of the pathogen-varying intervention effects on enteric pathogen prevalence will be assessed as the primary outcome.

Secondary Outcomes

1. The individual prevalence of each of the 27 pathogens assessed in child stool (including the 5 enteric viruses) will be analyzed simultaneously under an IPD random effects meta-analysis framework. The pathogen-specific intervention effects on prevalence of each pathogen will be assessed as secondary outcomes.
2. The class-level weighted-mean enteric pathogen prevalence will be analyzed separately for each of the four pathogen classes represented on the TAC (bacteria, protozoa, soil transmitted helminths, and viruses). Separate IPD random effects meta-analysis models

will be fit for each class, with the 13 bacteria to analyzed together to estimate the group mean of the bacterial pathogen-varying intervention effects on bacterial pathogen prevalence. Separate models will similarly be fit to the 4 protozoa, the 5 STH, and the 5 enteric viruses to estimate the pooled intervention effects on protozoa prevalence, STH prevalence, and virus prevalence, respectively, as secondary outcomes.

3. The weighted-mean gene copy density across the 22 primary outcome enteric pathogens (excluding enteric viruses) will assessed as a secondary outcome. Gene copy densities will be standard deviation-scaled for each pathogen and analyzed simultaneously using an IPD random effects meta-analysis framework with model-based censoring to create a zero class to represent non-detects. The group mean of the pathogen-varying intervention effects on gene copy density will be assessed as a secondary outcome.
4. The individual scaled gene copy density of each of the 27 pathogens assessed in child stool (including the 5 enteric viruses) will be analyzed simultaneously under an IPD random effects meta-analysis framework and censoring to account for non-detects. The pathogen-specific intervention effects on gene copy density will be assessed as secondary outcomes.
5. Child HAZ, WAZ, WHZ will each be analyzed separately. The intervention effects on the age-adjusted z-score of each anthropometry measure will be assessed as secondary outcomes.
6. Prevalence of stunting, underweight, and wasting and the 7-day period-prevalence of caregiver-reported diarrhea will each be analyzed separately. The individual intervention effects on stunting, underweight, and wasting prevalence and diarrhea period-prevalence will be assessed as secondary outcomes.

Effect Measures

For binary outcomes (e.g., pathogen detection, diarrhea), the conditional prevalence odds ratio (POR) for children living in intervention compounds relative to children in control compounds will be estimated as the measure of effect. Marginal prevalence differences (PD) between children in intervention and control compounds will also be estimated from the posterior predictive distribution at representative values of other model covariates.[10] Mean differences will be estimated as the measure of effect for continuous outcomes (e.g., gene copy density, HAZ).

Estimation Strategy

Enteric Pathogen Outcomes

We will concurrently assess 27 individual enteric pathogens in each child stool sample, but are interested in estimating the generalized effect of the sanitation intervention on enteric pathogen detection as a proxy for enteric infections—that is, the expected intervention effect on a *generic* enteric pathogen. We adopt an IPD random effects meta-analysis framework to estimate the weighted-average intervention effect across all the pathogens, in essence treating each pathogen as a separate study of the intervention effect on enteric pathogen detection (See Appendix A. Illustrative Model Specifications).[11–13] The intercept, intervention effect slope, and the slopes of other covariates are all allowed to vary by pathogen (the "random effects"). Each set of pathogen-varying effects (e.g., the pathogen-specific intervention effect slopes) is structured as arising from a population of parameters with shared mean and variance.[14,15] The population-level mean corresponds to the weighted-average expected effect across all pathogens and the population-level variance indicates the extent to which the effect differs by pathogen. We also estimate population-level covariances between the different sets of pathogen-varying effects to

account for dependencies between effects, for example if the effect of the intervention on a specific pathogen is greater when the background prevalence of that pathogen (represented by the pathogen-specific intercept) is also higher. By accounting for correlations between pathogen outcomes, the IPD random effects meta-analysis approach provides adaptive control of the individual treatment effect estimates for each separate pathogen as well as an estimate of the generalized effect across pathogens.[14,16] Such partial pooling of effect estimates helps control the false discovery rate for individual outcomes, avoiding the need for *post hoc* multiple comparison adjustments.[12,17]

The primary outcome will be assessed using the population-level mean slope for the intervention effect term from the model fit using only the 22 bacteria, protozoa, and soil transmitted helminths specified in the primary outcome description above. The raw parameter will be estimated on the log-odds scale and exponentiated to obtain the prevalence odds ratio as the measure of effect. Secondary outcomes include intervention effects on the prevalence of each individual pathogen, including enteric viruses, which are excluded from the primary outcome. The same IPD random effects meta-analysis approach will be applied to all 27 pathogens simultaneously, with the pathogen-specific intervention effect slopes providing the effect estimates for individual pathogens. A fully Bayesian model formulation will be used to account for multiple sources of uncertainty and provide estimation stability through the use of regularizing priors.[16] Parameter posterior density distributions will be summarized using the mean to represent the expected effect size and the central 95% probability interval to capture the range of effect sizes compatible with the data (the 95% compatibility interval [CI]). Parameters with 95% CIs that exclude the null will be considered significant, although the magnitude and

uncertainty of parameter estimates will also be considered holistically in evaluating the evidence for clinically or physically meaningful effects.[12,18]

Additional secondary outcomes include both pathogen-specific and population-level effects of the sanitation intervention on mean pathogen gene copy density. Density outcomes will also be analyzed with IPD random-effects meta-analysis by scaling gene copy densities for each pathogen by the empirical pathogen-specific standard deviation among samples in which the pathogen was detected. Non-detects will be considered true zeros and censoring will be used to create a zero class (as in Tobit regression).[19,20] For such "continuous abundance" data, positive values are treated as ordinary continuous data, while negative values are considered non-detects, such that increasingly negative values for the mean correspond to lower pathogen prevalence.

Continuous Anthropometry Outcomes

The effects of the intervention on mean HAZ, WAZ, and WHZ will be analyzed separately as secondary outcomes using generalized estimating equations (GEE) and robust standard errors with exchangeable correlation structure and clustering by compound (the level at which the sanitation intervention was delivered).[3,21,22] The estimated difference in age-adjusted z-scores by treatment assignment will be used as the measure of effect.

Binary Caregiver-Reported and Growth Faltering Outcomes

The effects of the intervention on the period-prevalence of diarrhea and the prevalence of growth faltering metrics (stunting, underweight, and wasting), as well as for caregiver-reported negative control outcomes (bruising, scrapes, and abrasions; toothache), will be analyzed separately as secondary outcomes by Poisson regression using GEE with robust standard errors to estimate

prevalence ratios as the measure of effect.[3] As with the continuous anthropometry outcomes, we will use an exchangeable correlation structure and clustering by compound.

Adjustment Set

All models will be fit both unadjusted (with only an indicator of treatment assignment and accounting for clustering at the compound level) and adjusted for a set of covariates selected *a priori* as potential confounders of the sanitation-enteric pathogen carriage relationship. The adjustment set includes child age and sex, caregiver's education, and household wealth index.[3,23]

Sub-group Analyses

Effect Measure Modification by Age

The prevalence and type of enteric infections are strongly related to child age.[2,3,24] We will examine effect measure modification of the primary and secondary outcomes stratifying by age group (1-11 months, 12-23 months, and 24-60 months).

Independently Upgraded Controls

Children living in control compounds deemed to have independently upgraded their sanitation infrastructure to conditions comparable to the original intervention will be excluded from the main analyses. Two sets of subgroup analyses will instead be conducted that include all participants: one in which children in independently upgraded controls are considered as part of the control (non-intervention) arm, and again considered as part of the intervention arm. We will compare parameter estimates from the three sets of analyses (independent upgrades excluded, independent upgrades as controls, and independent upgrades as interventions) to investigate

whether the sanitation improvements independently available in the study communities, which may represent more accessible options for achieving greater coverage of high-quality sanitation infrastructure, are comparable to the full sanitation intervention package assessed in the MapSan trial in terms of child health impacts.

Exclusion of *Giardia* spp. from the Outcome Set

Stool-based detection of a given pathogen is an unambiguous indicator of previous exposure.[4] *Giardia* spp. is one of the most commonly detected pathogens in child stool in low- and middle-income countries, including in the original MapSan study cohort and elsewhere in southern Mozambique.[2,3,25,26] The high prevalence of *Giardia* spp., which has been found to increase rapidly with age, demonstrates a failure to prevent exposure.[27] However, persistent shedding of *Giardia* spp. has also been observed in endemic areas, to the extent that it has been suggested it functions as something of a gut commensal in such settings, even potentially protecting against diarrheal illness.[28–30] Whether arising from persistent infection or rapid re-infection, the extended shedding suggests that detection of *Giardia* spp. may not serve as a meaningful indicator of recent exposure in the context of household sanitation infrastructure. Although household finished flooring was associated with reduced *G. duodenalis* prevalence in both Bangladesh and Kenya, onsite sanitation interventions were not associated with *Giardia* spp. in rural Bangladesh or Zimbabwe, nor in urban Mozambique.[3,31–33] Recognizing that its unique and insufficiently understood epidemiology may limit interpretation, we will repeat the primary outcome analysis with *Giardia* spp. excluded from the outcome set, using the remaining 21 non-viral pathogens to estimate the weighted-mean intervention effect on pathogen prevalence.

Negative Control Analyses

As objective measures of pathogen exposure, stool-based pathogen outcomes (including the primary outcome) are not subject to differential response by treatment arm and thus not amenable to traditional negative control analysis that uses other outcomes thought to be unrelated to the intervention to assess response bias.[4,34] However, negative extraction controls (NEC) and no-template controls (NTC) will be processed routinely during TAC analysis to monitor for sample cross-contamination.[35] We will assess two caregiver-reported negative control outcomes for each child: the 7-day period-prevalence of bruises, scrapes, or abrasions and the 7-day period-prevalence of toothache.[34,36] These outcomes will be ascertained in caregiver surveys and analyzed in the same manner as described for caregiver-reported outcomes of interest (e.g., diarrhea). We do not expect the intervention to impact either child bruising or toothache prevalence, so significant differences in these outcomes by treatment arm would suggest possible bias in our caregiver-reported outcomes.

Missing Data

Records missing covariate data will be excluded from adjusted analyses. Analyses will be repeated with missing covariate data imputed by multivariate imputation using chained equations (MICE) as a sensitivity analysis.[3,37]

Minimum Detectable Effect Size

The number of participants will be constrained by the number of compounds previously enrolled in the MapSan trial. At the 24 month follow-up, an average of 2.5 children per compound were enrolled from 408 compounds.[3] Compound-level intra-class correlation coefficients (ICCs) were

generally less than 0.1 for individual pathogens, corresponding to cluster variances of ~0.05. We calculate the minimum detectable effect size (MDES) on individual pathogen prevalence with 80% power, 5% significance level, and 0.05 compound cluster variance for both a conservative scenario with 200 compounds per treatment arm and 2 children enrolled per compound (for 800 children total, 400 per arm) and an optimistic yet realistic scenario of 220 compounds per treatment arm and 2.5 children enrolled per compound (550 children per arm, 1100 total).[38–40] For either scenario, the minimum baseline (untreated) prevalence required to obtain 80% power is 7-8%. On the multiplicative scale, the MDES for prevalence ratio decreases (that is, a smaller relative reduction is required to attain 80% power) as pathogen prevalence increases towards 100% (Figure 1). The difference between the two scenarios on the multiplicative scale is relatively minor, with the relative reduction MDES largely driven by pathogen baseline prevalence. A pathogen with baseline prevalence of 15% or less must have its prevalence more than halved (PR < 0.5) in order to attain 80% power, while a 25% reduction is detectable for baseline prevalence of 40-46%. We expect the simultaneous consideration of multiple pathogens to reduce the MDES for the primary outcome meta-analytic intervention effect by effectively increasing the sample size. Because this group-mean effect is dependent on the prevalence of each pathogen considered and the correlations between them, we will conduct simulation analyses to characterize plausible MDES ranges for the meta-analytic primary outcome.[13,39]

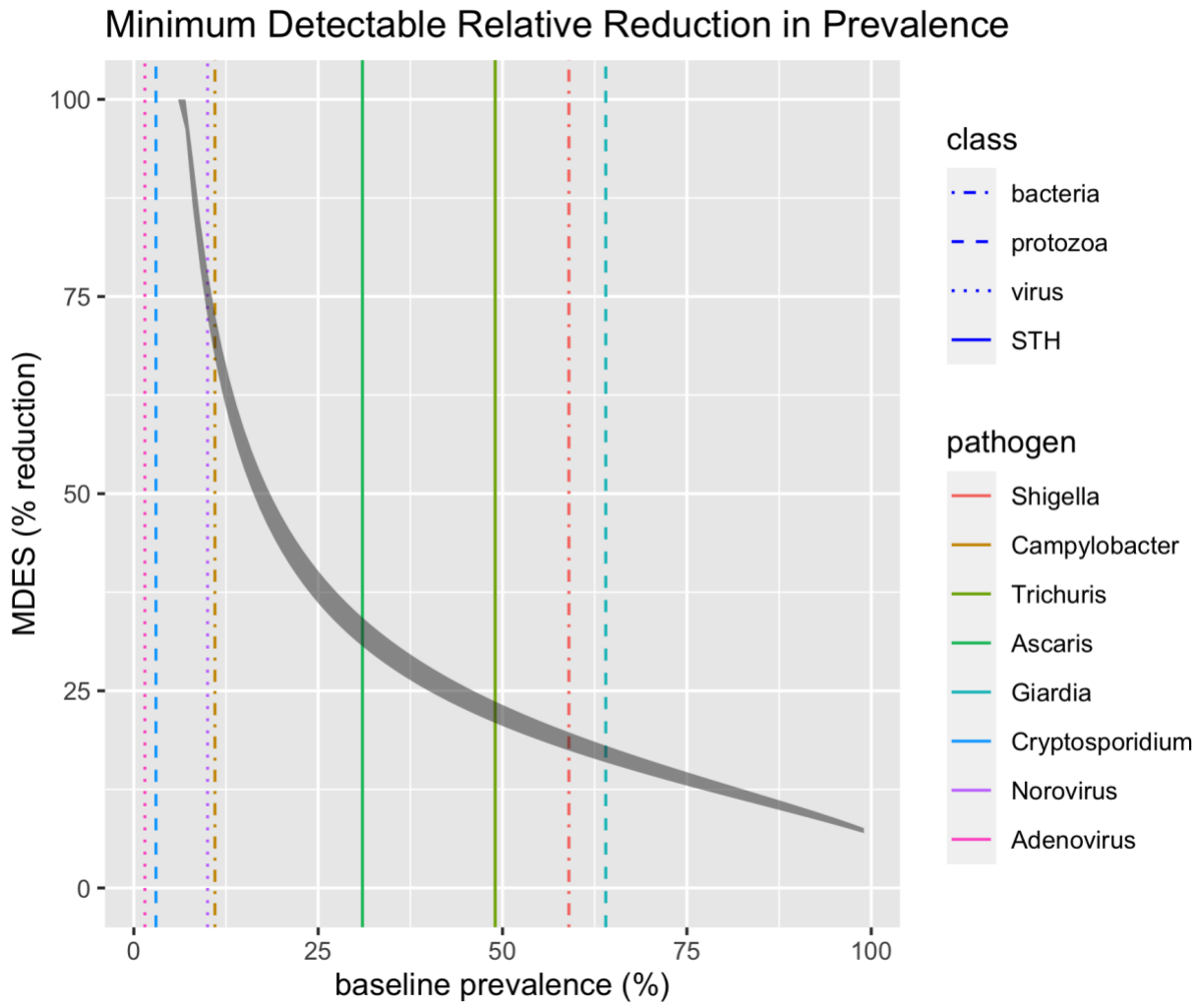

Figure 1. Range of minimum detectable effect sizes (shaded region) for the percent reduction in pathogen prevalence with 80% power, 5% significance level, and 0.05 cluster variance across two sample size scenarios. The upper edge of the shaded area represents a conservative scenario with 800 total participants (2 per compound, 200 compounds per arm) while the lower edge corresponds to a more optimistic scenario with 1100 total participants (2.5 per compound, 220 compounds per arm). The vertical lines show the prevalence of a subset of pathogens assessed in control compound children during the 24-month follow-up in the original MapSan trial. Line color indicates the specific pathogen and line pattern reflects the pathogen class.

Appendix A. Illustrative Model Specifications

The models used to conduct the IPD random effects meta-analyses will inevitably require iterative development and refinement to ensure estimation accuracy and computational stability.[41,42] The following model specifications for binary (Section A1) and continuous abundance (Section A2) outcomes illustrate the components likely to be incorporated into such models to estimate the quantities of interest specified in the analysis plan above. However, fitting the models with Markov chain Monte Carlo (MCMC) will at the very least require re-expressing the models using alternative parameterizations that support robust and efficient sampling; while mathematically equivalent, such reparameterizations trade interpretability for improved computational qualities.[14,43]

A1. Binary Outcome Model

Indices

children: $i \in 1, \ldots, N$

compounds: $j \in 1, \ldots, J$

pathogens: $q \in 1, \ldots, Q$

covariates: $k \in 1, \ldots, K$

Structure

$$y_{i,j,q} \sim \text{Bernoulli}\left(p_{i,j,q}\right)$$

$$\text{logit}\left(p_{i,j,q}\right) = \alpha_{kid[i]} + \alpha_{comp[j]} + \alpha_{path[q]} + \beta_{path[q]} x_i + \gamma_{1,path[q]} z_{i,1} + \cdots + \gamma_{K,path[q]} z_{i,K}$$

$$\alpha_{kid[i]} \sim \text{Normal}(0, \sigma_{\text{kid}})$$

$$\alpha_{comp[j]} \sim \text{Normal}(0, \sigma_{\text{comp}})$$

$$\begin{bmatrix} \alpha_{path[q]} \\ \beta_{path[q]} \\ \gamma_{1,path[q]} \\ \vdots \\ \gamma_{K,path[q]} \end{bmatrix} \sim \text{MVN}\left(\begin{bmatrix} \alpha \\ \beta \\ \gamma_1 \\ \vdots \\ \gamma_K \end{bmatrix}, \Sigma\right)$$

$$\Sigma = \tau \times \Omega \times \tau$$

$$\tau = \begin{pmatrix} \sigma_\alpha & 0 & \ldots & & 0 \\ 0 & \sigma_\beta & & & \vdots \\ \vdots & & \sigma_{\gamma_1} & & \\ & & & \ddots & 0 \\ 0 & \ldots & & 0 & \sigma_{\gamma_K} \end{pmatrix}$$

$$\Omega = \begin{pmatrix} 1 & \rho_{\alpha,\beta} & \ldots & \rho_{\alpha,\gamma_K} \\ \rho_{\beta,\alpha} & 1 & & \vdots \\ \vdots & & & \\ & & \ddots & \\ \rho_{\gamma_K,\alpha} & \ldots & & 1 \end{pmatrix}$$

Interpretation

Table A1. Interpretation of Binary Outcome Model Terms

Term	**Interpretation**
$y_{i,j,q}$	Detection status of pathogen q in child i from compound j
$p_{i,j,q}$	Probability of detecting pathogen q in child i from compound j
$\alpha_{kid[i]}$	Child-specific random effect for child i; the change in log-odds of any pathogen for child i
σ_{kid}	Group standard deviation for child-level random effects; larger value indicates greater clustering of pathogen outcomes by child and results in less pooling of information between children
$\alpha_{comp[j]}$	Compound-specific random effect for compound j
σ_{comp}	Group standard deviation of compound-level random effects; larger value indicates greater clustering of pathogen outcomes by compound and results in less pooling of information between compounds
$\alpha_{path[q]}$	Pathogen-specific intercept for pathogen q; the log-odds of pathogen q without the treatment and in the reference group for all covariates
α	Group mean of the intercept across all Q pathogens; the log-odds of a generic pathogen without the treatment and in the reference group for all covariates
$\beta_{path[q]}$	Pathogen-specific effect of the treatment on the log-odds of pathogen q, conditional on the other covariates; exp $(\beta_{path[q]})$ gives the conditional odds ratio for the effect of the treatment on pathogen q
x_i	Treatment condition for child i
β	Group mean conditional treatment effect across the population of Q pathogens; the meta-analytic estimate of the conditional effect of the treatment on a generic enteric pathogen
$\gamma_{k,path[q]}$	Conditional effect of covariate k on the log-odds of pathogen q
$z_{i,k}$	Value of covariate k for child i
γ_k	Group mean conditional effect of covariate k across the population of Q pathogens
Σ	Symmetric $K+2$ matrix with the group variance of each pathogen-varying effect $(\alpha, \beta, \gamma_k)$ on the diagonal and their covariances on the off-diagonals; decomposes into the scale matrix τ and the correlation matrix Ω
τ	The scale matrix for pathogen-varying effects α, β, γ_k: a $K+2$ diagonal matrix of the group standard deviations $\sigma_\alpha, \sigma_\beta, \sigma_{\gamma_k}$; these standard deviations reflect the extent to which each effect varies across the group of Q pathogens, with larger values indicating greater differences between pathogens
Ω	The correlation matrix for pathogen-varying effects α, β, γ_k: a $K+2$ square matrix with the pairwise correlations $\rho_{\alpha,\beta}$, etc. on the off-diagonals; these correlations reflect how the different effects co-vary by pathogen. The correlations between α and each of the other effects are of particular interest as they indicate how lower or high background pathogen prevalence may modulate the treatment effect and the other covariate effects

Anticipated Hyperpriors

$$\alpha \sim \text{Normal}(-1,2), \qquad \sigma_\alpha \sim \text{Normal}^+(0,1)$$

$$\beta \sim \text{Normal}(0,1), \qquad \sigma_\beta \sim \text{Normal}^+(0,1)$$

$$\gamma_k \sim \text{Normal}(0,1), \qquad \sigma_{\gamma_k} \sim \text{Normal}^+(0,1)$$

$$\Omega \sim \text{LKJcorr}(\eta), \qquad \eta \geq 1$$

$$\sigma_{kid} \sim \text{Normal}^+(0,1), \qquad \sigma_{comp} \sim \text{Normal}^+(0,1)$$

The $\text{Normal}(-1,2)$ prior on α, which is on the log-odds scale, implies an expected prevalence for a generic pathogen of $\text{logit}^{-1}(-1) \approx 27\%$, a 68% chance that the prevalence falls between 5% and 73%, and a 95% chance that the prevalence is between 0.7% and 95%.[16,44] Combined with the additional variation contributed by the group standard deviation σ_α, which is given a standard half-normal (positive constrained) prior of its own, this choice of priors allows the pathogen-specific intercept $\alpha_{path[q]}$ for each individual pathogen q to take on any reasonable prevalence value while providing gentle regularization towards values of prevalence greater than 0% and less than 50%. Because we will not include pathogens in the analysis that we believe to be truly absent (0% prevalence, which by definition cannot be affected by the intervention) and few individual enteric pathogens typically occur at >50% prevalence in previous studies, this weakly informative hyperprior generally reflects our prior knowledge while providing sufficient flexibility for strong signals in the data to change the parameter estimates accordingly. This approach can encourage good computational behavior by softly constraining the sampler away from extreme (unreasonable) values and introducing light smoothing, which is particularly desirable for complex, high dimensional models such as these, where unconstrained estimation can be susceptible to erratic, unreliable behavior in the presence of ordinary noise in the data.[14,44]

See Supporting Information S13 of Holcomb et al. (2021) for additional discussion of prior choice in hierarchical logistic models of enteric microbe prevalence.[16]

Similarly, the standard normal priors for β and γ_k on the log-odds scale imply that each effect has a 95% chance of reducing the prevalence of a generic pathogen by up to 22 percentage points (that is, an absolute risk difference of 0.22) for a pathogen with a background prevalence of 27% (the expected value of the intercept, α). This is a large effect size, though not impossible, and similarly provides gentle regularization towards moderate values (in this case, towards no effect) while allowing truly large effect sizes for sufficiently strong evidence from the data. In addition to assisting computationally, this weak regularization towards the null helps control false discoveries that would be expected to arise from ordinary noise in the data when comparing multiple outcomes by introducing light smoothing that requires stronger patterns in the data to register as credible effects.[12,17] The degree of smoothing applied to effect estimates for individual pathogens, $\beta_{path[q]}$ and $\gamma_{k,path[q]}$, is learned from the data and represented by the group standard deviations σ_β and σ_{γ_k}. Larger group standard deviation estimates correspond to greater variability by pathogen and thus impose relatively less smoothing on the effect estimates. The independent standard half-normal priors on the group standard deviations likewise allows for a wide range of plausible values when considered on the probability scale, while discouraging extremely large values.[16,45,46]

The group correlations between the pathogen varying effects ($\rho_{\alpha,\beta}$, ρ_{β,γ_1}, etc.) are collectively given an LKJ prior on the correlation matrix, which imposes the [-1,1] constraint on correlations but otherwise assigns approximately uniform prior density across that range when shape parameter $\eta = 1$.[14,47] Larger values of η increase the weight around zero, which can be used to regularize the correlation estimates towards smaller absolute values. $\eta = 2$ is likely a

reasonable default value to provide weak regularization for computational purposes while still permitting strong correlations when warranted.[14,43]

A2. Continuous Abundance Outcome Model

Indices

children: $i \in 1, \ldots, N$

compounds: $j \in 1, \ldots, J$

pathogens: $q \in 1, \ldots, Q$

covariates: $k \in 1, \ldots, K$

Structure

$$y_{i,j,q} = \begin{cases} w, & w > 0 \\ 0, & w \leq 0 \end{cases}$$

$$w_{i,j,q} \sim \text{Normal}\left(\mu_{i,j,q}, \sigma_{path[q]}\right)$$

$$\sigma_{path[q]} \sim \text{Normal}^{+}\left(\sigma_y, \sigma_\sigma\right)$$

$$\mu_{i,j,q} = \alpha_{kid[i]} + \alpha_{comp[j]} + \alpha_{path[q]} + \beta_{path[q]} x_i + \gamma_{1,path[q]} z_{i,1} + \cdots + \gamma_{K,path[q]} z_{i,K}$$

$$\alpha_{kid[i]} \sim \text{Normal}(0, \sigma_{\text{kid}})$$

$$\alpha_{comp[j]} \sim \text{Normal}\left(0, \sigma_{\text{comp}}\right)$$

$$\begin{bmatrix} \alpha_{path[q]} \\ \beta_{path[q]} \\ \gamma_{1,path[q]} \\ \vdots \\ \gamma_{K,path[q]} \end{bmatrix} \sim \text{MVN}\left(\begin{bmatrix} \alpha \\ \beta \\ \gamma_1 \\ \vdots \\ \gamma_K \end{bmatrix}, \Sigma\right)$$

$$\Sigma = \tau \times \Omega \times \tau$$

$$\tau = \begin{pmatrix} \sigma_\alpha & 0 & \ldots & & 0 \\ 0 & \sigma_\beta & & & \vdots \\ \vdots & & \sigma_{\gamma_1} & & \\ & & & \ddots & 0 \\ 0 & \ldots & & 0 & \sigma_{\gamma_K} \end{pmatrix}$$

$$\Omega = \begin{pmatrix} 1 & \rho_{\alpha,\beta} & \ldots & \rho_{\alpha,\gamma_K} \\ \rho_{\beta,\alpha} & 1 & & \vdots \\ \vdots & & & \\ & & \ddots & \\ \rho_{\gamma_K,\alpha} & \ldots & & 1 \end{pmatrix}$$

Interpretation

The continuous abundance outcome IPD meta-analysis model specification remains largely the same as for binary outcome model, exchanging the Bernoulli likelihood with probability $p_{i,j,q}$ for a Gaussian likelihood with child-, compound-, and pathogen-specific mean $\mu_{i,j,q}$ and pathogen-specific standard deviation $\sigma_{path[q]}$. All the additive components of $\text{logit}(p_{i,j,q})$ remain the same for $\mu_{i,j,q}$ (which is not subjected to a link function), although the hyperpriors assigned to each additive component are adjusted to reflect the different scale of the continuous abundance data. The pathogen-specific residual standard deviations $\sigma_{path[q]}$ are drawn from a half-normal distribution with mean σ_y, the population-level residual standard deviation that describes the variation in observed gene copy densities after accounting for the effects of the other model components that comprise $\mu_{i,j,q}$. The group standard deviation σ_σ functions similarly to other group standard deviations (e.g., σ_{comp}) in describing the extent to which the residual standard deviations vary between different pathogens. Such hierarchical variance parameter structures are often challenging to fit in practice due to poor identifiability and unfavorable geometries for efficient Markov chain Monte Carlo sampling (MCMC). It may therefore be necessary to simplify the pathogen-specific standard deviations into a single shared residual standard deviation σ_y. Because the gene copies densities will pre-scaled by their pathogen-specific empirical standard deviations, the scaled model inputs will already share a standard deviation of approximately 1, which should allow the single, global σ_y to adequately capture the residual standard deviation for all pathogens.

Besides the different likelihood to accommodate continuous outcomes and the additional variance parameter it requires, the key structural difference for the continuous abundance model is the introduction of the latent continuous gene copy density variable $w_{i,j,q}$. While the Bernoulli

likelihood is applied directly to observed binary outcome $y_{i,j,q}$, the normal likelihood in the continuous abundance model applies instead to the latent continuous variable $w_{i,j,q}$, which has unbounded support over $(-\infty, \infty)$. The observed gene copy density $y_{i,j,q}$ has a lower bound with $[0, \infty)$ support, however, which is realized by censoring negative values of $w_{i,j,q}$ at zero; otherwise, $y_{i,j,q}$ simply takes the value of positive $w_{i,j,q}$.[20] This creates probability mass at zero for an otherwise continuous outcome, with more negative values of $\mu_{i,j,q}$ (the mean of $w_{i,j,q}$) implying a lower probability of detecting the pathogen that was assessed in observation $y_{i,j,q}$.

Anticipated Hyperpriors

$$\alpha \sim \text{Normal}(0,2), \qquad \sigma_\alpha \sim \text{Normal}^+(0,3)$$

$$\beta \sim \text{Normal}(0,1), \qquad \sigma_\beta \sim \text{Normal}^+(0,1)$$

$$\gamma_k \sim \text{Normal}(0,1), \qquad \sigma_{\gamma_k} \sim \text{Normal}^+(0,1)$$

$$\Omega \sim \text{LKJcorr}(\eta), \qquad \eta \geq 1$$

$$\sigma_{kid} \sim \text{Normal}^+(0,1), \qquad \sigma_{comp} \sim \text{Normal}^+(0,1)$$

$$\sigma_y \sim \text{Normal}^+(0,1), \qquad \sigma_\sigma \sim \text{Normal}^+(0,1)$$

Because the input data are pre-scaled by the empirical pathogen-specific standard deviation, the hyperpriors selected assuming the unit scale for the binary outcomes largely continue to hold for the scaled continuous abundance data. A notable exception is the population-level mean α, for which an informative prior is used for the binary outcome case to reflect our prior knowledge that most pathogens can be expected to have a prevalence greater than 0% but less than 50%. We lack similar prior knowledge for gene copy density and therefore default to a zero-mean prior for the population-level scaled gene copy density across all pathogens, α. A challenge of the censoring-at-zero approach to modeling continuous abundance is that the magnitude of the

continuous outcome in positive samples and the probability of observing a positive are both controlled by a single mean parameter, μ, for the latent continuous variable w. While the choice of priors for the components of μ (namely α) are readily interpretable for positive values of μ, with higher values translating directly to scaled gene copy densities, negative values of μ are non-linearly related to decreasing prevalence of the target pathogen. Furthermore, while observed gene copy densities have been scaled by the standard deviation, such that approximately 95% of non-zero scaled densities should take values between zero and two, very low-prevalence targets may require mean values less than -2 to adequately reflect their low probability of detection. We therefore assume a standard deviation of 2 for α to extend the range of prior density to a wider range of values, and also increase the standard deviation of σ_a to 3 to consider greater between-pathogen variability in the pathogen specific mean gene copy density $\alpha_{path[q]}$.

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