IDM INSTITUTE FOR DISEASE MODELING

PROGRESS IN THE REACH SECONDARY ANALYSES

2025

Gates Foundation

Outline

Background

- Child mortality remains high in sub-Saharan Africa;
- MDA with azithromycin has emerged as promising intervention beyond trachoma;
- MORDOR trial: 13.5% reduction in under-five mortality with biannual treatment;
- **But:** Benefits not consistent across all settings
- **Concerns:** Antimicrobial resistance with repeated exposure

Current WHO guidance (2020): IMR $\geq$ 60/1,000 or U5MR $\geq$ 80/1,000 - thresholds based on expert opinion, not trial data.

This study: First data-driven foundation for cessation criteria using comprehensive trial data

Analytical Roadmap: Objectives

Five interconnected goals

1. **Reference age patterns**: derive robust neonatal, infant, and child hazard profiles from DHS birth histories.
2. **De-noised and spatially coherent baseline mortality**: generate accurate cluster-level estimates of underlying mortality from sparse REACH trial data.
3. **Contextual heterogeneity**: assess whether immunization coverage and malaria burden explain baseline variation and/or systematically modify treatment effects.
4. **Decision-ready thresholds**: identify mortality levels where azithromycin no longer improves survival.

Data integration: DHS birth histories (17 surveys), REACH trial mortality/person-time/coordinates, and contextual indicators (IHME immunization, Malaria Atlas).

Stage 1: Demographic Age Patterns

Goal: Establish reliable age profiles for mortality hazards and a robust neonatal to post-neonatal bridge.

- Convert DHS age-specific death probabilities to cumulative hazards: $H_a = -n_a \log(1 - p_a)$ across standard age bands.
- Pooled log-log regression with country intercepts to model neonatal hazard as function of early and late post-neonatal mortality:

$$\log H_0 = \alpha_{\text{country}} + \beta_1 \log H_{1\text{–}11} + \beta_2 \log H_{12\text{–}59} + \epsilon$$

- Output: age pattern priors and quantified uncertainty to inform trial-based modeling.

Stage 2: Trial-Anchored Baseline Mortality

Goal: Calibrate demographic priors to observed placebo data.

- **Baseline hazard (1–59m):** Fit a *quasi-Poisson GLM with offset and cluster-robust SEs* on placebo clusters:

$$\log \mathrm{E}[y_c] = \alpha_g + \log E_c$$

where y_c = observed deaths, E_c = person-time. Produces trial–country baseline hazard priors with uncertainty.

- **Age split (1–11 vs 12–59m):** Update DHS Beta prior with observed placebo deaths by age group:

$$p_g \mid \text{data} \sim \text{Beta}(\alpha_{g,0} + d_{g,1-11},\ \beta_{g,0} + d_{g,12-59})$$

giving the fraction of under-five hazard in 1–11m.

- **Outputs:** Group-specific hazard priors (μ_g) and calibrated age shares (p_g), passed forward to the hierarchical spatial model.

Stage 3: Bayesian Spatial Mortality Estimation

Goal: Derive spatially coherent cluster-level IMR and U5MR.

$$y_i \sim \text{Poisson}(E_i \exp\{\lambda_i\}), \quad \lambda_i = \mu_{g[i]} + u(\mathbf{s}_i) + v_i$$

- $u(\mathbf{s})$: Hilbert Space Gaussian Process (HSGP) approximation to a Matérn-3/2 field.
- v_i: cluster-specific deviations with a regularized horseshoe prior (adaptive shrinkage).
- Age decomposition: combine trial deaths and DHS bridge to recover neonatal, infant, and child hazards.
- Outputs: posterior distributions for cluster-level IMR and U5MR.

Stage 4: Contextual Heterogeneity

Goal: Test whether context explains baseline mortality or modifies treatment effects. Nested models (Poisson GLMM with age spline $f(a)$ and exposure offset):

$$\begin{aligned} \text{Base:} \quad & \log \mu_{iat} = \log E_{iat} + \beta_0 + f(a) + b_i \\ \text{+Covariate:} \quad & \log \mu_{iat} = \ldots + \beta_1 x_i \\ \text{+Interaction:} \quad & \log \mu_{iat} = \ldots + \beta_2 T_i + \beta_3 (x_i \times T_i) \end{aligned}$$

- Covariates: immunization gaps (DPT1–3, MCV1, BCG, Polio3) and malaria indicators (ITN, incidence, mortality).
- Likelihood ratio tests compare nested models to assess explanatory vs modifying effects.

Stage 5: Cessation Thresholds via Posterior Crossings

Goal: Identify mortality levels where azithromycin benefits vanish.

- Poisson interaction model with baseline mortality on log scale:

$$y_i \sim \text{Poisson}(\lambda_i t_i), \qquad \log \lambda_i = \alpha_{g[i]} + \beta_U U_i + \text{trt}_i\big(\beta_T + \beta_{U\times T} U_i\big)$$

where:

y_i	observed deaths in cluster i
t_i	person-time (exposure offset)
trt_i	treatment indicator $(0/1)$
U_i	latent baseline log mortality (sampled from baselines posterior)
$\alpha_{g[i]}$	group-level intercept

- Posterior predictive rates generated on dense mortality grid by treatment arm.
- Threshold U^* is by draw mortality level where predicted curves cross.
- Output: distribution of cessation thresholds (median, CrI) for IMR/U5MR.

Study Population

Trial	Country	Clusters	Children	Deaths	Person-years
AVENIR	Niger	2,158	619,228	3,837	298,683
CHAT	Burkina Faso	285	237,434	1,086	119,139
MORDOR I	Malawi	304	240,384	1,044	108,009
MORDOR I	Tanzania	613	131,095	360	63,127
MORDOR I/II	Niger	594	400,111	5,253	205,360
Total		**3,954**	**1.63M**	**11,580**	**794,318**

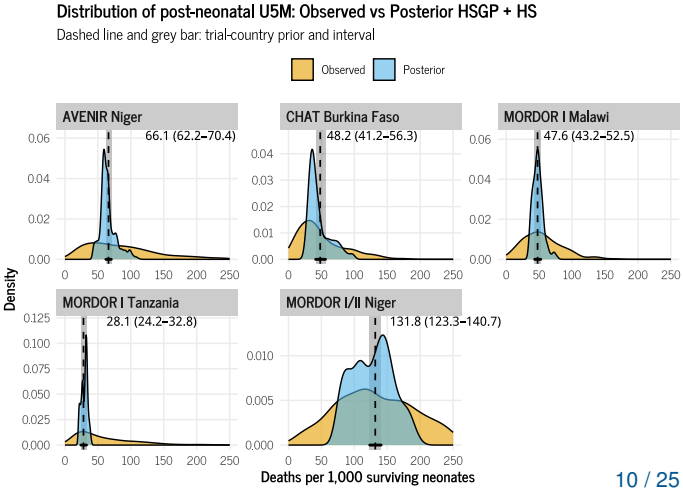
Coverage: Ages 1-59 months across diverse epidemiological contexts
Validation: Denominators match original trial publications

Baseline Mortality Patterns

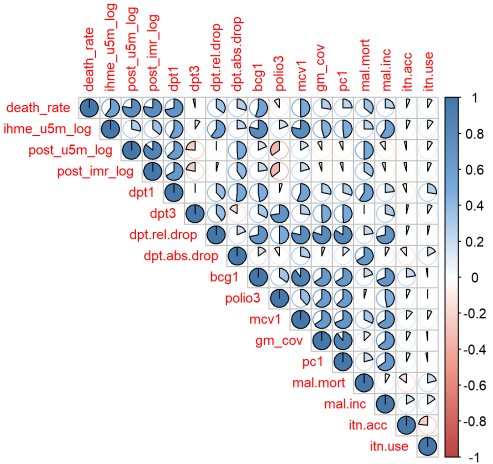
Spatial Model

$\mu_i = 1e3 * (1 - exp(-H_{i,1}^{59}))$:

- Orange: Raw cluster estimates
- Blue: Posterior cluster means
- Dashed (and grey): Trial-country priors
- Text (median and CrI): Trial-country priors



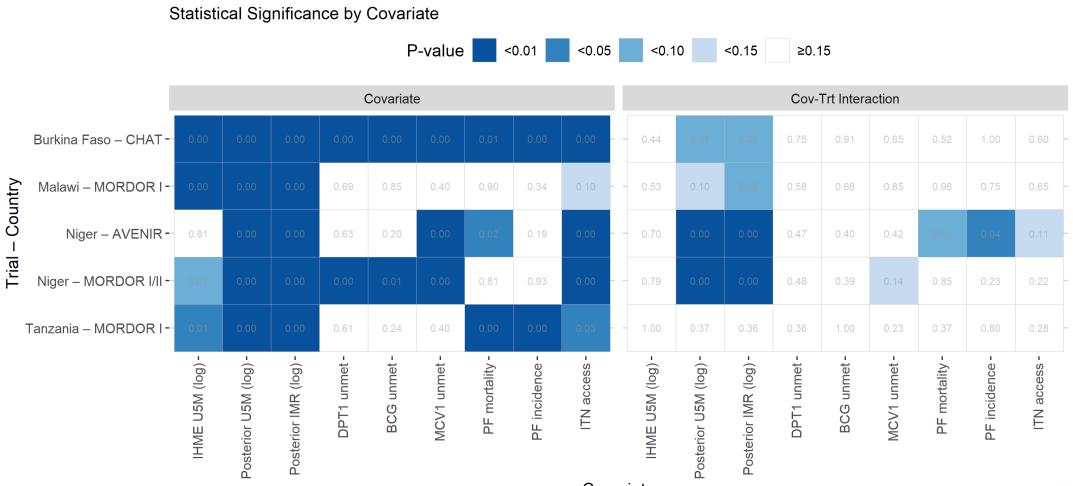
Contextual Heterogeneity: Correlations



- Immunization variables use vaccination gap (1 - coverage)
- Vaccination coverage generally strongly correlated with mortality
- Malaria burden positively associated
- Strong correlations between related indicators

Strong correlation between many of the indicators.

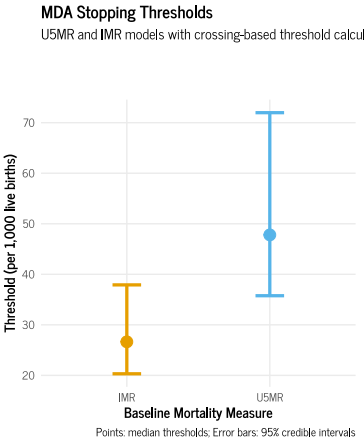
Contextual Heterogeneity: Treatment Interactions

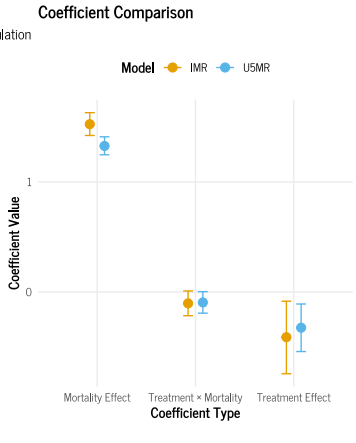


Cessation Thresholds: Main Results

Based on posterior crossings:

- **U5MR:** 47.8 per 1,000 live births (95% CI: 35.8-72.0)
- **IMR:** 26.6 per 1,000 live births (95% CI: 20.3-37.9)
- **Interpretation:** Treatment benefits vanish when mortality falls below these levels

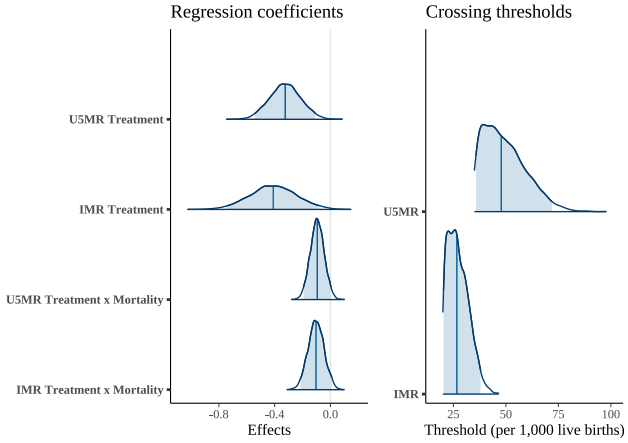




Cessation Thresholds: Model Evidence

Statistical evidence:

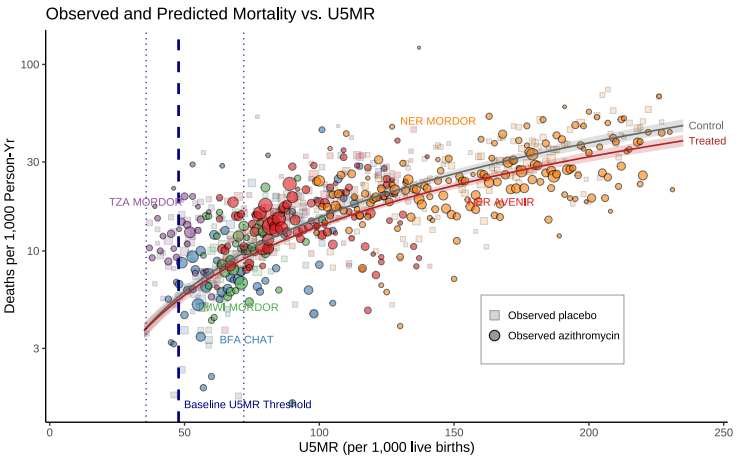
- Clear treatment-mortality interactions
- Negative interaction terms confirm diminishing benefits
- Threshold densities appropriately skewed
- Wider uncertainty in IMR effects



Model Fit: U5MR Predictions

Crossing visualization:

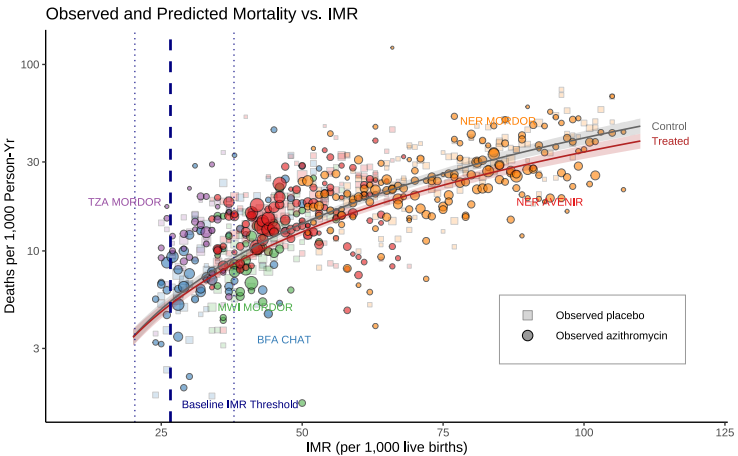
- Thick dashed line: threshold median
- Dotted lines: credible intervals
- Clear convergence of treatment/placebo curves
- Benefits above threshold, minimal below



Model Fit: IMR Predictions

Similar pattern to U5MR:

- Clear treatment-placebo convergence
- Narrower intervals at lower mortality
- Consistent evidence for threshold effects



Sensitivity Analysis: Mathematical Framework

Two approaches to threshold estimation:

1. Analytical Method: From the interaction model: $\log \lambda_i = \alpha + \beta_m U_i + \text{trt}_i(\beta_t + \beta_{mt} U_i)$
Treatment effect becomes zero when: $\beta_t + \beta_{mt} U^* = 0$
Solving: $U^* = -\frac{\beta_t}{\beta_{mt}}$ (threshold on log-mortality scale)

2. Crossing Method: Generate predicted rates on dense mortality grid:

$$\lambda_{\text{placebo}}(U) = \exp(\alpha + \beta_m U)$$
$$\lambda_{\text{treatment}}(U) = \exp(\alpha + \beta_m U + \beta_t + \beta_{mt} U)$$

Find U^* where $\lambda_{\text{treatment}}(U^*) = \lambda_{\text{placebo}}(U^*)$

Both methods: Full posterior uncertainty via MCMC draws

Sensitivity Analysis: Model Scenarios

Comprehensive robustness testing across 8 scenarios:

Stan Models:

- Random Baseline (group-specific)
- Fixed Baseline (pooled)

INLA Models:

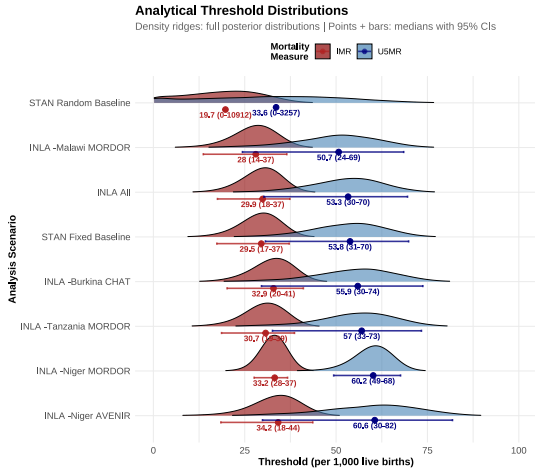
- All trial data
- Sequential exclusions by location

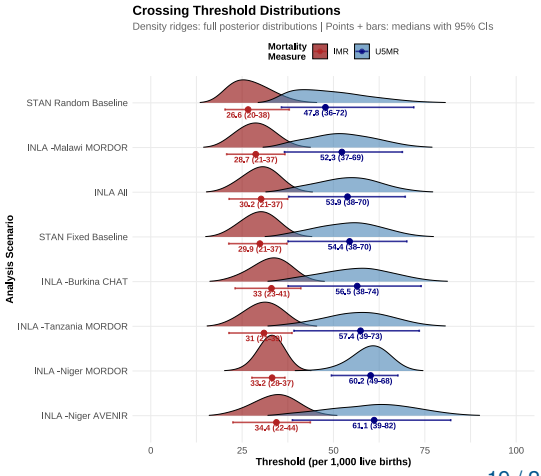
Exclusion Scenarios:

- Niger MORDOR
- Niger AVENIR
- Tanzania MORDOR
- Malawi MORDOR
- Burkina Faso CHAT

Purpose: Test sensitivity to influential sites and modeling assumptions

Ranked Threshold Densities





Sensitivity Analysis: Summary Threshold Distributions

Scenario	U5MR		IMR	
	Analytical	Crossing	Analytical	Crossing
STAN Random Baseline	33.6 (0.0-3257.3)	47.8 (35.8-72.0)	19.7 (0.0-10912.0)	26.6 (20.3-37.9)
STAN Fixed Baseline	53.8 (30.7-69.9)	54.4 (37.6-70.1)	29.5 (17.4-37.2)	29.9 (21.3-37.3)
INLA All	53.3 (30.2-69.6)	53.9 (37.7-69.6)	29.9 (17.5-37.4)	30.2 (21.4-37.5)
INLA -Niger MORDOR	60.2 (49.3-67.6)	60.2 (49.4-67.6)	33.2 (27.6-36.7)	33.2 (27.7-36.7)
INLA -Niger AVENIR	60.6 (29.9-81.9)	61.1 (38.8-82.1)	34.2 (18.5-43.6)	34.4 (22.5-43.7)
INLA -Tanzania MORDOR	57.0 (32.6-73.4)	57.4 (39.2-73.5)	30.7 (18.7-38.6)	31.0 (21.4-38.7)
INLA -Malawi MORDOR	50.7 (24.4-68.5)	52.3 (36.6-68.9)	28.0 (13.7-36.5)	28.7 (20.8-36.7)
INLA -Burkina CHAT	55.9 (29.6-73.7)	56.5 (37.6-74.0)	32.9 (20.2-41.0)	33.0 (23.1-41.1)

- Generally consistent across modeling approaches
- Analytical method unstable for STAN Random baseline (0 denominator)
- Crossing method typically yields slightly higher estimates

Sensitivity Analysis: Robustness Assessment

Model	Method	CV	Range	Assessment
IMR	Analytical	0.153	14.4	Robust
IMR	Crossing	0.083	7.7	Very Robust
U5MR	Analytical	0.162	27.0	Robust
U5MR	Crossing	0.078	13.3	Very Robust

Interpretation: Coefficient of variation (CV) measures relative dispersion across scenarios.

- U5MR estimates: Average CV = 0.120
- IMR estimates: Average CV = 0.118
- CV < 0.2 indicates robust estimates

Sensitivity Analysis: Method Comparison

Analytical vs Crossing:

- U5MR: Crossing 4.3% higher on average
- IMR: Crossing 3.7% higher on average

Convergence diagnostics:

- Stan models: $\hat{R} < 1.01$
- INLA models: Successful approximation
- Effective sample sizes: > 1000

Implications for policy:

- Threshold estimates robust across methods
- Location exclusions show limited impact
- Both analytical approaches converge
- Conservative: Use crossing method upper bounds

Uncertainty sources:

- Sampling uncertainty (MCMC)
- Model specification
- Site heterogeneity

Sensitivity Analysis: Conclusions

Summary of sensitivity analysis:

- U5MR thresholds range: 33.6 - 61.1 per 1,000
- IMR thresholds range: 19.7 - 34.4 per 1,000
- Estimates show good consistency across scenarios
- Method differences are within uncertainty bounds

Most robust estimates:

1. U5MR Crossing method (CV = 0.078)
2. IMR Crossing method (CV = 0.083)

Recommendations:

- Primary analysis provides robust point estimates
- Use sensitivity bounds for conservative planning
- Monitor resistance regardless of threshold approach

Comparison with Current Guidance

	WHO 2020	This Study
IMR threshold	60 per 1,000	26.6 per 1,000 (20.3-37.9)
U5MR threshold	80 per 1,000	47.8 per 1,000 (35.8-72.0)
Basis	Expert opinion	Trial data analysis
Uncertainty	Not quantified	Full posterior distributions

Implications:

- Programs might continue longer than current guidance suggests
- Important caveat: Resistance monitoring remains essential
- Balance mortality benefits with AMR concerns through surveillance

Limitations & Next Steps

Key limitations

- **Context alignment:** Outcomes cannot be perfectly matched with contextual drivers (vaccination, malaria, health systems, nutrition) in space and time.
- **External validity:** Analysis is based on a limited set of trial countries and sample sizes; findings may not generalize directly elsewhere.

Contribution

- **First data-driven** threshold analysis for REACH, with transparent assumptions and full uncertainty quantification.
- **Fully reproducible:**
  `https://github.com/IDM-Wmsemburi/reach-cessation-analysis`

Next steps

- Refine estimates by testing sensitivity to key modeling assumptions (e.g., age-splits, spatial priors, functional form of interactions).