



**IDM**

INSTITUTE FOR  
DISEASE MODELING

PROGRESS IN THE REACH SECONDARY ANALYSES

2025

**Gates Foundation**

# Outline

Introduction

Methods

Results

Sensitivity analysis

Discussion

# 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):**  $\text{IMR} \geq 60/1,000$  or  $\text{U5MR} \geq 80/1,000$  - 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:

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

- ▶ 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:

$$\log E[y_c] = \alpha_g + \log E_c$$

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 ( $\mu_g$ ) 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):

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

- ▶ 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:

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

where:

$y_i$  observed deaths in cluster  $i$

$t_i$  person-time (exposure offset)

$\text{trt}_i$  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
<b>Total</b>		<b>3,954</b>	<b>1.63M</b>	<b>11,580</b>	<b>794,318</b>

**Coverage:** Ages 1-59 months across diverse epidemiological contexts

**Validation:** Denominators match original trial publications

# Baseline Mortality Patterns

## Spatial Model

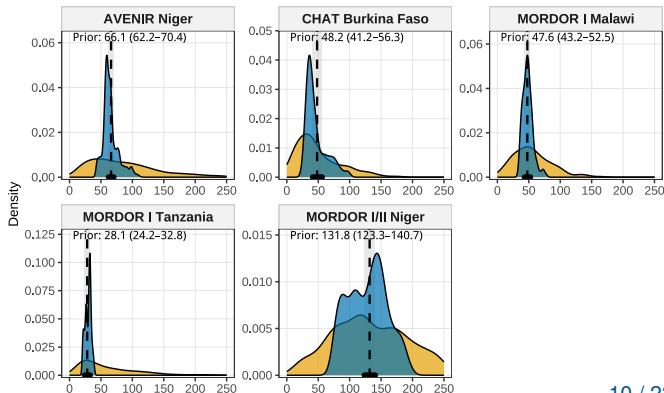
$$\mu_i = 1000 \times (1 - \exp(-H_{i,1}^{59})):$$

- ▶ **Observed data:** raw cluster estimates (placebo)
- ▶ **Posterior:** cluster posterior means
- ▶ **Prior:** trial–country prior (shaded band) with dashed prior mean (text labels also prior mean and 95% CI)

### Observed Data vs Model Posterior

Grey area and dashed line show prior distribution

■ Observed data ■ Model posterior



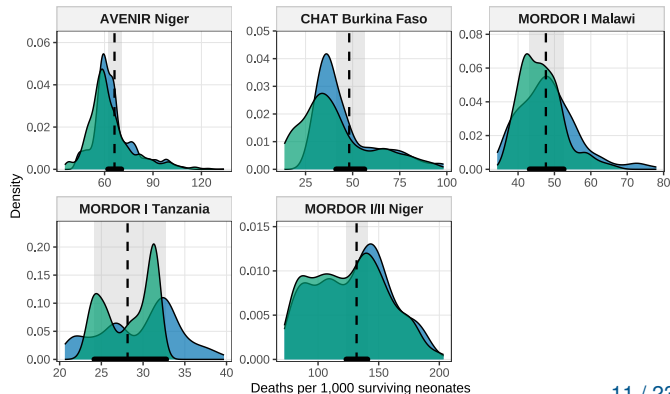
# Validating HSGP + HS using SPDE

- ▶ **SPDE posteriors** closely overlap **HSGP + HS**
- ▶ Both recover similar distributional shapes across clusters
- ▶ Independent approximation (mesh vs. basis) → cross-check
- ▶ Agreement confirms robustness of mortality estimates

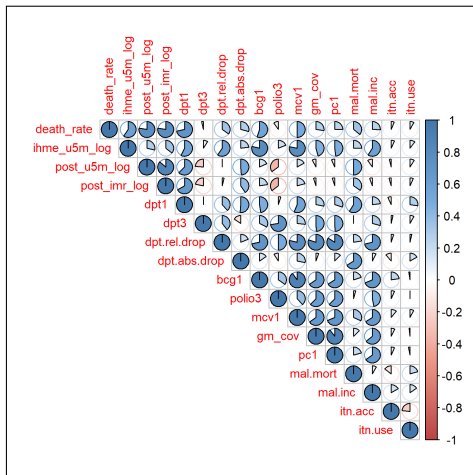
## Model Posterior vs SPDE Method

Grey area and dashed line show prior distribution

■ Model posterior ■ SPDE comparison



# Contextual Heterogeneity: Correlations




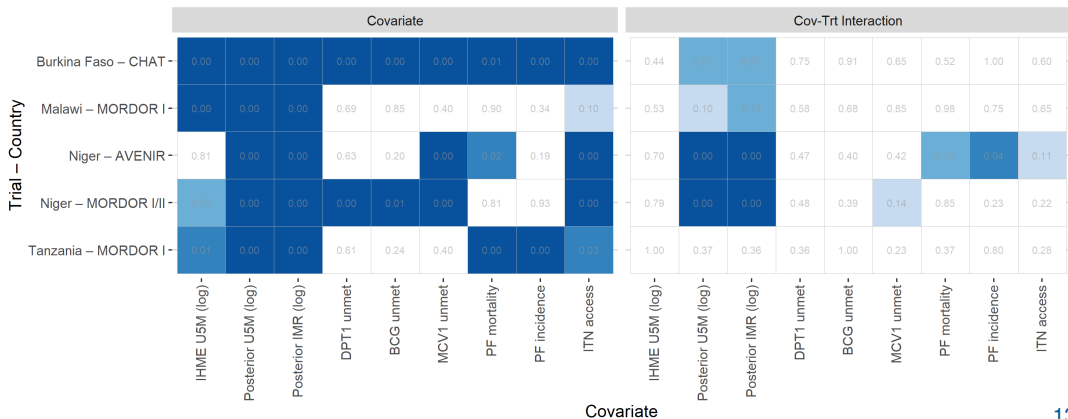
- ▶ Immunization variables use vaccination gap (1 - coverage)
- ▶ Vaccination coverage generally strongly correlated with mortality
- ▶ Malaria burden positively associated
- ▶ Strong correlations between related indicators

Strong correlation between many of the indicators.

# Contextual Heterogeneity: Treatment Interactions

Statistical Significance by Covariate

P-value  <0.01 <0.05 <0.10 <0.15 ≥0.15



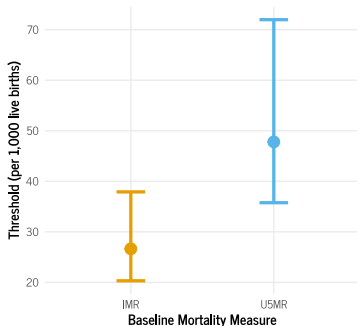
# Cessation Thresholds: Main Results

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

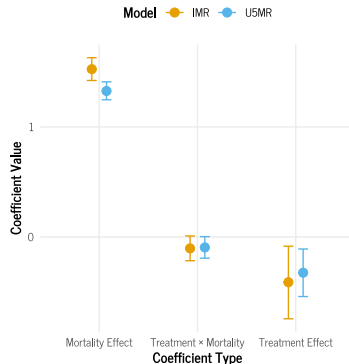
## MDA Stopping Thresholds

U5MR and IMR models with crossing-based threshold calculation



Points: median thresholds; Error bars: 95% credible intervals

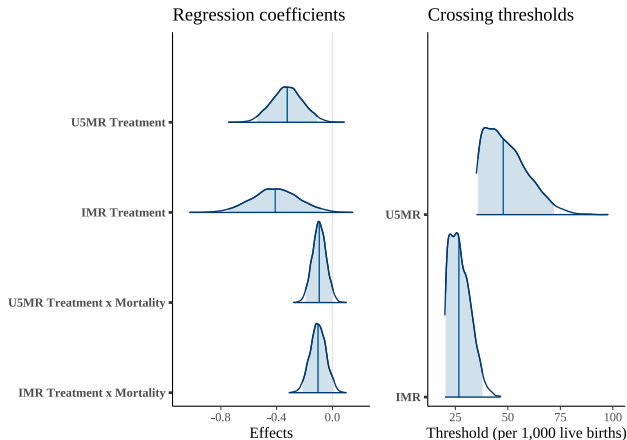
## Coefficient Comparison



# 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

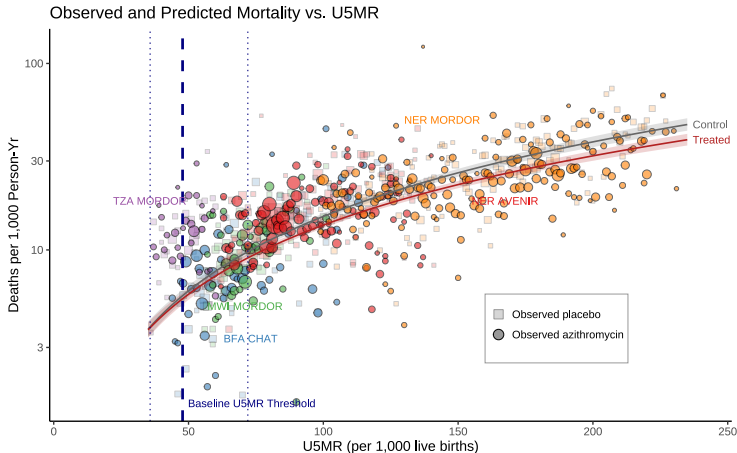




# Model Fit: U5MR Predictions

## Crossing visualization:

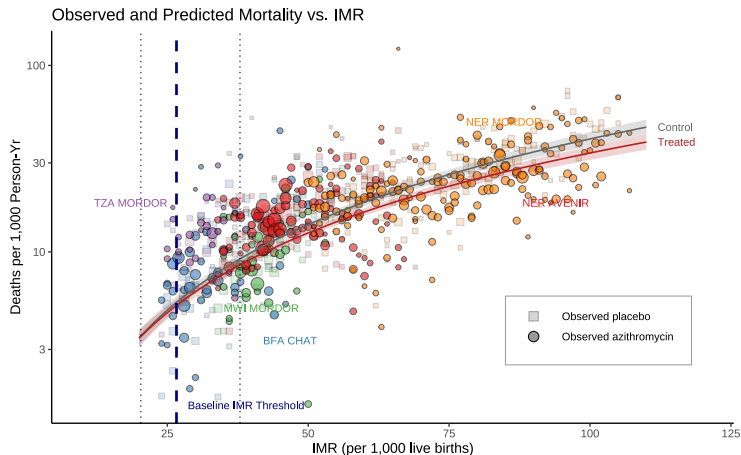
- ▶ Thick dashed line: threshold median
- ▶ Dotted lines: credible intervals
- ▶ Clear convergence of treatment/placebo curves
- ▶ Benefits above threshold, minimal below



# 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

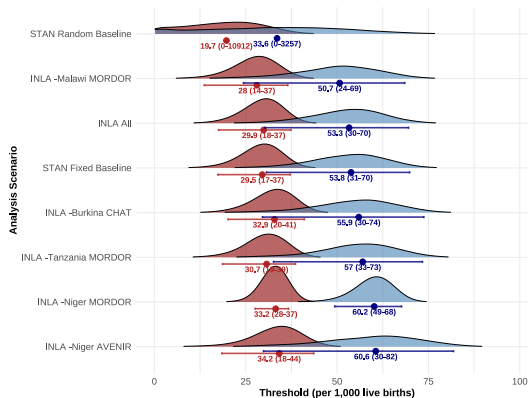
**Purpose:** Test sensitivity to influential sites and modeling assumptions

# Ranked Threshold Densities

## Analytical Threshold Distributions

Density ridges: full posterior distributions | Points + bars: medians with 95% CIs

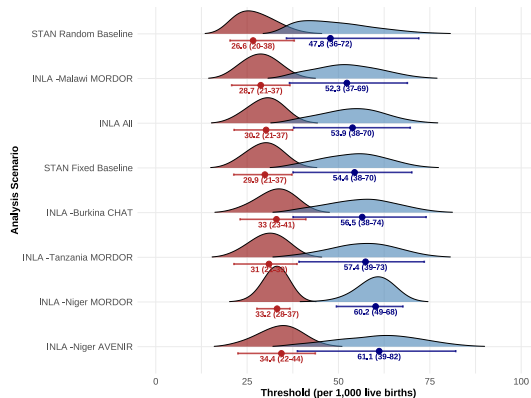
Mortality Measure IMR USMR



## Crossing Threshold Distributions

Density ridges: full posterior distributions | Points + bars: medians with 95% CIs

Mortality Measure IMR USMR



# 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

## 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).