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The Burden and Trend of Typhoid Fever in Low- and Middle-Income Countries: An Updated Meta-Regression Approach

13th International Conference on Typhoid and Other Invasive Salmonelloses, Kigali, Rwanda

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w/ Marina Antillon, Ottavia Prunas, Virginia Pitzer

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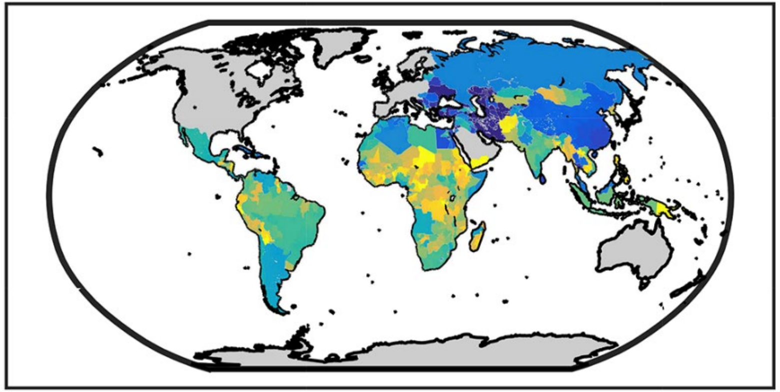
Previous efforts to model typhoid burden

RESEARCH ARTICLE

The burden of typhoid fever in low- and middle-income countries: A meta-regression approach

Marina Antillón[1]*, Joshua L. Warren[2], Forrest W. Crawford[2], Daniel M. Weinberger[1], Esra Kürüm[3], Gi Deok Pak[4], Florian Marks[4], Virginia E. Pitzer[1]



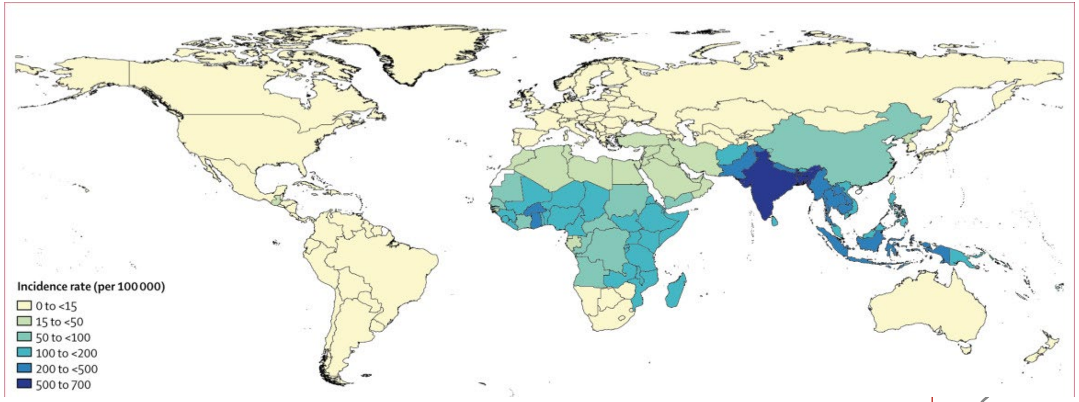
Emerg Infect Dis. 2003 May;9(5):539-44. doi: 10.3201/eid0905.020428.

Estimating the incidence of typhoid fever and other febrile illnesses in developing countries

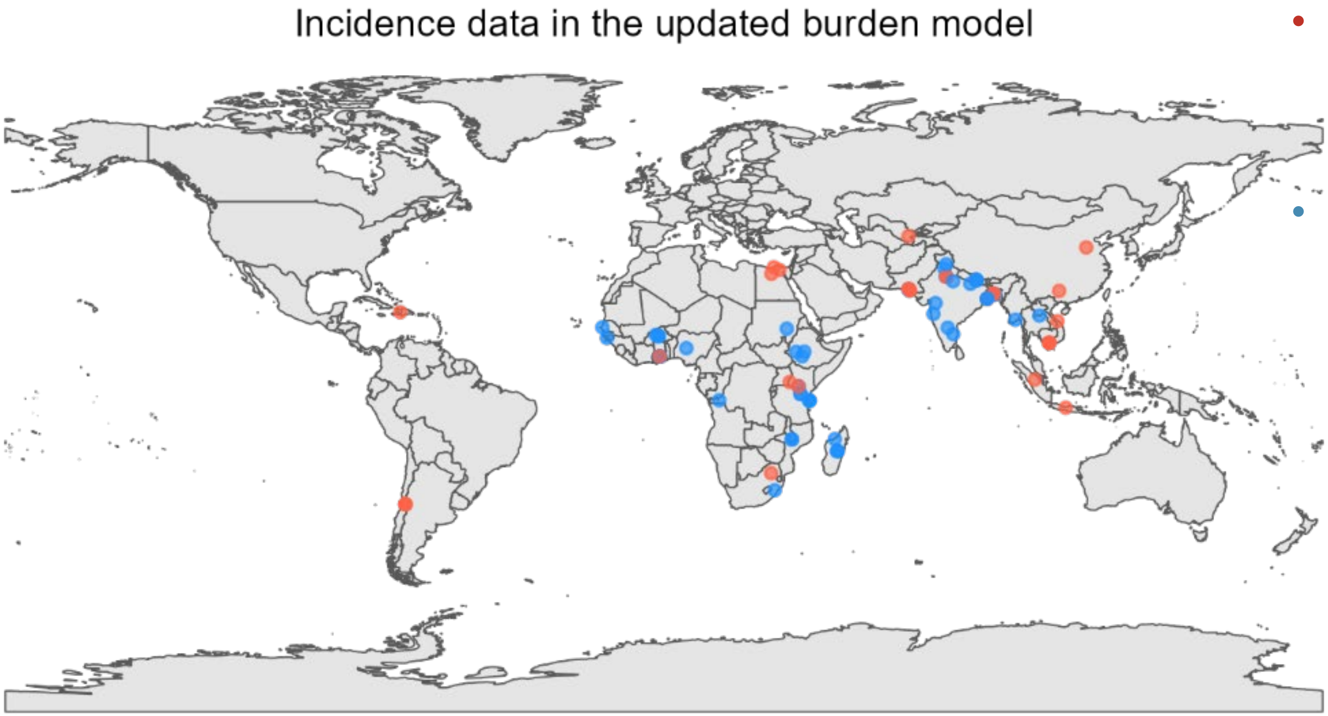
John A Crump [1], Fouad G Youssef, Stephen P Luby, Momtaz O Wasfy, Josefa M Rangel, Maha Taalat, Said A Oun, Frank J Mahoney

The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017

GBD 2017 Typhoid and Paratyphoid Collaborators † • Show footnotes

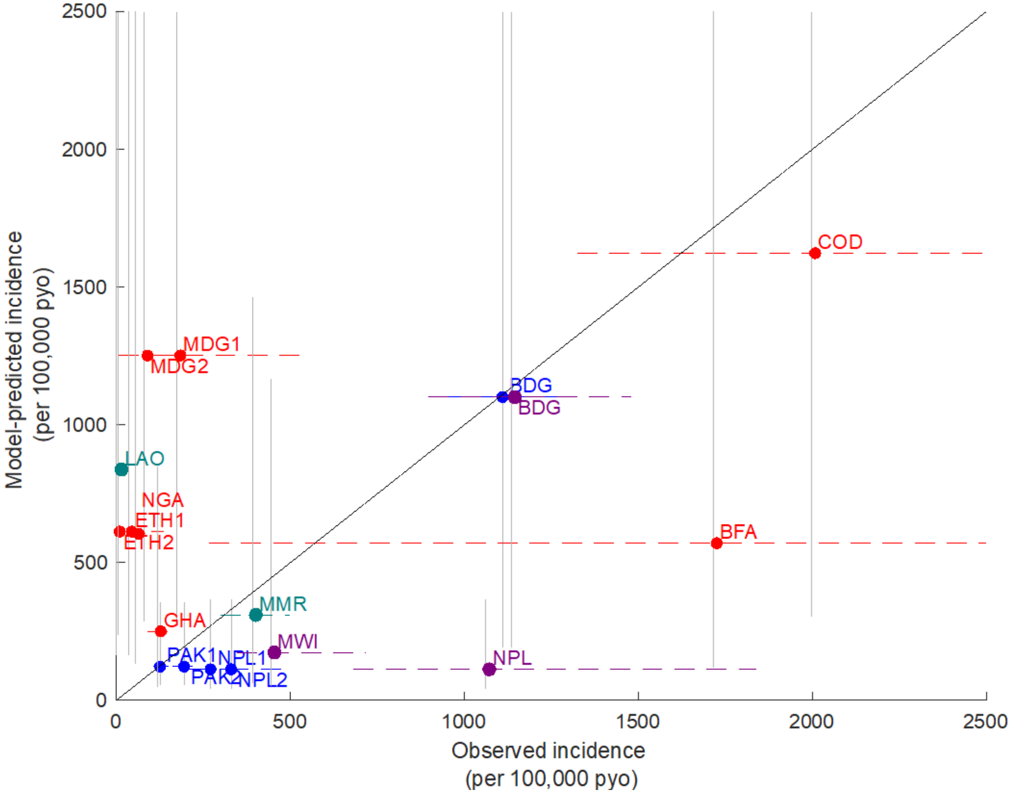


Additional population-based studies of typhoid fever



- Studies in previous model (published 1980-2013) (32 studies, 22 locations)
- Studies in new model (published 1980-2021) (43 studies, 60 locations)

Comparison to most recent incidence data



- SEAP
- SETA
- STRATAA
- Lao PDR & Myanmar

Objective

- Interpolate data from incidence studies (overall and for specific age-groups) to predict typhoid incidence at the national level, particularly for countries where no blood-culture-confirmed incidence evidence is available.
  - All LICs, LMICs, and UMICs – 145 countries
- Explore ways to estimate subnational variation in typhoid incidence
- Quantify uncertainty
  - It may not be necessary (or possible) to have a precise estimate of incidence, but knowing whether incidence is likely to be **low (<10 per 100K person-years)**, **medium (10-100 per 100K person-years**), **high** (**100-500 per 100K person-years**), or **very high (>500 per 100K person-years**) is important for informing policy decisions

Approach

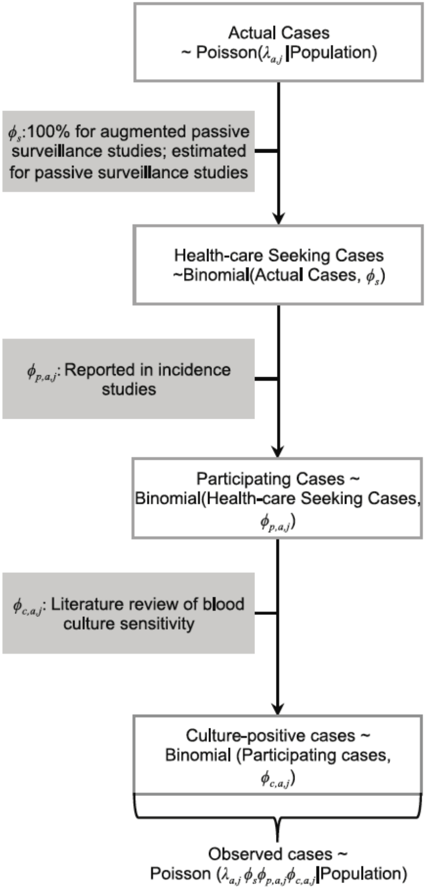
Data

- Population-based incidence studies with blood-culture confirmed cases
- Age groups noted: overall incidence, 0-2, 2-5, 5-15, 15+ years, or any combination of these
- Contextual information: catchment population, % individuals enrolled, blood culture volume collected.
- Widely available economic, environmental, and demographic covariates, which we map to the location of the study.

Methods

- Statistical model
- Bayesian approach to account for all sources of uncertainty.
- Using adjusted reported incidence from studies that report it

Adjustments to crude incidence data



Adjusted ”true” typhoid fever incidence

Adjustment for healthcare seeking (assumed to be 100% for active surveillance studies, estimated for passive surveillance studies)

Cases who sought care for fever at study facilities

Adjustment for proportion who met fever criteria who were enrolled

Cases who were enrolled and had blood collected for culturing

Adjustment for blood culture sensitivity (by age group)

Observed blood-culture-confirmed cases and person-time under surveillance

Antillon et al, *PLoS NTD* (2017)

Predictors included

Covariate	Resolution	Mean and range in estimation sample	Source
Population density	1/4x1/4 degree	3,643 (0-18,467)	NASA SEDAC
GDP per capita PPP, 2015 USD	1/12x1/12 degree	6,709 (736-37772)	Aalto University
Gini coefficient	Subnational	0.193 (0.024-0.638)	Global Data Lab
Access to piped water	Subnational	50.31 (0-100)	Global Data Lab
Open defecation	National	13.15 (1.02-68.10)	WHO JMP
% roads paved	National	39.31 (3.5-100)	International Roads Federation + WBDI
Prevalence of stunting	Subnational	23.94 (0-69.10)	Global Data Lab
Mean years of education, women	Subnational	6.55 (0.10-14.27)	Global Data Lab
HIV prevalence	National	1.96 (0.1-28.6)	World Bank
International Wealth Index <50 (% people)	Subnational	59.62 (6.27-95.31)	Global Data Lab
Low/high rainfall (binary variable)	2.5x2.5 degree	Low~10.35% High~8.11%	Global Precipitation Climatology Project (GPCP)

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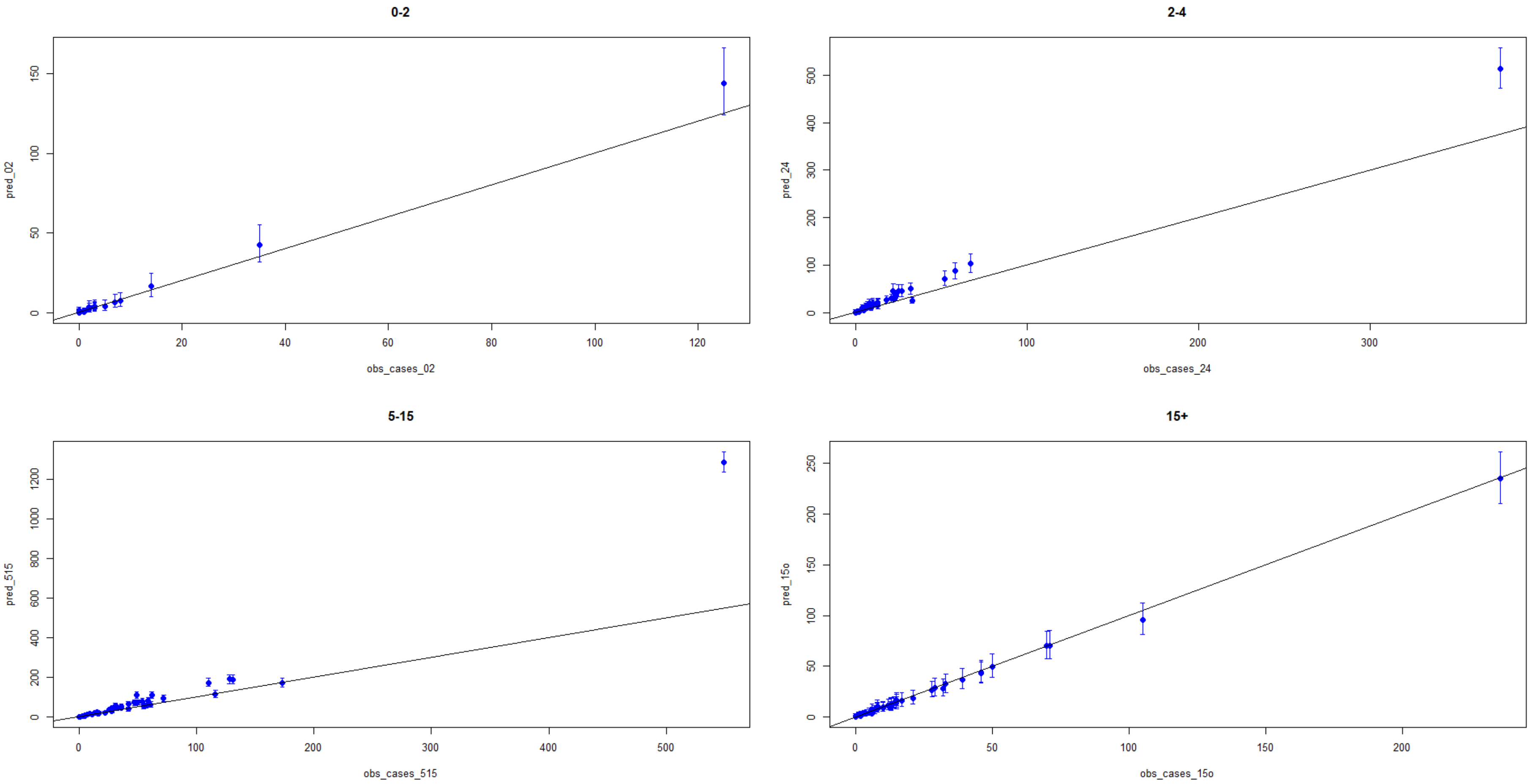
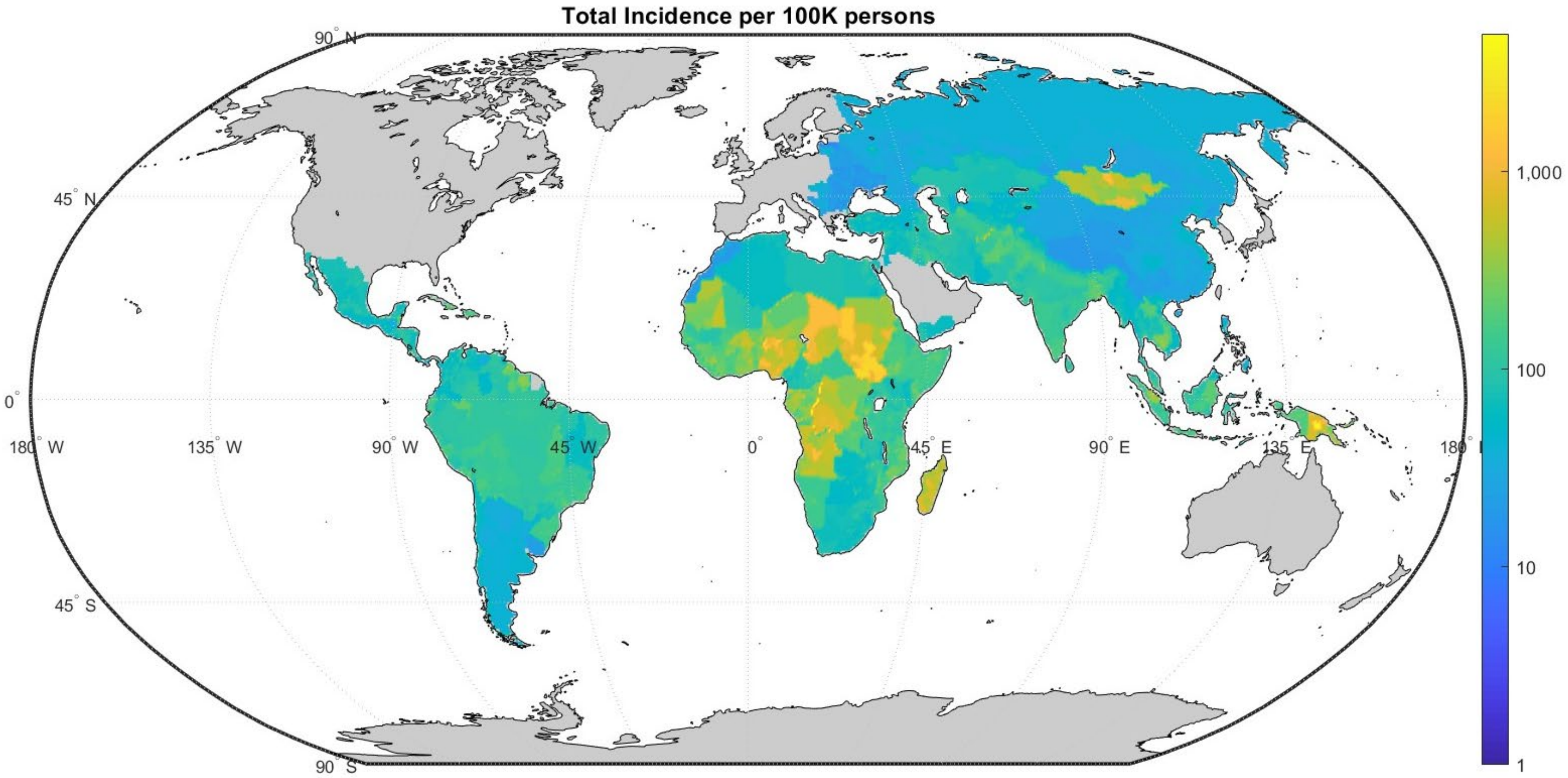
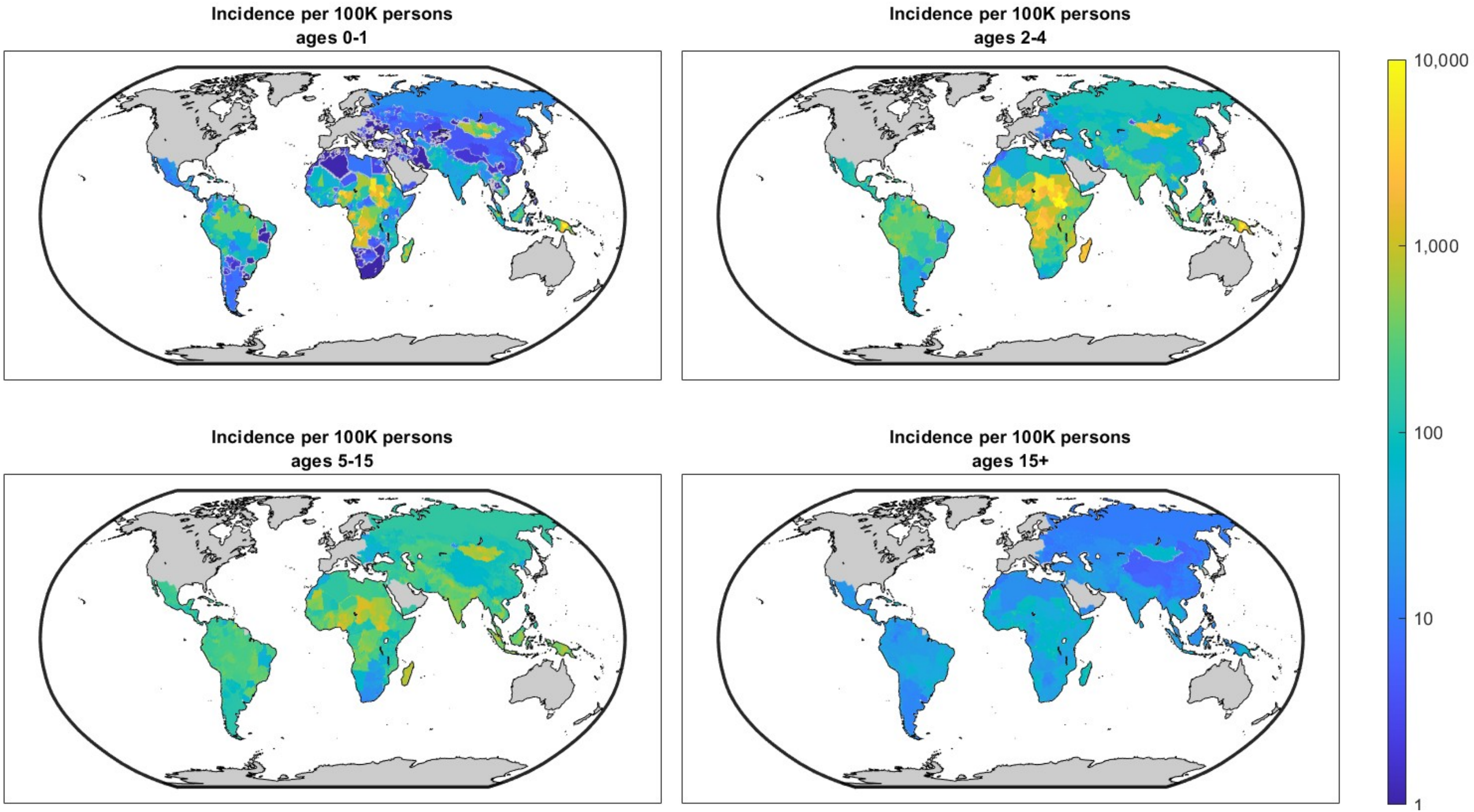
Model fit


0-2
pred_02
obs_cases_02
0
20
40
60
80
100
120
0
50
100
150
2-4
pred_24
obs_cases_24
0
100
200
300
0
100
200
300
400
500
5-15
pred_515
obs_cases_515
0
100
200
300
400
500
0
200
400
600
800
1000
1200
15+
pred_15o
obs_cases_15o
0
50
100
150
200
0
50
100
150
200
250

Global burden of typhoid fever: 19.3 million cases, 90% CI (6.5-64.2M)



Age-specific incidence



Work in progress, future directions

Ongoing efforts

- Further assessing model convergence
- Consider additional covariates and/or spatial random effects
- Potentially include serosurveillance data

Beyond scope

- Antibiotic resistance
- Additional outcomes: hospitalizations, complications, etc
- Typhoid fever as a proportion of all fevers, enteric infections, etc.
- Asymptomatic/subclinical infection

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Thank you!

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Yale SCHOOL OF PUBLIC HEALTH

TyVAC Typhoid Vaccine Acceleration Consortium

BILL & MELINDA GATES foundation

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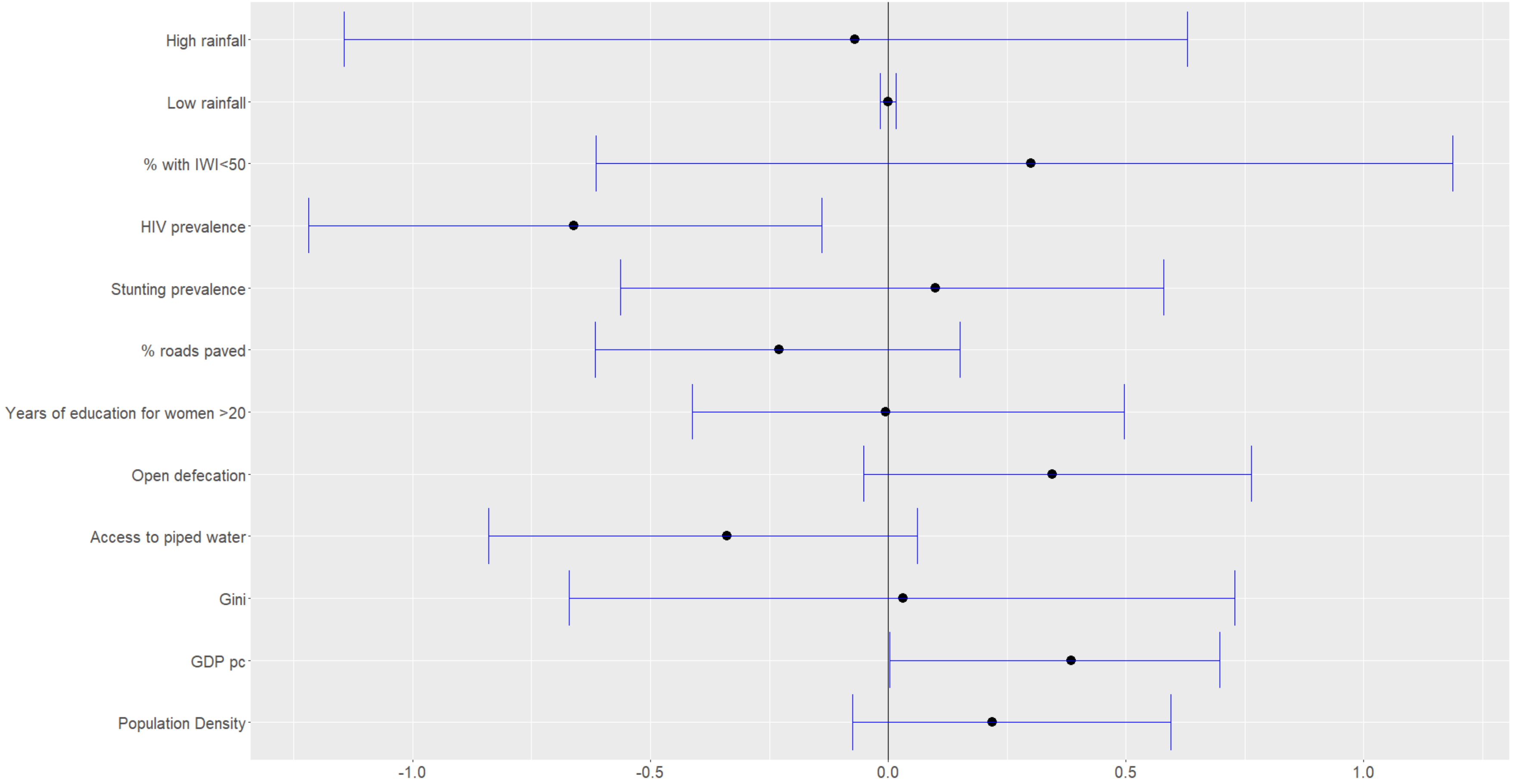
Appendix

Predictors of typhoid incidence



Model details

- Generalized linear mixed-effects model
  - **Age-group** and **location-specific** incidence modeled as a function of predictor variables and random effects

$$\text{Actual Cases}_{a,j} \sim \text{Poisson}(\lambda_{a,j} | \text{person-time}_{a,j})$$

$$\log(\lambda_{a,j}) = B_{0,j} + B_{a,j} + \log(\text{person-time}_{a,j})$$

Incidence in reference age group (5-15 yo)

IRR for other age groups vs reference

Intercept: Overall incidence

$$B_{0,j} = \beta_0 + \gamma X_j + \alpha_{0,j}$$

Slope: Relative incidence for age group *a*

$$B_{a,j} = \beta_a + \eta_a X_j + \alpha_{a,j}$$

random effects

Covariates

Probability of categories of overall incidence