THE LANCET **Global Health**

Supplementary appendix

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Supplement to: Sbarra AN, Mosser JF, Jit M, et al. Estimating national-level measles case–fatality ratios in low-income and middle-income countries: an updated systematic review and modelling study. *Lancet Glob Health* 2023; **11:** e516–24.

Supplementary Information: Estimating national-level measles case fatality ratios in low- and middle-income countries: an updated systematic review and modelling study

Section 1. Covariate selection via statistical analysis

Section 1.1. Rationale for covariate inclusion

We selected covariates for the remainder of this analysis based on a previous publication that used expert consultation to develop a conceptual framework of mechanisms related to measles CFR and literature review to assess the body of evidence related to population-level factors associated with these mechanisms.

Covariates associated with the underlying mechanism of health care access and care seeking were maternal education, mortality rate due to war and terrorism, and proportion living in urban settings. Each of these individual covariates contribute to the ability for persons to access health care as well as might influence behavior contributing to the decision to seek care, ultimately leading to higher CFR if care is not sought or accessed.

Covariates associated with the underlying mechanism of health care quality were under-5 mortality rate and GDP per capita. Higher under-5 mortality rates or lower GDP per capita might be associated with lower health care quality which might be related to higher CFR.

Covariates associated with the underlying mechanism of risk of secondary infection were HIV prevalence and total fertility rate (TFR). Based on the risk of secondary infection associated with higher HIV prevalence or TFR, CFR might be higher.

Covariates associated with the underlying mechanism of nutritional status were vitamin A deficiency prevalence and wasting prevalence. Higher vitamin A deficiency prevalence or wasting prevalence could be associated with higher CFR.

Covariates associated with the underlying mechanism of general measles control and epidemiology were MCV1 and MCV2 coverage. Lower MCV1 or MCV2 coverage values could be associated with higher CFR.

Section 1.2. Additional details on covariate interpolation

The following covariate sets did not require interpolation or use of regional values: education, maternal education, war rate due to mortality and terrorism, health access and quality index, universal health coverage, sociodemographic index, stunting prevalence, wasting prevalence, underweight prevalence, vitamin A deficiency prevalence, HIV prevalence, and MCV2 coverage. For 12 countries, we interpolated covariate values for GDP per capita; we also used regional values in 23 countries. For 7 countries, we interpolated covariate values for under-5 mortality rate; we also used regional values in 2 countries. We used regional covariate values in 6 countries for total fertility rate. We used regional covariate values in 14 countries for MCV1 coverage. For 1 country, we interpolated covariate values for proportion living in urban settings; we also used regional values in 2 countries.

Section 1.3. Test for collinearity per underlying mechanism

For the underlying mechanism of "health care access and care seeking", we tested covariate sets for education, maternal education, proportion living in an urban setting, and mortality rate due to war and terrorism. Education was correlated with maternal education; correlation coefficients shown below. As education was more correlated with the other covariates relative to maternal education, it was removed from further analysis. Covariates moving on to the second step of data analysis for the "health care access and care seeking" mechanism were: maternal education, proportion living in an urban setting, and mortality rate due to war and terrorism.

For the underlying mechanism of "health care quality", we tested covariate sets for under-5 mortality rate, health access and quality index, universal health coverage, GDP per capita, and sociodemographic index. Under-5 mortality rate, health access and quality index, universal health coverage and sociodemographic index were all correlated with each other; correlation coefficients shown below. Health access and quality index, universal health coverage, and sociodemographic index were more correlated with the other covariates relative to under-5 mortality rate, and so they were removed from further analysis. Covariates moving on to the second step of data analysis for the "health care quality" mechanism were: under-5 mortality rate, and GDP per capita.

For the underlying mechanism of "nutritional status", we tested covariate sets for stunting prevalence, wasting prevalence, underweight prevalence, and vitamin A deficiency prevalence. Stunting prevalence, underweight prevalence, and wasting prevalence were correlated with each other; correlation coefficients shown below. Stunting prevalence, and underweight prevalence were more correlated with the other covariates relative to wasting prevalence, and so they were removed from further analysis. Covariates moving on to the second step of data analysis for the "nutritional status" mechanism were: wasting prevalence and vitamin A deficiency prevalence.

For the underlying mechanism of "risk of secondary infection", we tested covariate sets for HIV prevalence and total fertility rate. The covariates were not correlated with each other; correlation coefficient shown below. Both covariates moved on to the second step of data analysis for the "risk of secondary infection" mechanism.

For the underlying mechanism of "measles control and epidemiology", we tested covariate sets for MCV1 and MCV2 coverage. The covariates were not correlated with each other; correlation coefficient shown below. Both covariates moved on to the second step of data analysis for the "measles control and epidemiology" mechanism.

Section 1.4. Test for predictive capacity per underlying mechanism

For the mechanism of "health care access and care seeking", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (maternal education, proportion living in urban setting, and mortality rate due to war and terrorism) were kept as covariate sets for the remainder of the analysis.

For the mechanism of "health care quality", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (under-5 mortality rate and GDP per capita) were kept as covariate sets for the remainder of the analysis.

For the mechanism of "nutritional status", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (wasting prevalence and vitamin A deficiency prevalence) were kept as covariate sets for the remainder of the analysis.

For the mechanism of "risk of secondary infection", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (HIV prevalence and total fertility rate) were kept as covariate sets for the remainder of the analysis.

For the mechanism of "measles control and epidemiology", MCV2 coverage had a p-value greater than 0.3 (see below). Therefore, MCV1 coverage was the only covariate sets kept for the remainder of the analysis.

Section 2. Model selection

Section 2.1. First stage model with age granular data

We analyzed the relationship between age and CFR in reported studies with age-specific data both with and without controlling for other covariates. There was a consistent relationship between covariate values and CFR values, particularly for measles incidence and MCV1 coverage (Supplementary Figures 5-6). Taken together, these suggested that the relationship between age and CFR was confounded by these other covariates, and therefore we elected to adjust for other covariates in our first-stage model.

Section 2.2. Knot selection

We ran both first and second stage models with both 4 knots (with 2 internal) and 5 knots (with 3 internal) placed uniformly on data density and selected the best performing model based on the lowest Akaike information criterion (AIC) score among results from the second stage model. This process selected the model with 5 knots (AIC: 174907) instead of 4 knots (AIC: 175086).

Section 2.3. Inclusion of random effects

We additionally tested the inclusion of random effects in our second stage model, by testing a random effect placed on each study. This approach caused the coefficient for the community versus hospitalsetting indicator to become 0, with a non-significant p-value (p-value=1). Because we know these sets of studies (i.e. those from community-based settings and those from hospital-based settings) were collected from different underlying populations with known difference in measles severity, we elected to use a model without the inclusion of random effects.

Section 3. Final covariate processing and model structure

For covariates requiring interpolation, we used the following formula:

$$
y = y_1 + \frac{(x - x_1)(y_2 - y_1)}{(x_2 - x_1)}
$$

Following transformation, covariates were standardized as follows such that μ represents the mean transformed covariate value and σ represents the standard deviation of the transformed covariate value:

standardized covariate =
$$
\frac{transformed covariate - \mu}{\sigma}
$$

Our final first stage CFR model (that only uses age specific input data) follows the following structure. Using transformed and standardized covariate values for each study midpoint year, we fit a Bayesian fixed-effects meta-regression model¹ with the outcome variable of the logit of CFR. We computed standard error in logit space per study using the delta transformation and used these values as weights in the meta-regression. Before transforming to logit space, CFR ratios equalling 0 were offset to 0.0002202378 and ratios equal to 1 were offset to 0.9999999999999.

Our regression equation is as follows:

$$
y_i = X_i(\beta) + \epsilon_i
$$

$$
\epsilon_i \sim N(0, \Lambda)
$$

where y_i is the vector of observations of logit of CFR from the i^{th} study, X_i is a vector of covariates paired with each data observation, β are regression coefficients (β _{community} indicator, β incidence,

 β mortality rate due to war and terrorism, β maternal education, β GDP per capita, β HIV prevalence,

 β MCV1 coverage, β total fertility rate, β under 5 mortality rate, β proportion living in urban setting, β vitamin A deficiency prevalence, β wasting prevalence, β_{age}), and ϵ_i are measurement errors with a given covariance Λ. For age, our β coefficient is represented as a function f representing a quadratic spline with 5 knots (3 internal) placed uniformly based on data density at locations 0, 0.68, 1.31, 3.83 and 34 years. This can be represented via the following generalized equation for each data interval i :

$$
s_i(x) = a_i x^2 + b_i x + c_i
$$

For $x \in [x_i, x_{i+1}]$ and $i = 1, 2, ..., n - 1$. Data intervals are based on knot locations. Additionally, we included a prior to ensure a right linear tail on our quadratic spline function.

Our final second stage model (that uses all data) is as follows. Model specifications are identical to the first stage as previously defined, except with the following additional priors:

> β community indicator ~ Unif orm $(-\infty, 0)$ $\beta_{incidence} \sim Uniform(0, \infty)$ β mortality rate due to war and terrorism $\sim Uniform(0,\infty)$ $\beta_{material \ education} \sim Uniform(-\infty, 0)$ $\beta_{GDP\,per\,cap} \sim Uniform(-\infty,0)$ $\beta_{HIV\ prevalence} \sim Uniform(0, \infty)$ $\beta_{MCV1\ coverage} \sim Uniform(-\infty, 0)$ $\beta_{total\,fertility\,rate} \sim Uniform(0, \infty)$ $\beta_{under 5 mortality\ rate} \sim Uniform(0, \infty)$ β proportion living in urban setting ~ Unif orm $(0, \infty)$ $\beta_{vitamin}$ A deficiency prevalence $\sim Uniform(0, \infty)$ $\beta_{wasting\,prevalence} \sim Uniform(0, \infty)$

Priors in this work were only used to impose directionality on covariates, such that the direction of association estimated was consistent with the observed relationship in the literature identified by previous literature review.² Therefore, we did not update the priors at any point in this analysis as these directions of association are fixed.

Following our first-stage model, we used the following method to age-split our input data that was reported from sources in age groups wider than 1 year. For the given age range, we computed the proportion of cases for each single age year within the age range given overall age incidence. We then split the number of reported cases per study based on those proportions to generate single age year specific case counts.

Using the total number of deaths reported in the study for the entire age range, we then used the following algorithm:

$$
X = \frac{D}{\sum_{a=b}^{B}(C_{a} * R_{a})}
$$

, where D was the total number of deaths reported for the age range per study, was the total number of C_a is the number of age-split cases per age a , and R_a was the reference proportion which was calculated taking the ratio of predicted age specific CFR from our first stage-model relative to the CFR among 0 year-olds CFR_a/C_0 . Then, we use the following to compute our adjusted CFR ($aCFR$) and adjusted number of deaths (aD_a) per single age year a to use as input data in our model:

$$
aCFR_a = X * R_a
$$

$$
aD_{a} = aCFR_a * C_a
$$

We then use our second stage model (similar in specifications) to produce final estimates of age-, year-, and location-specific CFR using our age-split input data.

In model fitting, we use linear point optimization via cyipopt³ described in detail in the technical d ocumentation¹ to the methods used in this paper. Therefore, as MCMC or another sampling algorithm was not used, a burn-in period was not applicable to our analysis. Since we used a numerical optimization technique¹ to fit our model, we do not need to perform replication tests as would be needed to assess stability from a model fit using MCMC. We generated 1000 posterior samples to allow for robust calculations for various uncertainty intervals. We calculated 95% uncertainty intervals (UI) for all estimates.

Section 4. Decomposition analysis for validating changes to model structure, covariates, and input data

To increase the robustness and rigor of measles CFR modeling, we considered various updates to the model structure, covariates, and input data sources relative to the model previously published by Portnoy et al.4 With updates to each component (model structure, covariates, and input data), we tracked the overall change in model performance to ensure updates were statistically beneficial in the estimation of measles CFR. Specific steps and validation at each step are described in each subsequent section.

Section 4.1. First stage, updates to model structure

We made the following sequential adaptations to the log-linear model published previously:

- Model 0: Generalized linear model, with log link and cases as weights
- Model 1.A: Generalized linear model, with log(CFR) as outcome and cases as weights
- Model 1.B: Generalized linear model, with logit(CFR) as outcome and cases as weights
- Model 1.C: Bayesian meta-regression, with logit (CFR) as outcome and standard error as weights

The structure of Model 0 is identical to the model previously published⁴, and serves as our baseline. In order to more accurately represent CFR as a ratio bounded between 0 and 1, we first removed the log link from the model and instead log (Model 1.A) then logit (Model 1.B) transformed CFR as our outcome. In order to best capture the underlying uncertainty from the data, we then implemented a Bayesian metaregression framework using standard errors as weights (Model 1.C). We compared both in- and out-ofsample validation for each model iteration. Model 1.C performed best among both in- and out-of-sample validation exercises across metrics (Supplementary Tables 8-9) yielding generally lower root mean squared error (RMSE), mean error and man absolute error and higher correlation.

Section 4.2. Second stage, updates to covariates

We made the following sequential adaptations to the best model (previously referred to as Model 1.C) from our first decomposition step:

- Model 1: Previously described Model 1.C with original covariates and original data inputs
- Model 2: Previously described Model 1.C with updated covariates and original data inputs

We compared the best model using original covariates and data inputs to a new model fit using the updated covariate set. We compared the performance of these two models to the original model version (Model 0) in Supplementary Tables 10-11. Model 2 performed best across most in- and out-of-sample validation metrics yielding generally lower root mean squared error (RMSE), mean error and mean absolute error and higher correlation.

Section 4.3. Third stage, updates to input data sources

We made the following sequential adaptations to the best model from our second decomposition step updates:

- Model 2: Previously described Model 1.C with updated covariates and original data inputs
- Model 3: Previously described Model 1.C with updated covariates and updated data inputs

There were 40 additional new studies added across 21 additional countries. Because the input data sources were changing, we did not compare validation metrics to previous decomposition steps. Full model validation can be found in Supplementary Tables 12-13.

The mean predicted CFR from 1990 to 2015 in the previously published model was 1.5% (95% confidence interval (CI): $0.5 - 3.1\%$) in community-based settings and 2.9% (95% CI: $0.9 - 6.0\%$) in hospital-based settings. Our findings had a mean case-weighted CFR from 1990 to 2015 of 2.2% (95% uncertainty interval (UI): 2.1 – 2.2%) in community-based settings and in 8.4% (95% uncertainty interval (UI): $8.1 - 8.8\%$) in hospital-based settings.

Section 5. Supplementary Results

Section 5.1. Age-standardized results

Because the age distribution of cases within a country impacts the ability to compare trends across locations, we also computed country-specific age-standardized CFRs using a reference population of the global age pattern of cases from 1990 as well as the general population age distribution from the UN in 1990 (Supplementary Figure 8). Age-standardized estimates of CFR allow users to more directly compare estimates across locations and years.

Section 5.2. Sensitivity analyses

We ran sensitivity analyses to investigate the implications of using all studies regardless of if they provided information on laboratory confirmation of cases or a definition of a death attributable to measles. Generally, studies that reported information on laboratory confirmation of cases were from countries and years with lower measles incidence, higher MCV1 coverage, and lower CFRs relative to studies that did not report information on laboratory confirmation (Supplementary Figures 10-11). In a sensitivity analysis excluding first studies without information on laboratory confirmation of cases, we were estimated systematically lower CFRs than when including all studies in our model (Supplementary Figures 13).

Additionally, studies reporting definitions of deaths attributable to measles were most often from hospital-based settings rather than community-based settings (Chi-squared p-value < 0.0001). When excluding studies without information on a death definition, we also estimated systematically lower CFRs than when including all studies in our model (Supplementary Figures 14).

Section 5. Supplementary Tables

Supplementary Table 1. GATHER compliance checklist.

Supplementary Table 2. PRISMA compliance checklist.

Supplementary Table 3. PRISMA abstract compliance checklist.

Supplementary Table 4. Input data sources for final model.

Supplementary Table 5. Proxy covariate sets used for analysis.

Supplementary Table 6. Covariate set values by country in 2019.

Supplementary Table 8. In-sample validation metrics from first stage decomposition analysis.

Supplementary Table 9. Out-of-sample validation metrics from first stage decomposition analysis.

Supplementary Table 10. In-sample validation metrics from second stage decomposition analysis.

Supplementary Table 11. Out-of-sample validation metrics from first and second stage decomposition analysis.

Supplementary Table 12. In-sample (IS) and out-of-sample (OOS) validation metrics from final model using age split input data for comparison.

Supplementary Table 13. In-sample (IS) and out-of-sample (OOS) validation metrics from final model using original (pre-age split) data for comparison.

Supplementary Table 14. Age-specific CFR by region in 2019.

Section 7. Supplementary Figures

Supplementary Figure 2. Recent data available by country.

For countries with data available, year of most recent data available by country shown in map.

Supplementary Figure 3. Relative age pattern from first-stage model with 4 knots (with 2 internal).

Supplementary Figure 4. Relative age pattern from first-stage model with 5 knots (with 3 internal).

Supplementary Figure 5. Relationship between age of input data and standardized measles incidence from country-year input data was collected.

Grey lines represent a smooth loess curve, and black lines represent a loess curve weighted on standard error of each input data.

Supplementary Figure 6. Relationship between age of input data and standardized first-dose measlescontaining vaccine (MCV1) coverage from country-year input data was collected. Grey lines represent a smooth loess curve, and black lines represent a loess curve weighted on standard error of each input data.

Supplementary Figure 7. Mean age of measles cases by country and year.

Grey lines represent the mean age of cases by year for each country included in analysis, and the red line is a smoothed LOESS curve through individual country lines.

Supplementary Figure 8. Standardized and unstandardized estimates of case-weighted measles CFR across all countries from 1990 to 2019.

Case-weighted mean CFR across LMICs is presented in yellow, by year. Using the UN standard population from 2019, we age-standardized case-weighted mean CFR estimates for LMICs (shown in red). In blue, we additionally age-standardized case-weighted mean CFR estimates using the age distribution across cases in LMICs in 1990 as our "standard population".

Supplementary Figure 9a-d. Age-specific, community-based, case-weighted case fatality ratio (CFR) estimates among 0–14-year-olds for low- and middle-income countries – for single years 1990, 2000, 2010 , and 2019 .

Supplementary Figure 11. Heat maps of age- and year-specific CFR by community- and hospital-based settings by country.

Supplementary Figure 12. Distribution of CFR values for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).

Supplementary Figure 13. Distribution measles incidence values used for covariates of country-years for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).

Supplementary Figure 14. Distribution MCV1 coverage values used for covariates of country-years for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).

Supplementary Figure 15. CFR estimates from framework using all studies versus only studies providing information on laboratory confirmation of cases, for select years.

Supplementary Figure 16. CFR estimates from framework using all studies versus only studies providing definition of death attributable to measles, for select years.

References

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3. cyipopt. 2022. [https://cyipopt.readthedocs.io/en/stable/.](https://cyipopt.readthedocs.io/en/stable/)

4. Portnoy A, Jit M, Ferrari M, Hanson M, Brenzel L, Verguet S. Estimates of case-fatality ratios of measles in low-income and middle-income countries: a systematic review and modelling analysis. *Lancet Glob Health* 2019; **7**(4): E472-E81.