Supplementary Materials for

**Burden is in the eye of the beholder: Sensitivity of yellow fever disease burden estimates to modeling assumptions**

T. Alex Perkins*, John H. Huber, Quan M. Tran, Rachel J. Oidtman, Magdalene K. Walters, Amir S. Siraj, Sean M. Moore

*Corresponding author. Email: taperkins@nd.edu

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Supplementary Text

Probabilities of different infection outcomes

There were two steps in our analysis for which we needed to make assumptions about the probabilities of different infection outcomes. In Step 2, we placed priors on the proportion of reported events that were cases or deaths. In the final step of translating ensemble projections of force of infection into deaths, we made an assumption about the proportion of infections that result in death.

We based both of these assumptions on a re-analysis of data compiled by Johansson et al. (3). While we were amenable to using estimates of the probabilities of different infection outcomes by Johansson et al., information was only presented in that paper about marginal distributions of the probability of each infection outcome. We felt that it was important to make use of estimates for which correlation structure among the probabilities of different infection outcomes was accounted for.

A natural distribution for representing uncertainty in multiple probabilities that together sum to one is a Dirichlet distribution (70). Accordingly, we used maximum likelihood to estimate parameters of a Dirichlet distribution describing the probabilities of the same four infection outcomes considered by Johansson et al.: A = asymptomatic infection; M = mild symptomatic infection; S = severe symptomatic infection; and F = infection resulting in a fatality. We used all data presented in Tables 1 and 2 of Johansson et al. in which two or more combinations of infection outcomes were reported in the same row. In some cases, this included sums of infection outcomes; namely, A+M and M+S, given ambiguity in some studies about these infection outcomes. To do this, we leveraged the property that the four concentration parameters of the Dirichlet distribution—\( \alpha_A, \alpha_M, \alpha_S, \) and \( \alpha_F \)—can be summed to obtain concentration parameters of a lower-dimensional Dirichlet distribution (including a beta distribution in the case of two outcomes) that are consistent with the higher-dimensional Dirichlet distribution (70).

Our analysis resulted in maximum-likelihood estimates (MLE) of \( \alpha_A = 8.69, \alpha_M = 2.74, \alpha_S = 4.10, \) and \( \alpha_F = 2.05. \) This corresponds to mean estimates (and 95% credible intervals, by which we mean the 0.025-0.975 quantile range under the MLE Dirichlet parameters) of the probability that an infection results in outcomes of A, M, and S+F of 0.49 (0.27-0.72), 0.16 (0.03-0.35), and 0.35 (0.15-0.58), respectively. This compares with estimates by Johansson et al. (3) 0.55 (0.37-0.74), 0.33 (0.13-0.52), and 0.12 (0.05-0.26), respectively. For the probability of death given severe disease, we obtained a mean estimate (and 95% credible interval) of 0.33 (0.04-0.57), as compared to an estimate of 0.47 (0.31-0.62) by Johansson et al. Together, this meant that our mean estimate of the probability of death upon infection of 0.12 was twice that of Johansson et al. (0.05), although there was also wider uncertainty in our estimate (0.01-0.27) than that of Johansson et al. (0.02-0.12). The differences between our estimates could be due either to the different distributions we used (Dirichlet vs. binomials) or the additional step in the analysis by Johansson et al. that estimated the prevalence of infection in the outbreaks from which the underlying data came.
Variance partitioning

Given our interest in evaluating the sensitivity of disease burden and vaccination impact to model assumptions, quantifying the proportion of variance in those measures attributable to different sources was an important focus of our results. To do that, we applied the law of total variance (71) to draws of outputs of interest—force of infection (FOI), deaths averted, and deaths—from their posterior distributions.

For a given output of interest (e.g., force of infection), $Y$, and a single explanatory factor (e.g., first-level administrative unit, adm1), $X$, total variance in $Y$ can be partitioned according to

$$\text{Var}(Y) = \mathbb{E}[\text{Var}(Y \mid X)] + \text{Var}(\mathbb{E}[Y \mid X]),$$

where the first term on the right-hand side represents variance in $Y$ not accounted for by $X$ (which we referred to as statistical uncertainty) and the second term represents variance in $Y$ that is accounted for by $X$. This equation was used to calculate the proportion of variance in log$_{10}$ FOI ($Y$) attributable to adm1 ($X$) in Step 3 and regression model ($X$) in Step 4.

In the case of two explanatory factors, $X_1$ and $X_2$, the above equation can be extended to

$$\text{Var}(Y) = \mathbb{E}[\text{Var}(Y \mid X_1, X_2)] + \mathbb{E}[\text{Var}(\mathbb{E}[Y \mid X_1, X_2] \mid X_1)] + \text{Var}(\mathbb{E}[Y \mid X_1]),$$

where the first term on the right-hand side represents variance in $Y$ not accounted for by $X_1$ or $X_2$, the third term represents variance in $Y$ accounted for by $X_1$, and the second represents variance in $Y$ accounted for by $X_2$ conditional on $X_1$ (72). This equation was used to calculate the proportion of variance in log$_{10}$ FOI ($Y$), deaths averted ($Y$), and deaths ($Y$) attributable to adm1 ($X_1$) and serology scenario ($X_2$). We selected adm1 as $X_1$ given that spatial heterogeneity in yellow fever due to heterogeneity in underlying environmental drivers is considerable, making it logical to consider it as a primary source of variation in yellow fever’s burden.
Figure S1. Comparison of seroprevalence based on estimates of force of infection from Step 1 (red) and simple estimates of seropositivity based on conjugate prior relationships (black) under serology scenario 1. The conjugate prior estimates assumed a flat beta prior with shape parameters equal to 1 and a binomial likelihood applied independently to each data point (66). Within each panel, different pairs of estimates correspond to different age strata. Points indicate median, thick line segments indicate 50% posterior predictive intervals (PPIs), and thin lines indicate 95% PPIs. See Table S1 for more information about these studies. Results for other serology scenarios were similar and are not shown.
Figure S2. Distributions of predictions of force of infection from Step 4 (x-axis) under eight alternative regression models. These distributions pool predictions across all adm1s and reflect the full uncertainty in each model's predictions. Results shown here pertain to serology scenario 1 only.
Figure S3. Comparison of regression predictions of force of infection from Step 4 (x-axis) against projected values from Step 3 (y-axis). Green circles indicate median values, and gray line segments indicate 95% uncertainty intervals. The coefficients of determination, $R^2$, in each panel were calculated based on median values.
Figure S4. Uncertainty in spatial prediction of force of infection from eight regression models. Standard deviations of values on a log$_{10}$ scale are shown from serology scenario 1. Color axes for each model differ so as to maximize contrast within each panel. Other serology scenarios produced similar results, but with magnitude varying according to differences in the estimated average reporting probabilities shown in Fig. 3.
Figure S5. Country partitioning for cross-validation. Each color signifies a different set of countries for which data was withheld from model fitting and used to assess out-of-fit prediction. This partitioning was determined so as to maximize the evenness of the number of first-level administrative units (adm1s) across partitions. To do this, the first partition took the country with the most adm1s and the two countries with the fewest and grouped them together (i.e., Uganda, South Sudan, and Sierra Leone in purple). The second partition took the country with the second most adm1s and the two countries with the third and fourth fewest adm1s (i.e., Burkina Faso, Togo, and Equatorial Guinea in dark blue). This process was repeated until ten partitions of three to four countries each were obtained. Countries in white were not included in our analysis.
Figure S6. Associations between spatial covariates and log_{10} force of infection. Each dot corresponds to an adm1, with median values shown here and used to compute coefficients of determination, R^2. All spatial covariates were centered and scaled for this and other analyses.
Figure S7. Population and vaccination coverage maps. Both maps reflect an average across 2021-2030. In the case of vaccination coverage, age-specific values of vaccination coverage were averaged proportion to population by age. All population and vaccination coverage estimates used in this analysis were generated by Hamlet et al. (8).
Figure S8. Deaths averted by country during 2021-2030. Results from the ensemble model corresponding to each serology scenario are shown in each panel.
Figure S9. Principal component loadings for spatial covariates with monthly values. Each principal component results from summing the product of these loadings and the monthly values of a given spatial covariate for each administrative unit. For example, NDVI PC1 results from taking the loadings in the upper left panel, multiplying them by monthly NDVI values for each administrative unit, and then taking the corresponding sums. This reduces the dimensionality of the twelve monthly values of these three variables (a total of 36 variables) down to the eight represented here. The number of principal components for each of NDVI, precipitation, and temperature was chosen such that 95% of variation in those variables was accounted for by these principal components. Maps of the resulting principal components are displayed in Fig. S10. As can be gleaned from the loadings, many of these principal components appear to capture differences in seasonal climatic patterns across the study region.
Figure S10. Spatial covariates used in the regression analysis in Step 4. All variables shown here have been centered and scaled, which is how they were used in the regression analysis and is sufficient to convey their relative spatial patterns. Rather than making inferences about relationships between these variables and force of infection, our goal was ensuring that we had variables with sufficiently diverse spatial patterns that the regression models would have sufficient flexibility to capture patterns in force of infection projected from Step 3.
Table S1. Characteristics of serological studies. Columns include characteristics that: allow for cross-referencing with Fig. 2, Fig. S1, and Fig. 3 (country, year, order therein); are related to how the serology scenarios were defined (vaccination status, vaccination coverage, outbreak investigation); determine force of infection (seropositive, number tested); and determine estimates of site-specific reporting probabilities (reported cases, deaths). Note that the number seropositive and number tested are totals across all age groups, which varied across studies and are not shown in this table in the interest of space. Vaccination coverage pertains to the year of the study and reflects a population-weighted average across age groups in the study.

| Country | Year | Vacc. status | Vacc. cov. | Outbreak investig. | Sero. pos. | Sero. tested | Cases | Deaths | Ref. |
|---------|------|--------------|------------|--------------------|------------|-------------|-------|--------|------|
| CAF     | 2008 | No           | 0.37       | No                 | 0          | 18          | 0     | 0      | (54) |
| CAF     | 2008 | No           | 0.39       | No                 | 48         | 339         | 0     | 0      | (54) |
| CAF     | 2008 | No           | 0.40       | No                 | 10         | 80          | 0     | 0      | (54) |
| CAF     | 2008 | No           | 0.39       | No                 | 18         | 112         | 0     | 0      | (54) |
| CAF     | 2008 | No           | 0.39       | No                 | 8          | 211         | 0     | 0      | (54) |
| CAF     | 2008 | No           | 0.44       | No                 | 11         | 64          | 2     | 0      | (54) |
| CAF     | 2008 | No           | 0.37       | No                 | 30         | 164         | 0     | 0      | (54) |
| CMR     | 1984 | No           | 0.20       | Yes                | 10         | 90          | 3     | 2      | (55) |
| CMR     | 1984 | No           | 0.36       | Yes                | 17         | 24          | 8     | 2      | (55) |
| CMR     | 2000 | No           | 0.28       | No                 | 13         | 55          | 4     | 0      | (56) |
| CMR     | 2000 | No           | 0.19       | No                 | 30         | 59          | 3     | 0      | (56) |
| CMR     | 2000 | No           | 0.19       | No                 | 13         | 85          | 0     | 0      | (56) |
| CMR     | 2000 | No           | 0.27       | No                 | 9          | 27          | 4     | 1      | (56) |
| CMR     | 2000 | No           | 0.19       | No                 | 4          | 30          | 2     | 0      | (56) |
| ETH     | 2014 | No           | 0.00       | No                 | 0          | 64          | 6     | 0      | (57) |
| ETH     | 2014 | No           | 0.00       | No                 | 0          | 135         | 0     | 0      | (57) |
| ETH     | 2014 | No           | 0.00       | No                 | 8          | 1,313       | 0     | 0      | (57) |
| ETH     | 2014 | No           | 0.00       | No                 | 2          | 152         | 0     | 0      | (57) |
| KEN     | 2010 | Unknown      | 0.06       | No                 | 22         | 433         | 119   | 46     | (58) |
| KEN     | 2010 | Unknown      | 0.01       | No                 | 6          | 36          | 0     | 0      | (58) |
| NGA     | 1986 | No           | 0.36       | Yes                | 37         | 207         | 1,295 | 564    | (59) |
| NGA     | 2008 | No           | 0.29       | No                 | 25         | 310         | 407   | 46     | (60) |
| SDN     | 2005 | No           | 0.06       | Yes                | 3          | 3           | 0     | 0      | (61) |
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