Author’s response to reviews

Title: Estimating the burden of dengue and the impact of release of wMel Wolbachia infected mosquitoes in Indonesia: a modelling study

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Author’s response to reviews:

Please see "personal covers" section for correctly formatted response to reviewers comments
Reviewer #1 Abdallah M. Samy: Authors addressed all of my concerns.

We are grateful for the reviewer’s approval of the changes we have made in response to their useful comments.

Reviewer #2 Giorgio Guzzetta: The authors have addressed in detail a large number of my initial comments and I commend them for their effort. I have no further comments on total estimates and mapping of infection burden.

However, I still have some important concerns on the model used for estimating Wolbachia effectiveness, and on the consistency and clarity of corresponding results. These concerns are especially relevant because the Wolbachia effectiveness estimation is the most important and innovative result of this study and can be used to support decisions related to control policies.

1) My main concern refers to the newly added lines 288-291, where the authors provide details on the way they fitted the transmission rates. The available incidence data against which the model is calibrated do not represent a setting at epidemiological equilibrium because only 27 years have passed since the first notification of "continual urban nationwide transmission of dengue in Indonesia" (1988) and the year of incidence data (2015). Therefore, if I understand correctly, the authors decided to calibrate the equilibrium incidence of the model to available incidence data after adjusting the human life expectancy to 27 years. The obtained estimates for the disease transmissibility are then used to project the long-term effectiveness of the intervention via estimates of the reduction in dengue uptake by Wolbachia-infected mosquitoes.

I understand the problems related to fitting data from non-equilibrium, and I agree that reducing the life expectancy goes in the right direction by reducing the transiently high fraction of susceptibles due to the relatively recent spread of dengue in Indonesia, and by forcing the model to reach equilibrium much more quickly. However, it is very difficult for me to assess the appropriateness of this choice. The age-structured model adopted by the authors is heavily sensitive to age via the lifetime history of infections of individuals, therefore using an unrealistic age distribution (due to the artificially short life expectancy) can have a dramatic impact on the overall qualitative model dynamics. I am therefore not at all convinced that the resulting disease transmissibility estimates are somewhat close to the real underlying transmissibility (and
therefore that the provided effectiveness estimates have any predictive value). I think that the authors should either provide a mathematical proof (or literature reference) demonstrating the appropriateness of this critical choice, or some validation that the estimated transmission rates plausibly represent actual dengue dynamics in Indonesia under a realistic profile for the age distribution. For example, how do the model-estimated profiles of seroprevalence by age compare to observed ones, under the assumption of a realistic age distribution and using the estimated transmission rates? What are the incidence rates after 27 years since initialization? Maybe the authors can come up with more meaningful quantities for assessing the validity of their choice, which I find highly controversial.

We thank the reviewer for highlighting this issue and agree that it is challenging to fit a transmission model to an epidemic when only data on the average annual disease incidence in the latter years are available. We believe your concern noted above has primarily emerged due to an incomplete description of this new addition to the methods, but nonetheless, the suggested additional validation is a good idea which we have now undertaken and present in a new supplementary figure.

First, we neglected to clarify that life expectancy is only reduced to 27 years during model fitting to generate accurate estimates for transmission intensity (beta). When making predictions about the effectiveness of Wolbachia under an assumption of endemicity we use a model with a current day realistic Indonesian life expectancy (average 67 years) and age distribution (Figure S1).

Second, we neglected to describe how we restrict life expectancy to 27 years during model fitting. To do this we maintain current-day realistic mortality rates between the ages of 0 and 27, then apply total mortality at the end of each individuals 27th year. This maintains a realistic age (or time exposed to dengue) distribution in the fitting model.
To clarify this difference between fitting and prediction models we have made these two changes in the manuscript:

Line 274: “To enable our model to fit these temporarily high symptomatic case incidence rates we reduced the life expectancy to 27 (2015 – 1988) years by imposing 100% mortality after the 27th year to represent the shorter period of exposure during transmission coefficient fitting. For high reported incidence where model estimates are outside of the 5% tolerance, the nearest fitting parameter estimate was selected as we assumed that these high incidence values were representative of anomalous years or symptomatic case rates. This only affected < 3% of values but may under-estimate transmission and thus over-estimate Wolbachia effectiveness in very high transmission environments. After obtaining accurate estimates of the transmission parameter, it was applied to a model with current-day realistic Indonesian life expectancy and age distribution (Figure S1). The ability of this model to reconstruct accurate age-specific seroprevalence was assessed (Figure S2), then it was used to simulate symptomatic case incidence with and without Wolbachia to calculate effectiveness at equilibrium.”

We have also added the new age-specific seroprevalence validation analysis in a new figure S2:

Figure S2. Comparison of fitted model predicted age-specific seroprevalence and observed age specific prevalence as measured by survey data [10,11]. Comparable model-based estimates were made by averaging predicted mean incidence in the 50km around the area of the survey then extracting model-predicted age-specific seroprevalence for the specific value of incidence. Mean and range of estimates are shown in this figure with uncertainty due to different mathematical model parameterisations (Table S6 and S7). Blue points represent datapoints where the range of model predictions falls within the true value. The percentage of datapoints where the model prediction is within the true value are as follows: Age 1-4: 57%, Age 5-9: 80%, Age 10-14: 73%, Age 15-18: 63%.

This shows broad concurrence between model estimated seroprevalence and survey measured seroprevalence with slightly lower correlation in younger ages (Age 1-4: 57% model predicted value range within the true value) as would be expected given the higher effect of inter-annual variability in this age group.

We hope that the above additions clarify and increase the robustness of our approach.
2) I now understand the rationale for the definition of the force of infection in the model (end of page 6, Supplementary Material), but I am confused by the author's declaration (in the response and Supplementary text) that "the force of infection of the first stage is approximately 0.75 of the value of the second stage"; as far as I understand, it should actually be the opposite given that the first stage is susceptible to 4 groups while the second stage to only 3. Furthermore, in the equations there is still an undefined quantity $S(a)$, which I think should be substituted by the stage-specific fraction of susceptibles, i.e. $S_1(a)$ for $\lambda_1$, $S_2(a)$ for $\lambda_2$ and so on. Because of the role of the force of infection in the model formulation, it is key that the authors clarify this point, justifying their responses, in order to assess the correctness of the methods.

We apologise, as correctly pointed out the description provided is incorrect. This has been amended to “Essentially, the force of infection of the second stage is approximately 0.75 of the value of the first stage, and so on”.

Thank you for taking the time to check the equations. The error (where $S(a)$ should indeed be $S_1(a)$, etc) has been amended. We have also added a small amount of text further describing the equations,

“The following set of differential equations describe the transitions across stages and age-groups, consisting of 960 equations (80 age-groups with 12 infection classifications). The first age groups ($S_1(1)$, $I_1(1)$, $R_1(1)$, $S_2(1)$, etc.) are specified separately to older age groups as a (continuous) birth rate is included in $S_1(1)$ and there are no age-associated influxes for the remaining infection compartments (equivalent to $\phi(a-1)=0$).”
3) Reported results for the Wolbachia effectiveness are very confusing. Comparing Table 3 to Table 1, the Wolbachia intervention seems to reduce Self-managed, Outpatient, Hospitalized and Total cases by about ~74% (close to the overall effectiveness value given in the abstract); averted fatalities and DALYs losses amount to about 86% of the total estimated burden.

3.1) why is the reduction in the number of deaths not proportional to the decline in hospitalizations (which are related to severe dengue cases, I guess)?

3.2) why is the proportion of averted DALY losses the same as the proportion of averted deaths? Three quarters of DALYs lost, according to Table 1, are composed of Years Lost to Disabilities (due to hospitalized cases, I assume?);

3.3) Self-managed and outpatients cases appear switched between Table 3 and Table 1

Furthermore, the effectiveness value given in the abstract is lower than any predicted value depicted in Figures 5 and 6 (under the 100% coverage). My interpretation is that 73.8% refers to symptomatic cases while Figures 5 and 6 refers to a reduction in hospitalized incidence (as declared in lines 314-315), although this is not reflected in the numbers proposed in Table 3 and Table 1, as pointed out.

We have now corrected this mistake that arose from an inconsistent method of averaging over the 1000 prediction realisations. This has now been corrected and all measures of severity show an 86.2% (UI 36.2 – 99.9%) reduction which is the only figure used in the text. As we do not take into account change in age distribution, our estimates of DALY percentage reduction are equivalent to those of symptomatic cases. Self-managed and outpatient were, indeed, swapped in Table 3 and have now been corrected.

Since the first resubmission the effectiveness model now works from baseline incidence of all symptomatic cases not hospitalised incidence. One typo in the main manuscript has been made to update this change. The predicted effectiveness of 86.2% quoted in the results and abstract aligns closely with the median pixel value (thick dotted line) in Figure 5.
3.4) is 100% coverage the baseline scenario? In such case, this should be made more explicit and, to avoid further confusion, the 50% coverage scenario in Fig. 5 might be moved to the Supplementary Material.

We have added the words “100% coverage forms the baseline scenario for subsequent analyses.” To the legend of figure 5 to clarify this. And have made reference to this in the results section to clarify. We still believe having the 50% coverage scenario is useful as it shows how consensus among the models increases with decreasing coverage.

3.5) (if my interpretation is correct) it is confusing that Figures 5 and 6 provide a different definition of effectiveness compared to results given in the abstract and in other parts of the paper.

Please see above. The definitions of effectiveness are consistent throughout the main manuscript including the figures.

Minor issue:

- Supplementary material, p. 7-8: in model equations, \( \mu(a) \) should be made explicit and not included in the \( \phi(a) \) component. For example, the equations for the demographic processes for a generic age group \( a \) should be written as

\[
\frac{dP(a)}{dt} = \phi(a-1) P(a-1) - (\mu(a) + \phi(a)) P(a)
\]

where \( \phi(x) \) represents the rate at which individuals of age \( x \) move to age \( (x+1) \) and \( \mu(x) \) is the mortality rate.

The distinction of the two processes (aging and mortality) is necessary because in the current formulation of model equations (though certainly not in model implementation), the same number of individuals coming out of age class \( x \) would flow into age class \( x+1 \), resulting in a conservation of individuals between age classes \( x \) and \( x+1 \), i.e. in a constant population distribution over age (contrary to what Figure S1 shows).
We have added in the notation for the age-specific mortality rates in the relevant section of the supplementary information as requested.

Typos:

- Line 186: I think the authors meant 2.5-97.5% Uncertainty Intervals?
- 357: UIs (0.22 - .9) do not include the mean (1.1); perhaps the authors meant 0.2-2.9?
- Table S4: 0.025% and 0.975% UI; again, I think the authors meant 2.5-97.5% UI.

Yes, thank you all of these have been corrected as suggested.

- In Table S1.4, the Hopkins model is reported to assume a duration of infection of 100 days, lying completely out of the range of all other models; can you confirm that it is not a typo?

We have clarified this with the original authors of the Hopkins model and had made the updates in the previous submission but neglected to correct the error in Table S1.4. This has now been corrected to 4 days.

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