Reviewer’s report

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

Version: 1 Date: 27 Jun 2019

Reviewer: Giorgio Guzzetta

Reviewer's report:

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.

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.
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.

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.

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.
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).

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.

- 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?
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