Author's response to reviews

Title: Mass campaigns with antimalarial drugs: A modeling comparison of artemether-lumefantrine and DHA-piperaquine with and without primaquine as tools for malaria control and elimination

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Version: 3
Date: 24 February 2015

Author's response to reviews: see over
Feb 24, 2015

Dear Editors,

Please see below for our responses (in blue) to reviewer feedback.

Thank you,
Jaline Gerardin

Editor's Comments:

-There needs to be explicit statement in methods for the combination drugs necessitating a double exponential.

The text has been clarified to explain that the double exponential arises from 2-compartment pharmacokinetics rather than combinations of drugs.

-Technically, a hill function with hill coef of 1 is a Langmuir adsorption model and would be better described as such.

While it is true that an equation of this form is also a Langmuir adsorption model, in the PKPD field it is commonly referred to as a Hill function. We believe it would be better to stay with convention here to avoid confusion.

-Constant EIR (here, 50) breaks the transmission process; it does not allow for reduced infection levels in subsequent populations and obscures knock-on effects in immunity etc...DEFINITELY REQUIRES EXPLICIT MENTION AS A POTENTIALLY IMPORTANT MODEL SIMPLIFICATION.

We have clarified the text to state that the campaign simulations modeled transmission between humans and vectors rather than forcing a constant EIR, thus allowing for reduced transmission as the infectious reservoir is depleted.

-For the reinfection rate calibration, semi-immunes were subjected to constant infection rates of 3 infectious bites per person per month; why not EIR/12?"

The text has been clarified to state that a forced annual EIR of 36 was used to match clinical trial conditions. Thanks for pointing out the inconsistency of using a monthly EIR in this subsection and annual EIR elsewhere.

Reviewer 1

1. I recommend the manuscript have separate results and discussion sections.

2. In the results, please use subheading to allow the reader to understand what is being compared (what factors are being varied) and what factors are being held constant. For the given set of major variables –
drug, EIR, coverage (pop coverage and compliance), 2 vs 3 rounds, MDA vs MSAT and time since last round (1 vs 4 months), please be consistent and specify what is varying in the model, and what is remaining constant. I suppose this could be done through consistently denoting this at the beginning of each comparison, but sub-heading would be better.

3. There is a substantial amount of the methods repeated in the results which results in a good amount of redundancy throughout much of the paper. Please streamline the results accordingly.

The manuscript has been restructured following the very helpful suggestions in 1, 2, and 3.

4. To the best of my knowledge, elimination programs do not, and are not, expected to target areas of high transmission (e.g. EIR of 50) for elimination using drugs alone. The finding that prevalence quickly returns to pre-campaign levels is completely expected. I recommend discussions around such findings be discussed/interpreted accordingly.

Drug campaigns are typically considered for situations where vector control has already reduced transmission. In regions of extremely high transmission (EIR > 200), it is not unreasonable to expect that vector control methods may only reduce EIR to 50. We investigate whether drugs can do the rest of the work, and EIR is one factor that limits success of drug campaigns. We consider EIR explicitly in Figures 4 and 5.

5. Why was population movement of individuals with infections into the simulation cohort population not included? This is a significant weakness of this study. If such population movement would not be expected to significantly change the modelling results given the relatively short follow-up period post last round in these simulations, then that needs to be clearly stated.

Population movement is also a crucial factor in near-elimination scenarios. Human movement around the campaign area such that some people are not at home during campaigns can be approximated with lower coverage. The reintroduction of malaria from people carrying infections into the campaign area and the robustness of elimination to reintroductions are critical to consider when modelling near elimination and will be addressed in subsequent work.

6. I assume EIR values across simulations could be a proxy for effective vector control coverage, but I would argue not entirely. There is likely an interaction between host acquired immunity, potential/historical EIR and vector control coverage level (including length of time since introduced) that may very well impact the parameters assessed in this modelling exercise. If the inclusion of vector control cannot be reasonably accommodated, or if you feel EIR serves as a valid proxy, please include this rationale/discussion in the paper.

While it is true that EIR is not entirely a proxy for vector control, we use this first-order approximation in this study to reduce dimensionality of presenting analytical results.

7. Same as point 6 above- why was coverage of diagnosis and treatment not included in the model? Please either include it or provide a solid rationale for its exclusion.
Diagnosis and treatment affects only those who are symptomatic for malaria, and case management is not the limiting factor for interrupting transmission. Reactive case detection and scenarios with reintroduction are important to consider but beyond the scope of this paper.

8. Coverage of MDA was assumed independent in each campaign round and across all individuals; this is a problematic assumption as this is clearly not true in the real world. Would missing dependent chunks of the same individuals (subgroups) across rounds not have an effect on transmission and the effect of the MDA strategies? I suspect it would. And I would make the same argument that independence across individual level adherence is equally problematic. This either needs to be addressed in the modeling, or a solid rationale as to why it is not needs to be given.

Very true, especially for large populations. However, interaction between variable coverage and geography/reintroduction/accessibility is perhaps less dramatic at a 1000-person site. Outcomes for campaigns with independent coverage between rounds show a best-case scenario, and we expect that correlated coverage will result in benefits on par with lower levels of independent coverage. Since improving adherence appears to only minimally affect outcomes, we anticipate that modeling correlated adherence patterns will only negligibly change results. We have expanded the discussion to address these issues.

9. A linear regression is used to assess differences of model outcomes for rounds with and without PQ across a range of EIRs- is this relationship expected to be linear?

We have expanded the methods to discuss this issue. The relationship is expected to be linear at low EIR but not at high EIR. The EIR range we consider is on the low end, and we do not observe bowing of the +/- PQ curve in this range (see supplemental figure 3), so we believe the linear regression is a reasonable choice.

10. The language around relative vs. absolute reductions is confusing- i.g. that on p 11 lines 430-437. I suggest using ‘relative’ reduction to reference percent reduction (i.e. 50% reduction from 30 to 15%) and ‘absolute’ reduction be used to explain going from XX% to XX%.

We have clarified the text using the “relative” and “absolute” terms.

11. Last sentence of conclusions- this hypothesis is not ‘based on your (our) findings’ as no vector control or case management was included in this modelling study.

Reworded for consistency with response to #4 above.

Reviewer 2

1) Limitations are not well stated which could include inability to model effect of MDA on malaria transmission to mosquitoes/transmission blocking and its effect on EIR, use of a high detection threshold leading to much of the parasitaemia undetected, not modelling the roll of sub-patent parasitaemia or effect of MDA on sub-patent parasitaemia etc
The text has been clarified to state that the campaign simulations modeled transmission between humans and vectors rather than forcing a constant EIR, thus allowing for reduced transmission as the infectious reservoir is depleted. We have addressed the issue of detection threshold and sub-patent parasitemia in the section on MDA vs MSAT.

2) On page 5 line 187, semi-immune patients are mentioned and it is not clear who these patients are. Non-immune patients are clearly understood, but semi-immune patients need to be defined. We have revised the text to define “semi-immune” immediately after the first introduction of the term. “Semi-immune” describes individuals who are parasitemic but possess enough immunity to avoid developing clinical symptoms.

3) If possible, the model could be adjusted to include EIR beyond 50 infectious bites per person per year since some places in Africa have EIRs of as high as 500. Drug campaigns are typically considered for situations where vector control has already reduced transmission, which is not the case for areas where EIRs are in the hundreds. We investigate whether drugs can do the rest of the work after vector control has resulted in a new, lower, EIR.