Author’s response to reviews

Title: Dealing with indeterminate outcomes in antimalarial drug efficacy trials: A comparison between complete case analysis, multiple imputation and inverse probability weighting

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Title: Dealing with indeterminate outcomes in antimalarial drug efficacy trials: A comparison between complete case analysis, multiple imputation and inverse probability weighting

Dear Dr Krüger,

Thank you for giving us the opportunity to revise and resubmit our paper. The reviewers’ comments were very constructive (especially the second reviewer) and we have revised the manuscript to address the editorial and reviewers’ comments.

Thank you for your attention.

Yours sincerely,
Alexander Robitzsch (#Reviewer 1):

#Reviewer 1: The ms improved with respect to clarity. I am still not convinced that one can learn a lot from such a "real data simulation" (although one can find similar approaches in the literature). The specification of the imputation model should be described in more detail. Moreover, mathematical notation in the ms is flawed.

Author’s response: We thank the reviewer for making several helpful comments to improve our manuscript. We have made further revision/correction on mathematical notations to be consistent and made several changes to the main text regarding the description of the imputation model (lines 241-269).

#Reviewer 1: My major concern is the compatibility of the analysis model and the imputation model. The analysis model is the non-parametrically estimated Kaplan-Meier survival function. Authors should make clear how this function is accommodated in the imputation model. It seems that the authors just plainly apply mice for imputation based on a logistic regression with linearity assumptions and additive effects of predictors (please describe it clearly in the ms what you have done). I do not see why this should be compatible with the analysis model.

Author’s response: The analysis model is the Kaplan-Meier survivor function for estimating efficacy of the three treatment regimens. To ensure compatibility of the imputation model with the analysis model, we have included the variable of substantive interest “treatment regimen” and the observed “time to parasite recurrence” (i.e. the “time to the event” in the target analysis) in the imputation model. The imputation model also included six auxiliary variables selected a priori to be potentially related to indeterminate parasite recurrence. We have made several changes to the main text regarding the description of the imputation model (lines 241-269). Interactions or non-linear relationships between the variables in the imputation model were not considered.

Our approach of using a parametric imputation model (logistic regression for imputing missing outcome event) and non-parametric method for carrying out substantive analysis (estimating non-parametric cumulative incidence of failure) has been used previously by Lee et al (2011), and Lee, Dignam and Han (2014). For example in the Lee, Dignam and Han (2014) paper, they performed a simulation study where the time of event was known but the cause of event unknown (similar to our example) and found minimal bias when imputing the cause of the event using a logistic regression model. We have included these references as a justification for our selected imputation model.


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4190095/

#Reviewer 1: 191 Equation. Please define $\pi_i$ which appears without definition in 197.

Author’s response: $\pi_i$ is the probability of the outcome being missing for subject $i$ and this definition has now been added (lines 206-208).

#Reviewer 1: 191 Equation. I think that the equation cannot be correct. There must be coefficients $\beta_{11}$, $\beta_{12}$, $\beta_{21}$, $\beta_{22}$ with appropriate predictors. The notation in the ms does not make sense.

Author’s response:

The reviewer is referring to the following equation:

$logit(\pi(\delta_i=1))=\beta_0 + \beta_{1k} transmission_{ik} + \beta_{2j} treatment_{ij}$

$\beta_1$ has been reserved for transmission level and $\beta_2$ for treatment arm. The subscript $k$ has been used to explicitly refer to the levels of the transmission variable and the subscript $j$ has been used for treatment arm. We have now corrected the equation to include the following sigma terms (i.e. summation notation) and thank the reviewer for noticing the mistake in our notation.

$logit(\pi(\delta_i=1))=\beta_0 + \sum_{(k=1)^2} \beta_{1k} transmission_{ik} + \sum_{(j=1)^2} \beta_{2j} treatment_{ij}$

#Reviewer 1: Moreover, they use $\beta_{1k}$ and $\beta_{2j}$, but later "($\beta_{1k}; \beta_{2k}$)".

Author’s response: We would like to thank the reviewer for identifying this. The error in notation has now been corrected (line 202).
#Reviewer 1: 248. Please provide the details about the computation of weights. Is it just a logistic regression with main effects?

Author’s response: The weights were computed based on a logistic regression with main effects as stated by the reviewer. The weights were the inverse of their estimated missingness probability. The text has been slightly modified to highlight that only main effects were included in the missingness model (lines 270-283). The variables incorporated in the missingness model are provided in Table 4.

#Reviewer 1: 260: Authors use index "i" for replications but "i" stands for cases in the sections before. This should be avoided.

Author’s response: Thank you for pointing this out. We have now used a new notation s to indicate the simulation run and reserve i for cases.

#Reviewer 1: 268 ff.: The notation for "Bias", "ModSE" and "EmpSE" does not make sense. "n_sim" is set to a number (I assume 1,000) but in the equation (268) it is written n_sim = 1, 2, …, 1000. Moreover, in the sum symbol the index "i" is used, but \iota for the terms. The same is true for the formulas for the standard error.

Author’s response: We would like to thank the reviewer for pointing this out. We have now revised the index to avoid this error.

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Roderick Joseph Little (Reviewer 2):

#Reviewer 2: Abstract, and elsewhere. "The Kaplan- Meier (K-M) probability of drug efficacy." The K-M method does not estimate a probability, it is a curve that estimates the probability of an event (here, recurrence) as a function of time. You are estimating the probability of 28 day recurrence, derived from the K-M curve. Furthermore, this probability is not a measure of efficacy, which requires a comparator treatment.

Author’s response: Thank you for pointing this out. We have made changes throughout the manuscript to address this point.

#Reviewer 2: Abstract, 58. Technically IPW and MI estimates are not unbiased, the correct term is "consistent".

Author’s response: We have made appropriate changes throughout the manuscript to use the terminology consistently.
#Reviewer 2: lines 147-151. "the remaining data … with known outcomes" is confusing, because
the use of K-M implies that some outcomes are censored, and the censored outcomes are not
known. In fact "complete-case analysis" is a bit of a misnomer since the censored cases are being
included but are censored and hence not "complete".

Author’s response: In antimalarial trials, cure is defined based on a patient reaching the planned
end of the study without observing any parasitic recurrence. There were two reasons for
censoring when constructing the K-M curve:

Patients who reached the planned end of the study (day 28) without observing any
parasitic recurrence. Such patients were censored on the last day of the study (i.e.
administrative censoring).

Patients in whom new infection occurred were considered as censored on the day of
recurrence.

The former cases are classified as “cured” as per the WHO definition and in the latter, the cases
have a known outcome (despite being considered as censored). Hence, the remaining 3,369
observations used for the purpose of this simulation study can be regarded as complete as we
didn’t consider individuals who were censored due to loss of follow-up for the purpose of this
simulation study.

However, we acknowledge that data cannot be considered as being “complete” when the
censoring is due to other causes such as lost-to-follow-up.

#Reviewer 2: What is the extent of censoring in the groups? If minor (I gather only 28 days of
follow-up are required), then my analytical results in the previous review still essentially apply;
see also next two comments.

Author’s response: For the purpose of this simulation study, we only used participants with
known outcomes (cured, recrudescence, or new infection). In the Kaplan-Meier method for
estimating the day 28 probability of cure, new infections were considered as censored
observations. The percentages of censoring (new infection), were 21.5% (243/1131) in AL,
14.3% (127/889) in ASAQ, and 6.3% (85/1349) in DP group (data are presented in Table 1).
These differing percentages by treatment arm are reflective of the underlying pharmacokinetic
properties of the respective drugs, i.e. the prophylactic effect of the antimalarials on new
infections.

We would like to thank the reviewer again for the analytical results. The analytical solution has
been described and stated in the main text: (lines 86-93). We have also analysed the simulated
datasets for each of the three missingness scenarios to derive estimates of the bias using the
analytical solution and present the mean bias from 1,000 simulation runs for the three
missingness scenarios in Table 6.
Reviewer 2: The use of K-M implies that censoring is "noninformative" or "coarsening at random" - is that a reasonable assumption?

Author’s response: We consider the assumption of non-informative censoring as a reasonable assumption in the context of this simulation study as the majority of the censoring was for administrative reason (i.e. at day 28 follow-up).

The differences in the underlying pharmacokinetic properties of the respective drugs mean that they provide protection from a new infection for different lengths of period. One can suggest that such differential prophylaxis might lead to informative censoring; for example, new infections are expected earlier with AL drug, which offers shorter prophylaxis compared to the DP drug regimen (thus appearances of late new infections). Censoring due to new infections can be possibly considered as having minor influence.

Reviewer 2: While I appreciate the acknowledgement of my analysis of the bias of complete-case analysis in a supplementary file (which, however, I suspect very few people read, including myself -- when I click on the "supplemental material" all I can see is the rebuttal letter). However, it seems that some discussion of the analytical result belongs in the main text. If complete-case analysis is biased without censoring, then it's obviously still going to be biased with censoring, since censoring is just an added wrinkle, and tangential to the main issue with complete-case analysis. The analytical result makes clear the reason for the bias in this method, and is much more powerful than a simulation study, which is limited by the simulation conditions considered.

Author’s response: We agree with the reviewer regarding the influence of censoring and bias. As stated in our earlier response, the analytical solution has been described and stated in the main text: (lines 86-93). We have also analysed the simulated datasets for each of the three missingness scenarios and provide a comparison of the bias estimates for the MI, IPW and CC analysis together with the analytical solution in Table 6 of the main text.

We would like to thank the reviewer again for this critical input on our manuscript and formally acknowledge this (lines 516-517).

Reviewer 2: Another comment is that censoring is mentioned in the author's response as a justification for doing a simulation study, but censoring is not varied as a factor in the simulation, it being fixed by the censoring in the full data set.

Author’s response: We considered censoring as fixed for this simulation study and did not vary. As mentioned in our responses to earlier comments, the censoring structure in the dataset resulted from two sources: administrative censoring and recurrence due to new infection. Those who were censored for administrative reasons were kept as fixed (as this satisfies the current WHO definition of the cure).
In this simulation study we wanted to explore the effect of exclusion of data with no outcome (patient have recurrence but the distinction couldn’t be made) for a fixed scenario with patients who were had new infection being censored. In most malaria studies, we also have some patients who are lost to follow up (10-20%) and their treatment outcome is not known and therefore we chose Kaplan-Meier method for analysis (also recommended by the WHO).

Temesgen Zewotir, PhD (Reviewer 3):

The paper is well written. The authors clearly argued and responded to the reviewers comments. Though I am not in favour of few of their arguments/responses, it has no wrongness. I therefore recommend the manuscript for acceptance.

Author’s response: We would like to thank the reviewer for recommending publication of our manuscript.