Author's response to reviews

Title: Cost-effectiveness analysis of malaria chemoprophylaxis for travellers to West-Africa

Authors:

Lukas L Widmer (lukas.widmer@sunrise.ch)
Patricia R Blank (patricia.blank@ifspm.uzh.ch)
Koen Van Herck (koen.vanherck@ua.ac.be)
Christoph Hatz (Christoph.Hatz@ifspm.unizh.ch)
Patricia Schlagenhauf (pat@ifspm.uzh.ch)

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Author's response to reviews: see over
Dear Prof. Akintunde Sowunmi,

Thank you very much for the reviews of our manuscript "Cost-effectiveness analysis of malaria chemoprophylaxis for travellers to West Africa". We found the reviewers’ comments helpful and constructive and have noted our responses below, in bold text. The new text sections are shown in blue. We submit a revised manuscript according to the reviewers’ recommendations and look forward to your consideration for publication in BMC Infectious Diseases.

Yours sincerely,

PD Dr. Patricia Schlagenhausf, corresponding author

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REVIEWER COMMENTS

Reviewer: Dirk H Müller

Reviewer’s report:
This is an interesting study about an underestimated issue. The model appears to be comprehensive and appropriate. Although the style is scientific and the manuscript is well understandable, from my point of view, various sections are too long. For example, some aspects in the method section are mentioned both in tables and in text. Not for all of the data provided in tables additional information in written form is needed. The manuscript should be thoroughly revised because redundant aspects were found in all sections.

Before the manuscript can be recommended for publication, several points have to be clarified (see points 3 and 4 which I did not understand with the information provided).

Authors response: Thank you for your constructive review. We have shortened the paper as much as possible while still providing enough explanations for the reader who is not familiar with cost-benefit analyses.

1) Methods, study design, para 5 ("To make the model probabilistic...”): the model was probabilistic by applying triangular distributions. Why the authors had not performed a probabilistic sensitivity analysis running all variables simultaneously? This would be an appropriate method to confirm the ro-
bustness of the results. Or: why the model was made probabilistic if no probabilistic sensitivity analysis was performed.

Authors response: *We agree that in a health economic evaluation, a probabilistic sensitivity analysis to assess the uncertainties around the base-case should be performed. Hence, besides the one-way sensitive analysis we added a PSA to the results. This is shown in figure 2 “Probabilistic sensitivity analysis”*

2) Methods, analysis, para 2: the sentence “The lower the ICER, the more cost-effective the intervention” is dispensable.

Authors response: *We agree and have removed this sentence.*

3) What is the reason for providing details on Supracycline and Malarone although the analysis is made for cheaper Mefloquine. From my point of view, this makes only sense if a cost-effectiveness ratio is provided for all drugs in the base-case. Otherwise, it is sufficient to mention these drugs as more expensive therapeutic options. Providing detailed data such as in table 2 is confusing.

Authors response: *Currently in most countries there is a choice of three priority malaria medications for West Africa. All three options are are effective but vary considerably in price and in adverse event profile and applicability. This is why we provided data on all choices especially price data in Table 2). As you suggested we will remove excess reference on the other options from the text but will retain two lines of data regarding these options in table 5).*

4) Strengths and weaknesses, para 4: “In our model we considered the three recommended …agents”. This also is a little bit confusing. If I understood the authors right, the analysis was performed only for Mefloquine? At least this is stated (for example in the abstract). I think more information is needed here.

Authors’ response: *This is clarified in Table 2) and in the text. We will make it clearer in the abstract.*

5) Sensitivity analysis, para 2: it should be “cost saving and more effective” (not efficient)

Authors’ response: *Thank you. We have changed this as suggested.*

6) The term willingness to pay is mentioned first in the conclusion section at the end of the manuscript. This point should be discussed earlier.

Authors response: *We have now introduced this concept in the „Methods“ section.*

6) Table 1 and 2: While in table 1 the direct costs of mefloquine for 2 weeks in the 80% strategy are €17.77, in table 2 these costs are €4.20. What is the reason for this difference?

Authors’ response: *In Table 2, €4.20 refers to the reduced 80% reduced cost to the traveller if the reimbursement strategy is adapted. The cost for the Swiss Health System is €17.77. We have slightly
changed the title of Table 2. to make this more easily understood.
Reviewer: Paul Arguin
Reviewer’s report:

Minor comments:

1. The conclusions stated in the abstract do not match the findings of the article or the conclusions stated at the end. The abstract states that the 80% reimbursement was not cost effective. However, the conclusions section of the manuscript first states that no clear statement on cost effectiveness can be made— and then says that it can be considered cost effective. In addition, earlier the authors state that according to the NICE guidelines, it can be considered cost effective. Please change the abstract to agree with the text.

Authors response: Thank you for this very helpful review. We have modified our paper according to all your suggestions and the abstract now has a clear statement which is also now more appropriate after taking the new malaria attack rate into the model.

2. In the 4th paragraph of the discussion and table 2, I was confused by the description of the maximum days of protection. Is it the case in Switzerland that only whole packages of medicine can be dispensed? I am used to pharmacies being able to dispense the exact number of tablets required to an individual. If that is not the case in Switzerland, perhaps a note of explanation would help.

Authors response: Usually in Switzerland, where both pharmacists and physicians are involved in the dispensing of medicines, it is customary to dispense original packs rather than broken bulk. We will add a note on this to the paper.

Major comments:

1. I strongly disagree with the value of 0.9% chosen by the authors as the attack rate for malaria in West Africa. They list 5 references for the attack rate for a 2 week stay in West Africa. The Pistone article did not calculate their own attack rate, rather they used and referenced the Steffan article. The Schlagenhauf 2008 article is a review article that references the Askling article and another UK study. The Stager and Askling articles do not account for the amount of time spent at the destination. More importantly they do not account for chemoprophylaxis use. It is very likely that the people who traveled who did not become infected were taking chemoprophylaxis. This extremely important and large part of the traveling population is not accounted for in these studies. Thus the .9% attack rate used in this study could be a vast underestimation of the actual attack rate. The Steffan article is the only one that accounted for the entire cohort of travelers. In this study the attack rate for West Africa was 2.4%. This appears to be the only reasonable number to use in the model. Interestingly, the sensitivity analysis that evaluated 30% above and below the 0.9% rate ranged from 0.4 (should be 0.6?) to 1.2% - which is well below the 2.4%. I would suggest using the 2.4% instead and the sensitivity analysis should use 1.7 and 3.1% for a more accurate estimate of the attack rate.

Authors response: We agree to use the attack rate data from the 1990
Steffen article and have now changed our model using 2.4% as the attack rate. This is a solid reference and makes our calculations more robust but as a result we need to change the data in Table 4 and redo all models and tables. The corrected, modified data are all highlighted in blue. However, we would like to point out that our original model used an estimated average length of stay for travellers to West Africa of 14 days whereas the attack rate in the Steffen paper is based on a duration of stay of one month and secondly the Steffen data dates from the late 80’s and the transmission of malaria in West Africa has decreased to some extent in the interim.

2. The authors included outpatient management, inpatient management, and loss of productivity time in the costs section. Later in the manuscript they added a brief discussion of years of life lost. However the cost of a death and the cost of a permanent disability were not included in the cost calculation. These numbers should be included or else the cost effectiveness equation is being skewed.

Authors response: Life years lost due to possible death were included in a paragraph of the discussion on a hypothetical NICE evaluation. In the main model or analysis however, the focus was on direct costs and the indirect costs of death and life years lost were not included on the advice of our health economics statistician. The other analyses in the literature on malaria chemoprophylaxis concur on this and do not include death costs in their analyses (refs. 11, 27). This is the practice for many health economics analyses. We found no evidence for permanent disability due to malaria in travellers.