PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	EFFICACY OF ANTI-MALARIAL HERBAL MEDICINES USED BY COMMUNITIES IN MALARIA AFFECTED REGIONS GLOBALLY: A PROTOCOL FOR SYSTEMATIC REVIEW AND EVIDENCE AND GAP MAP
AUTHORS	Ocan, Moses; Loyce, Nakalembe; Ojiambo, Kevin Ouma; Kinengyere, Alison; Apunyo, Robert; Obuku, Ekwaro A.

VERSION 1 – REVIEW

REVIEWER	Saito, Makoto WorldWide Antimalarial Resistance Network (WWARN)
REVIEW RETURNED	11-Nov-2022

GENERAL COMMENTS	This is a protocol of a systematic review and aggregated data meta-analysis on the potential herbal treatment for malaria. The authors have published some protocols of systematic reviews before, and the manuscript is reported following the PRISMA-P statement. The systematic review is also registered to PROSPERO in advance. Overall, it is well written, but some additional explanations and clarifications will be helpful. Major comments 1. The dates of the study (eg, when the search will be or was started) should be included in the manuscript. 2. There is no description of “evidence and gap map”. I am afraid I am not familiar with the Campbell Review, probably because it seems to be primarily for social and behavioural science. I would be grateful if you could explain how the map will be produced. 3. Compared with a recent systematic review and meta-analysis (Ref #11. Tajbakhsh, et al Malar J 2021:20:349), the novelty of the current review includes: this review covers all world (rather than Africa); and compares efficacy between herbal medicines and artemisinin (Line 97). However, I am not fully convinced of the feasibility and the importance of the latter and it is not clear whether the authors are planning to do this. Firstly, the previous review found only one clinical study, which was not a comparative study. It is likely that clinical efficacy cannot be compared because there are no studies. Secondly, in-vitro studies can be valid even without internal comparators, for example using the historical data of IC50 of artemisinin. In addition, the authors did not include this (ie, only comparative studies are included) as the eligibility criteria. In Table 2, the comparator is indicated as “None” for clinical outcomes. On the other hand, the effect measurements listed in Lines 335-7 are all derived from comparisons (ie, ratios or differences). What kind of effect measurements will be used for clinical outcomes? Please clarify whether you include only

	comparative studies or not (for which outcomes?) and update the whole manuscript consistently. 4. Outcomes. Although improvement of symptoms is important, parasitological clearance is a more direct consequence of the antimalarial effect. I would suggest you include parasitological clearance or ACPR (adequate clinical and parasitological response) defined by WHO to assess antimalarial efficacy. 5. Secondary outcome includes safety. Are you going to include LD50 and some other safety outcomes in animal studies? It looks your focus is only on efficacy. Please clarify whether you are going to assess safety as well. If yes, what kind of measurements will be gathered? 6. The search strategy is not easy for me to figure out what is the exact search terms and conditions. Do you combine all categories of PICOST with "AND"? 7. Risk of bias. How do you assess the risk of bias of in-vitro studies. Please explain. 8. Publication bias. Egger's test is only valid (recommended) for binary outcomes. How would you assess other types of outcomes? 9. Quality assessment. AMSTAR-2 is to appraise systematic reviews, rather than to assess "(individual) articles' quality" (Line 307). GRADE is to assess the strength of evidence rather than "quality of evidence" (Line 308). 10. References do not include the journal titles. Please update them. Minor comments 1. Line 76. Something (possibly "in") is missing before "various malaria endemic regions". 2. In-vivo usually means animal studies, whereas clinical studies means studies done in humans. In Table 2, in-vivo is used as clinical (ie, in humans). Please clarify the terminology used in your manuscript. 3. Table 2. Setting. I agree that clinical studies should be done in malaria-endemic countries. However, I believe in-vitro and in-vivo (animal) studies can be done anywhere. Why do they need to be done in malaria-endemic countries? 4. Table 2 Setting. How can the data (eg, prevalence) from cross-sectional studies be used for assessing the efficacy of drugs? 5. Line 175. I do not understand the meaning of this sentence. Could you please consider rephrasing it? 6. Please reformat the inclusion criteria. The first four are probably combined with OR, but the last two must be combined with AND. The last two can be in the exclusion criteria (published before 2000, non-English literatures). 7. Excluding non-English literatures (eg, Chinese) might be a potential limitation of your search. Please remind that artemisinin is originally from China and quinine is from Peru. 8. Line 191. There will be different kinds of situation when "full text cannot be retrieved". This can include situations that your institution does not subscribe some specific journals, or you are not willing to pay the cost for getting individual papers (which should be ideally avoided). On the other hand, it is possible that electronic copies are not available from the publisher and hard copies are difficult to obtain in case of local journals. As this is a protocol paper, it would be nice if you clarify what kind of efforts will be made to retrieve full texts. 9. Line 200. Please specify the way you are going to search for grey literature.

	10. Search terms 9-1. Why other standard antimalarials such as artesunate, mefloquine, amodiaquine are not included in the search term? 9-2. Line 223 Do you need “OR”? 9-3. Clinical outcome terms require reconsideration. It is too specific and not comprehensive. For example, “febrile” will not be found. How did you choose these symptoms: why muscle pain, headache, abdominal pains are not included? 9-4. I think it is better to exclude by region after the search, rather than using it in the first place even if you want to include only studies in malaria-endemic countries. And one pair of brackets are needed: (Malaria-affected AND (region* OR countr* OR area*)) OR […]. “malaria-endemic” might be another commonly used term. Overall, I might not add this limitation by area at the stage of database searching. 11. Line 307. AMSTAR-2 has 16 domains rather than 10 in AMSTAR. 12. Line 326. “In case of none response” should be “in case of no response”. 13. Line 332. Adding a reference for this equation would be helpful. 14. Line 338. It is probably “metan” command rather than “mean”.

REVIEWER	Alqaisi, Amjed University of Baghdad Al-Jaderyia Campus College of Science, Department of Biology
REVIEW RETURNED	29-Dec-2022

GENERAL COMMENTS	Check the line number that found in PRISMA-P 2015 checklist with line number in manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer’s comments
Reviewer: 1
Dr. Makoto Saito, WorldWide Antimalarial Resistance Network (WWARN), The University of Tokyo Institute of Medical Science
Comments to the Author:
Re: bmjopen-2022-069771

This is a protocol of a systematic review and aggregated data meta-analysis on the potential herbal treatment for malaria. The authors have published some protocols of systematic reviews before, and the manuscript is reported following the PRISMA-P statement. The systematic review is also registered to PROSPERO in advance. Overall, it is well written, but some additional explanations and clarifications will be helpful.

Major comments

Reviewer Comment, reviewer #1: The dates of the study (eg, when the search will be or was started) should be included in the manuscript.

Response: The scoping searching to develop the search strategy and inform protocol development was started on 7th November 2022. The last search was done on 17th Nov 2022 and the dates have been incorporated in the revised manuscript.

Reviewer comment, reviewer #1: There is no description of “evidence and gap map”. I am afraid I am not familiar with the Campbell Review, probably because it seems to be primarily for social and behavioural science. I would be grateful if you could explain how the map will be produced.

Response: Thank you so much for your comment and observation, indeed we didn’t seem to include a description of how the map will be produced and moving forward this has now been included in the manuscript. However, in a nutshell, this will be an interactive evidence and gap map of studies that provide evidence on efficacy of anti-malaria herbal medicines used by communities in malaria affected regions globally.

Evidence and Gap Map (EGM). This will be a secondary product in addition to the systematic review. Our approach to the Evidence Gap Map (EGM) will be informed by the Campbell Collaboration approach (Saran & White 2018). An EGM highlights where the evidence is and where more evidence is needed in terms of interventions and outcomes contained in the studies identified for this systematic review. They consolidate what is known and what is not known by mapping out existing and ongoing studies and providing a graphical representation of areas with strong, weak, or no evidence on the effect of interventions.

Briefly, we will apply the data already identified, screened and coded from this systematic review to develop the EGM. Using the EPPI mapper adds-on for EPPIR Web software for conducting systematic reviews we will produce an EGM in visual presentation of the evidence matrix. The intervention categories lie on the y-axis whilst outcome domains will run in the x-axis. Additional dimensions of the study or intervention characteristics, such as study design, geographical region and country income subgroup status or population sub-group will be applied as filters.

The Campbell guidelines simply provide guidance for the creation of an evidence and gap map and can be adapted for any field, much as they were originally intended for social and behavioral science given that is the area of research in which the Campbell collaboration produces. EPPI-Mapper was also created to support the Campbell Collaboration's evidence gap maps.

This has been incorporated in the revised manuscript.

Reviewer comment, reviewer #1: Compared with a recent systematic review and meta-analysis (Ref #11. Tajbakhsh, et al Malar J 2021:20:349), the novelty of the current review includes: this review covers all world (rather than Africa); and compares efficacy between herbal medicines and artemisinin (Line 97). However, I am not fully convinced of the feasibility and the importance of the latter and it is not clear whether the authors are planning to do this. Firstly, the previous review found only one clinical study, which was not a comparative study. It is likely that clinical efficacy cannot be compared because there are no studies. Secondly, in-vitro studies can be valid even without internal comparators, for example using the historical data of IC50 of artemisinin. In addition, the authors did not include this (ie, only comparative studies are included) as the eligibility criteria. In Table 2, the comparator is indicated as “None” for clinical outcomes. On the other hand, the effect measurements listed in Lines 335-7 are all derived from comparisons (ie, ratios or differences). What kind of effect measurements will be used for clinical outcomes? Please clarify whether you include only comparative studies or not (for which outcomes?) and update the whole manuscript consistently.

Response: Thanks for the comment (s), we have reviewed this and here below is the summary of our response

On the issue of no clinical studies that have been done on antimalarial activity of herbal medicines. There exist several clinical studies that have been done on antimalarial activity of herbal medicines. Here below are examples of some of the studies that have been done in this area. Therefore, our review is feasible. However, our review also intends to generate an EGM that will help provide information on the status of the current evidence on antimalarial activity of herbal medicines in malaria affected countries.

1. Boye GL. Studies on the antimalarial action of Cryptolepis sanguinolenta extract. Proceedings of an international symposium on East-West medicine, Seoul, Korea, 1989: 242-51.

2. Mueller MS, Runyambo N, Wagner I, Borrmann S, Dietz K, Heide L. Randomized controlled trial of a traditional preparation of Artemisia annua L (Annual Wormwood) in the treatment of malaria. Trans R Soc Trop Med Hygiene 2004;98(5): 318-21.

3. Koita N. A comparative study of the traditional remedy “Suma-Kala” and chloroquine as treatment for malaria in the rural areas. In: Mshigeni KE, Nkunya MHH, Fupi V, Mahunnah RLA, Mshiu E, eds. Proceedings of an international conference of experts from developing countries on traditional medicinal plants, Arusha, Tanzania, 18-23 Feb 1990. Dar Es Salaam: Dar Es Salaam University Press, 1991.

4. Benoit-Vical F, Valentin A, Da B, Dakuyo Z, Descamps L, Mallie M. N'Dribala (Cochlospermum planchonii) versus chloroquine for the treatment of uncomplicated Plasmodium falciparum malaria. J Ethnopharmacol 2003;89: 111-4.

5. Valecha N, Devi CU, Joshi H, Shahi VK, Sharma VP, Lal S. Comparative efficacy of Ayush-64 vs chloroquine in vivax malaria. Curr Sci 2000;78: 1120-2.

Secondly, in-vitro studies can be valid even without internal comparators, for example using the historical data of IC50 of artemisinin

We thank the reviewer for the comment, it is true in-vitro studies can be valid even without internal standards as stated by the reviewer. Our review is however not intended to establish validity of in-vitro studies. In this review we intend to compare through analysis, the in-vitro activity of herbal medicines with those of artemisinin agents. This could be reported in the same article or reported in separate articles. Like the reviewer suggests we shall in addition, use historical values reported on the activity of artemisinin agents against Plasmodium parasites. This has been adjusted in the revised manuscript to incorporate both comparative and non-comparative studies since we shall establish our intended outcome through statistical comparison of the reported in-vitro estimates of antimalarial activity of herbal medicines and artemisinin agents.

The comparator for clinical studies in Table 2 has been corrected. For clinical studies the comparator will be artemisinin agents. This has been adjusted in the revised manuscript. We shall use odds ratios for clinical outcomes. In this review we shall include comparative and non-comparative studies. Comparative studies will be for clinical outcomes and in-vivo studies, and non-comparative studies for in-vitro antimalarial activity. Additionally, clinical studies done using non-comparative methods will also be included in the review. This has been adjusted in the revised manuscript.

Reviewer comment, reviewer#1: Outcomes. Although improvement of symptoms is important, parasitological clearance is a more direct consequence of the antimalarial effect. I would suggest you include parasitological clearance or ACPR (adequate clinical and parasitological response) defined by WHO to assess antimalarial efficacy.

Response: Thanks for the comment, we have added adequate clinical and parasitological response (ACPR) as a measure of the antimalarial effect. This has been adjusted in the revised manuscript.

Reviewer comment, reviewer#1: Secondary outcome includes safety. Are you going to include LD50 and some other safety outcomes in animal studies? It looks your focus is only on efficacy. Please clarify whether you are going to assess safety as well. If yes, what kind of measurements will be gathered?

Response: Thanks for the comment, the primary outcome of this review is antimalarial efficacy of herbal medicines used by communities in malaria affected countries globally. In addition to other secondary outcomes of the review will also include safety of the herbal medicines. For safety measures, in in-vivo studies our target is LD50, organ toxicity, teratogenicity, carcinogenesis, and mutagenesis. While for clinical studies, we shall capture any reported side effects/adverse drug reactions.

This section was present in the original manuscript but has been further clarified in the revised manuscript.

Reviewer comment, reviewer#1: The search strategy is not easy for me to figure out what is the exact search terms and conditions. Do you combine all categories of PICOST with “AND”?

Response: The search strategy used in PUBMED database has been provided in the revised manuscript. For each of the elements of PICOST different terms were developed. In searching for the articles in the different databases terms related to a particular element of PICOST are combined using Boolean operator ‘OR’ and when combining terms representing different elements of PICOST the Boolean operator ‘AND’ is used. This is described in the revised manuscript. This search strategy showing how the terms were combined is also provided as an additional file.

Reviewer comment, reviewer#1: Risk of bias. How do you assess the risk of bias of in-vitro studies. Please explain.

Response: Thanks for the comment, the risk of bias of in-vitro studies will be assessed using QUIN tool (Sheth et al., 2022). The tool has a twelve-item criterion which will be scored, and the scores used to grade the in-vitro study as high (<50%), medium (50% to 70%), or low (>70%) risk of bias.

Sheth VH, Shah NP, Jain R, Bhanushali N, Bhatnagar V. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry: The QUIN. J Prosthet Dent. 2022 Jun 22:S0022-3913(22)00345-6.

For in-vivo studies, risk of bias will be assessed following SYRCLE’s risk of bias tool for animal studies (Hooijmans et al., 2014). The following risk of bias will be assessed, selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting). The in-vivo studies will be scored and assigned a judgement of low, high, or unclear risk of bias.

Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW (2014): SYRCLE’s risk of bias tool for animal studies. BMC Med Res Methodol 14, 43 (2014).

This has been described in the revised manuscript.

Reviewer comment, reviewer#1: Publication bias. Egger's test is only valid (recommended) for binary outcomes. How would you assess other types of outcomes?

Response: Thanks for the comment, Egger's test is commonly used to assess potential publication bias in a meta-analysis via funnel plot asymmetry. The test (Egger's test) is a linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance. The performance of Egger's tests has been extensively studied for binary outcomes, but not for continuous ones. In this study we shall use Egger's test for binary outcomes. For continuous outcomes, we shall assess baseline risk of bias in the included studies and assess publication bias using standard errors.

This has been incorporated in the revised manuscript.

Reviewer comment, reviewer#1: Quality assessment. AMSTAR-2 is to appraise systematic reviews, rather than to assess "(individual) articles' quality" (Line 307). GRADE is to assess the strength of evidence rather than "quality of evidence" (Line 308).

Response: Quality assessment is achieved in the risk of bias assessment. The risk of bias assessment for the different study designs of the studies that will be included in this review has been incorporated in the revised manuscript. For In-vitro studies, risk of bias will be assessed using QUIN tool (Sheth et al., 2022). The tool has a twelve-item criterion which will be scored, and the scores used to grade the in-vitro study as high (<50%), medium (50% to 70%), or low (>70%) risk of bias. For randomized we shall use Cochrane risk of bias tool and for non-randomized studies, we shall use ROBINS-I tool and will assess the following risk of bias, selection bias, measurement bias, performance bias, detection bias, attrition bias, and information bias. For cross-sectional studies, we shall use the Newcastle Ottawa tool to assess risk of bias. The following risk of bias will be assessed in observational studies, selection bias, information bias, reporting bias, recall bias, detection bias and reporting bias. For In-vivo studies, the risk of bias will be assessed using SYRCLE's risk of bias tool for animal studies (Hooijmans et al., 2014). The following risk of bias will be assessed, selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting). The in-vivo studies will be scored and assigned a judgement of low, high, or unclear risk of bias. The AMSTAR-2 tool will only be used for assessing risk of bias in systematic review articles that will be used in the EGM. This has been described in the revised manuscript.

Sheth VH, Shah NP, Jain R, Bhanushali N, Bhatnagar V. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry: The QUIN. J Prosthet Dent. 2022 Jun 22:S0022-3913(22)00345-6.

Additionally, the risk of bias in in-vivo (animal) studies will be assessed using SYRCLE's risk of bias tool

Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014 Mar 26;14:43.

This has been incorporated in the revised manuscript

Reviewer comment, reviewer#1: References do not include the journal titles. Please update them.

Response: Thanks for the comment, we have updated all our references to follow the BMJ Open guidelines.

Minor comments
Reviewer comment, reviewer#1: Line 76. Something (possibly “in”) is missing before “various malaria endemic regions”.

Response: Thanks for the comment, this has been adjusted in the revised. Manuscript.

Reviewer comment, reviewer#1: In-vivo usually means animal studies, whereas clinical studies means studies done in humans. In Table 2, in-vivo is used as clinical (ie, in humans). Please clarify the terminology used in your manuscript.

Response: Thanks for the comment, we are sorry for miss using these terms. We have corrected this in the table 2 in the revised manuscript.

Reviewer comment, reviewer#1: Table 2. Setting. I agree that clinical studies should be done in malaria-endemic countries. However, I believe in-vitro and in-vivo (animal) studies can be done anywhere. Why do they need to be done in malaria-endemic countries?

Response: Thanks for the comment, yes in-vitro and in-vivo studies can be done in any setting as suggested by the reviewer, our review is focused on malaria affected countries not only malaria endemic countries as suggested by the reviewer. The review focuses on herbal medicines used by communities in management of symptoms of malaria in malaria affected regions. Additionally, since malaria does not occur in some countries of the world it is unlikely that communities in those countries would use herbal medicines to manage malaria which is why our focus is all malaria affected countries/regions of the world.

Reviewer comment, reviewer#1: Table 2 Setting. How can the data (eg, prevalence) from cross-sectional studies be used for assessing the efficacy of drugs?

Response: Thanks for the comment, cross-sectional studies cannot generate evidence that can be used in evaluating the efficacy of drugs. This has been corrected in the revised manuscript. In this review cross-sectional studies will be used to collect evidence of the prevalence of use of herbal medicines in management of malaria symptoms in communities in malaria affected regions of the world. This study design is also relevant for the EGM. We shall use In-vitro, in-vivo (animal) and clinical trial studies in assessing the efficacy of herbal medicines used for management of symptoms of malaria by communities in malaria affected countries.

This has been corrected in the revised manuscript.

Reviewer comment, reviewer#1: Line 175. I do not understand the meaning of this sentence. Could you please consider rephrasing it?

Response: Thanks for the comment, this has been adjusted in the revised manuscript

Reviewer comment, reviewer#1: Please reformat the inclusion criteria. The first four are probably combined with OR, but the last two must be combined with AND. The last two can be in the exclusion criteria (published before 2000, non-English literatures).

Response: Thanks, this has been incorporated in the revised manuscript

Reviewer comment, reviewer#1: Excluding non-English literatures (eg, Chinese) might be a potential limitation of your search. Please remind that artemisinin is originally from China and quinine is from Peru.

Response: Thanks for the comment, we have removed language restriction in the review. This has been affected in the revised manuscript.

Reviewer comment, reviewer#1: Line 191. There will be different kinds of situation when “full text cannot be retrieved”. This can include situations that your institution does not subscribe some specific journals, or you are not willing to pay the cost for getting individual papers (which should be ideally avoided). On the other hand, it is possible that electronic copies are not available from the publisher and hard copies are difficult to obtain in case of local journals. As this is a protocol paper, it would be nice if you clarify what kind of efforts will be made to retrieve full texts.

Response: Thanks for the comment, the study librarian has access to external information sources like Web of Science, EMBASE, Sci-Hub, Lib-Hub and PDF Drive. The study librarian will also contact other librarians in their networks for retrieval of full text articles. This has been incorporated in the revised manuscript.

Reviewer comment, reviewer#1: Line 200. Please specify the way you are going to search for grey literature.

Response: Thanks for the comment, we shall search grey literature from organization websites such as WHO, Medicines for malaria venture, institutional repositories, and contact experts/researchers in malaria field.

This has been incorporated in the revised manuscript.

Reviewer comment, reviewer#1: Search terms
9-1. Why other standard antimalarials such as artesunate, mefloquine, amodiaquine are not included in the search term?
9-2. Line 223 Do you need “OR”?
9-3. Clinical outcome terms require reconsideration. It is too specific and not comprehensive. For example, “febrile” will not be found. How did you choose these symptoms: why muscle pain, headache, abdominal pains are not included?
9-4. I think it is better to exclude by region after the search, rather than using it in the first place even if you want to include only studies in malaria-endemic countries. And one pair of brackets are needed: (Malaria-affected AND (region* OR countr* OR area*)) OR […]. “malaria-endemic” might be another commonly used term. Overall, I might not add this limitation by area at the stage of database searching.

Response: Thanks for the guidance, in searching for the articles we have removed the limitation of malaria affected or malaria endemic settings from the search strategy. However, this will be applied during article screening stage.

Reviewer comment, reviewer#1: Line 307. AMSTAR-2 has 16 domains rather than 10 in AMSTAR.

Response: This has been corrected in the revised manuscript. Other tools that will be used for risk of bias assessment have also been described in the revised manuscript.

Reviewer comment, reviewer#1: Line 326. “In case of none response” should be “in case of no response”.

Response: Thanks, this correction has been incorporated in the revised manuscript

Reviewer comment, reviewer#1: Line 332. Adding a reference for this equation would be helpful.

Response: Thanks, reference has been added, Andrade, 2020.

Andrade C. Understanding the difference between standard deviation and standard error of the mean, and knowing when to use which. Indian J Psychol Med. 2020;42(4):409-410

Reviewer comment, reviewer#1: Line 338. It is probably “metan” command rather than “mean”.

Response: Thanks for the comment, this has been corrected in the revised manuscript

Reviewer: 2
Dr. Amjed Alqaisi, University of Baghdad Al-Jaderyia Campus College of Science
Comments to the Author:

Reviewer comment, reviewer#2: Check the line number that found in PRISMA-P 2015 checklist with line number in manuscript.

Response: Thanks for the comment, this has been addressed in the revised manuscript

VERSION 2 – REVIEW

REVIEWER	Saito, Makoto WorldWide Antimalarial Resistance Network (WWARN)
REVIEW RETURNED	01-Mar-2023

GENERAL COMMENTS	Authors have responded to my previous comments adequately. There are some minor comments. 1. Lines 15 & 103. Artemisinin”-based” combination treatment. 2. Lines 33-4. ACPR is not a lab parameter, but an outcome assessing clinical efficacy (as is correctly mentioned in Line 255). 3. Table 1. The reference for defining ACPR (i.e. WHO 2009. Methods for surveillance of antimalarial drug efficacy.) should be added. 4. Line 185. Rate of symptom resolution is listed as both primary (Line 177) and secondary (Line 185) outcomes.

	5. Line 251. Why do you include only lumefantrine and piperaquine, but not the other partner drugs (such as mefloquine, amodiaquine, pyronaridine) or other antimalarial drugs (e.g. chloroquine and quinine)? 6. Reference #25 should be a published article (https://doi.org/10.1002/jrsm.1414) rather than a webpage. Additionally, the methodology describe in Lines 340-1 does not seem to be the one described in Reference #25. Please correct it appropriately. 7. Line 346. Please correct the cut-off values (ranges) of heterogeneity categories. They were correctly written in your reply. 8. Reference #29 does not support the mathematical equation for the standard error. Please cite the right reference(s) here.

VERSION 2 – AUTHOR RESPONSE

Comment reviewer #1: Authors have responded to my previous comments adequately. There are some minor comments.

Response: Thanks for the comment

Comment reviewer #1: Lines 15 & 103. Artemisinin"-based" combination treatment.

Response: This has been adjusted in the revised manuscript

Comment reviewer #1: Lines 33-4. ACPR is not a lab parameter, but an outcome assessing clinical efficacy (as is correctly mentioned in Line 255).

Response: The statement has been deleted as it is already covered under 'clinically important efficacy and adverse drug reactions'

Comment reviewer #1: Table 1. The reference for defining ACPR (i.e. WHO 2009. Methods for surveillance of antimalarial drug efficacy.) should be added.

Response: A reference has been added to table 1 for the definition of ACPR

Reference

World Health Organization (2009): Methods for surveillance of antimalarial drug efficacy, Geneva, Switzerland

Comment reviewer #1: Line 185. Rate of symptom resolution is listed as both primary (Line 177) and secondary (Line 185) outcomes.

Response: Thanks for the observation, 'rate of symptom resolution' has been deleted from secondary outcome and left as a primary outcome. This has been corrected in the revised manuscript

Comment reviewer #1: Line 251. Why do you include only lumefantrine and piperaquine, but not the other partner drugs (such as mefloquine, amodiaquine, pyronaridine) or other antimalarial drugs (e.g. chloroquine and quinine)?

Response: Thanks for the comment, more medicines have been included, amodiaquine, pyronaridine, chloroquine, quinine. This has been corrected in the revised manuscript.

Comment reviewer #1: Reference #25 should be a published article (https://doi.org/10.1002/jrsm.1414) rather than a webpage. Additionally, the methodology describe in Lines 340-1 does not seem to be the one described in Reference #25. Please correct it appropriately.

Response: Thanks for the comment, we have included an appropriate methodology statement and updated the reference as advised

Refere: Doleman B, Freeman SC, Lund JN, Williams JP, Sutton AJ. Funnel plots may show asymmetry in the absence of publication bias with continuous outcomes dependent on baseline risk: presentation of a new publication bias test. Res Synth Methods. 2020 Jul;11(4):522-534. doi: 10.1002/jrsm.1414. Epub 2020 May 6. PMID: 32362052.

Comment reviewer #1: Line 346. Please correct the cut-off values (ranges) of heterogeneity categories. They were correctly written in your reply.

Response: Thanks for the comment, in our response we addressed the issue raised on risk of bias assessment which we adequately responded to. The section your raising concern on is for measurement of heterogeneity which is different from risk of bias assessment. The cut-offs for heterogeneity provided are appropriate as guided by the Cochrane handbook on assessment of heterogeneity. https://training.cochrane.org/handbook

Comment reviewer #1: Reference #29 does not support the mathematical equation for the standard error. Please cite the right reference(s) here.

Response: Thanks for the comment, the reference has been corrected in the revised manuscript. The formula is on p.433 here:

https://researchonline.lshtm.ac.uk/id/eprint/4663958/1/2021_ITD_PhD_Waddington_H.pdf

VERSION 3 – REVIEW

REVIEWER	Saito, Makoto WorldWide Antimalarial Resistance Network (WWARN)
REVIEW RETURNED	18-May-2023

GENERAL COMMENTS	Authors have responded to my previous comments adequately. I am afraid, artemisinin-based combination "therapy" is more commonly used than artemisinin-based combination "treatment". This is my mistake in my previous comment, please accept my appologies.

VERSION 3 – AUTHOR RESPONSE