# Optimal long-acting antimalarial regimens for seasonal malaria chemoprevention: Mapping review and Network Meta-analysis

Dhruv Darji[1,2,*], Dhol Samuel Ayuen[1,2], Mary Scott[1,2], Boris-Enock Zinsou[2,3], Adama Kazienga[1,2], Farhad Shokraneh[1,2], Prabin Dahal[1,2], Philippe J. Guerin[1,2], James A. Watson[1,2]

**1** Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom;

**2** Infectious Diseases Data Observatory, Oxford, United Kingdom;

**3** Université Paris Cité, Paris, France

*dhruv.darji@gtc.ox.ac.uk

Preprint not peer reviewed



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## Abstract

### Background

Over 50 million children receive seasonal malaria chemoprevention (SMC) each year with the combination of sulphadoxine-pyrimethamine (SP) plus amodiaquine (AQ). However, alternative chemoprevention regimens may be more effective due to drug resistance and more suitable pharmacokinetics.

### Methods

A systematic review was undertaken to identify all prospective efficacy and safety studies of malaria chemoprevention in children (WWARN ChemoMap). A Bayesian network meta-analysis (bNMA) was then conducted using randomised trials assessing antimalarial efficacy of SMC drug regimens. Regimens were grouped by their long-acting antimalarials and frequency of administration. The co-primary outcomes were incidence of uncomplicated malaria and severe malaria.

### Findings

The WWARN ChemoMap includes 150 studies and of these, 19 randomised trials of SMC were included in the bNMA. 18 trials were conducted in West Africa and one in East Africa (Uganda), and nine active antimalarial regimens were evaluated. For uncomplicated malaria, the combination of SPAQ plus seasonal RTS,S vaccination had the highest efficacy relative to no chemoprevention (incidence rate ratio [IRR] 0·07 [95% CrI 0·06-0·09]). This was followed by SP plus piperaquine (SPPQ; IRR 0·14 [95% CrI 0·04-0·22]), dihydroartemisinin plus piperaquine (DHAPQ; IRR 0·20 [95% CrI 0·16-0·23]), and SPAQ (IRR 0·25 [95% CrI 0·24-0·27]). The efficacy of SPAQ plus seasonal RTS,S was approximately multiplicative when compared with the individual effects of SPAQ and seasonal RTS,S. For severe malaria, the same combination (SPAQ plus seasonal RTS,S) also demonstrated greater efficacy (IRR 0·12 [95% CrI 0·06-0·28]) than SPAQ (IRR 0·42 [95% CrI 0·27-0·65]) and seasonal RTS,S (IRR 0·42 [95% CrI 0·22-0·79]).

### Interpretation

Combining SMC with seasonal malaria vaccination and using piperaquine-based regimens as an alternative to SPAQ could substantially increase its efficacy.



### Funding

Malaria Consortium, The Rhodes Trust


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## Research in context

### Evidence before this study

We conducted a literature search for meta-analyses of the efficacy of SMC against uncomplicated and severe malaria using several bibliographic databases (Pubmed, Embase, and Cochrane central). We searched for articles published from inception to February 21, 2025. We found four systematic reviews and meta-analyses, which have consistently shown that seasonal malaria chemoprevention (SMC) substantially reduces malaria morbidity and mortality in children. These meta-analyses have relied on pairwise comparisons of individual antimalarial drug regimens used for SMC to no chemoprevention, limiting the ability to compare between existing options. SMC is now the standard of care across the Sahel and randomised trials cannot include no chemoprevention arms. Because there has not been a systematic comparison of available chemoprevention options there is no clear consensus on the optimal regimens for SMC in Africa.

### Added value of this study

To the best of our knowledge, this is the first network meta-analysis (NMA) comparing all trialled long-acting antimalarials as well as seasonal malaria vaccination, for SMC. We systematically identified studies for this NMA using the WorldWide Antimalarial Resistance Network chemoprevention living mapping review (WWARN ChemoMap), a publicly available and yearly updated living library of safety and efficacy studies of malaria chemoprevention in children. This resource can help streamline future systematic reviews and meta-analyses as well as support the development of individual participant data (IPD) repositories for malaria chemoprevention studies.

Our NMA included 19 randomised trials evaluating nine distinct long-acting antimalarial regimen combinations, enabling comparison and ranking of efficacy across drug regimens that have not previously been directly compared. Our findings suggest that using piperaquine-based regimens instead of amodiaquine-based regimens for SMC could offer greater protection against malaria. However, there is limited randomised evidence regarding sulphadoxine pyrimethamine plus piperaquine (SPPQ) which could be potentially more effective than sulphadoxine pyrimethamine plus amodiaquine (SPAQ), the currently recommended regimen for SMC. We also found that combining long-acting antimalarial drugs with seasonal malaria vaccination could substantially improve the efficacy of SMC. Our findings also demonstrated a multiplicative benefit of combining seasonal chemoprevention with seasonal vaccination.

### Implications of all the available evidence

Our findings show that the efficacy of SMC with SPAQ is sub-optimal and can be further improved. Piperaquine-based regimens could be a more efficacious alternative to SPAQ, however further randomised evidence of SPPQ against SPAQ is needed to support policy decisions on the ideal antimalarial drug choices for SMC. While seasonal vaccination can substantially enhance the effectiveness of SMC, the costs and logistical challenges of this intervention require substantial investment.



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## Background

Malaria disproportionately affects young children in sub-Saharan Africa (SSA) who bear the highest burden of morbidity and mortality.[1] Seasonal Malaria Chemoprevention (SMC) was initially introduced in areas of highly seasonal malaria transmission in the Sahel region to prevent malaria amongst young children during the peak transmission periods.[2] SMC using the current recommended combination of sulphadoxine-pyrimethamine (SP) plus amodiaquine (AQ) reduced the risk of uncomplicated malaria in children under-five by approximately two thirds during the high transmission season.[3] Owing to its demonstrated safety,[4] efficacy,[3] cost-effectiveness,[5] and scalability in West Africa,[6] the World Health Organization (WHO) revised its policy in 2022 to allow for flexible deployment of SMC with SPAQ in other parts of Africa where malaria transmission may be seasonal, and to expand the eligible age range of target populations.[2] In 2024, approximately 54 million children across 19 African countries received SMC.[1]

Several factors warrant the need for alternative regimens for SMC following the 2022 expansion policy. Firstly, in the presence of high antifolate resistance in East and Southern Africa, the efficacy of SP is substantially reduced, thus the efficacy of SMC relies primarily on the AQ component.[7-9] Secondly, SMC with SPAQ cannot be given in areas that use amodiaquine-containing treatment regimens (artesunate-amodiaquine and, soon, the triple combination therapy artemether-lumefantrine plus amodiaquine) due to concerns around overdosing for AQ.[2, 10] Finally, as malaria vaccines are rolled out in SSA, there is a need to better understand their effect when given along with SMC and how they compare with other antimalarial drug-only regimens for SMC.[11]

The primary therapeutic objective of SMC is to prevent malaria illness. This is achieved by using antimalarial medicines with long terminal elimination half-lives ($t_{1/2}$). Current SMC is administered as monthly treatment regimens, therefore the slowly eliminated drugs must be above the minimal inhibitory concentration (MIC) in most children for one month to suppress parasite growth.[12] Monthly SPAQ, which combines two slowly eliminated antimalarials, has been the most extensively studied SMC regimen. Other long-acting antimalarials for SMC, including piperaquine-based and amodiaquine- or SP-only regimens have also been evaluated in randomised trials.[13-15] However, a comprehensive characterisation of relative efficacies of all antimalarial regimens for SMC has not been undertaken. In the absence of direct randomised comparisons, a network meta-analysis (NMA) can inform how different long-acting antimalarial regimens compare with each other for SMC by using the indirect evidence. These results can then guide future policy for the selection of optimal regimens for SMC. In this paper, we present a systematic review, conducted within the WorldWide Antimalarial Resistance Network Chemoprevention Living Mapping Review (WWARN ChemoMap), and aggregate-level Bayesian NMA to assess the relative efficacies of long-acting antimalarials regimens used in SMC.

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## Methods

### Search strategy and selection criteria

We systemically developed a living mapping review of all chemoprevention studies done in children in sub-Saharan Africa (WWARN ChemoMap).[16] Searches were conducted across multiple bibliographic databases and trial registries (including Embase, MEDLINE, Global Health (all via Ovid)) from inception to 21 February 2025. Details of the search strategy are outlined in Supplementary Appendix 1. The search will be updated annually each February until 2027 (protocol registered on Open Science Framework).

Dual independent screening (DD, DSA, and BZ) was undertaken, with disagreements resolved by a third reviewer (JAW or PD). We included prospective studies (randomised and non-randomised) of malaria chemoprevention, encompassing interventions delivered alone or with co-interventions in children younger than 16 years, and reporting various clinical, anthropometric, parasitological, molecular, and safety outcomes (Table S1). Each identified study was then categorised based on the type of intervention as SMC, perennial malaria chemoprevention (PMC), post-discharge malaria chemoprevention (PDMC), intermittent preventive treatment in school children (IPTsc), or “other chemoprevention".

Using the WWARN ChemoMap, we conducted a systematic search for randomised trials assessing the efficacy of different antimalarial regimens used in SMC (PROSPERO CRD420251126777). The eligibility criteria are outlined in Table S2.

### Data extraction

Two authors (DD and DSA) independently extracted data using a piloted data extraction form, with discrepancies resolved through discussion with a third reviewer (JAW or PD). For uncomplicated malaria, arm-level data on case counts and person-time were extracted, while for severe malaria, total case counts and numbers of participants per trial arm were extracted. In addition, the reported treatment effects with corresponding standard errors were extracted for both outcomes. Details on data extraction are provided in Table S3.

### Within-study risk of bias

The risk of bias was assessed independently by two reviewers (DD and DSA), with discrepancies resolved through a third reviewer (JAW or PD). Risk of bias was assessed using the Cochrane RoB 2 tool.[17] Outcome-specific domains (domains 3, 4, and 5) were assessed separately for uncomplicated malaria and severe malaria.

### Quality of evidence rating

The Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) guidelines adapted for network meta-analysis were applied to assess the quality of evidence for uncomplicated malaria. This was performed independently by two authors (DD and DSA) and discrepancies were resolved by consulting a third author (JAW or PD). Details of the quality of evidence assessment are provided in Supplementary Appendix 4.

### Statistical analysis

The co-primary efficacy outcome were uncomplicated clinical malaria, defined as presence of clinical symptoms indicative of malaria together with parasitological confirmation by microscopy or rapid diagnostic test, and severe malaria, defined according to WHO criteria or as malaria-related



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hospitalisations. Post-hoc, we assessed tolerability outcomes: vomiting, diarrhoea, loss of appetite, fever, headache, and cough reported within one week of drug administration. For each outcome, treatment arms were grouped into NMA nodes based on distinct combinations of long-acting antimalarial regimens, including sulphadoxine-pyrimethamine, amodiaquine, piperaquine, and seasonal RTS,S/AS01E vaccine. The RTS,S/AS01E vaccine was considered equivalent to a long-acting antimalarial regimen because of its sustained prophylactic effect against clinical malaria following repeated administration.[11] The contribution of the artemisinin derivatives (dihydroartemisinin or artesunate) to chemopreventive efficacy was ignored, because they do not significantly contribute to post-treatment prophylaxis due to their very rapid elimination.[12] Regimens with the same long-acting drugs with or without artemisinin derivatives were thus grouped within the same node (e.g. SP would be considered the same as SP plus artesunate). Different dosing frequencies of long-acting antimalarials were treated as separate nodes. Multi-arm trials with similar interventions (e.g. multiple placebo SMC arms) were combined into a single arm to avoid unit-of-analysis errors.[18]

A two-stage Bayesian hierarchical contrast-based model was used to perform the NMA for all efficacy and tolerability outcomes using the estimated relative treatment effects from the included studies. For uncomplicated malaria, the treatment effect summary was the incidence rate ratio (IRR) from the start of SMC until the earliest follow-up visit after completion of the first SMC round, capturing the efficacy at the earliest post-SMC interval. For severe malaria, the treatment effect summary was the odds ratio (OR) and further analysis details are given in Supplementary Appendix 3. For both outcomes, a common effect model was specified given the small number of studies, assuming a normal likelihood with an identity link function and uninformative priors on model parameters. Pooled estimates were obtained using the Markov Chain Monte Carlo method (four chains with 10,000 iterations each, including 5000 burn-in iterations). Convergence was assessed using trace plots and Gelman-Rubin plots. Results were summarised as the mean IRR or mean OR with 95% credible intervals (CrI).

Inconsistency was assessed using the node-splitting method, and within-design heterogeneity in the direct evidence was explored using pairwise meta-analyses. Network geometry was illustrated using network plots and all relative treatment effects were summarised in league tables. Network estimates for active treatments versus placebo/no SMC comparisons were presented using forest plots. Treatment hierarchy was assessed for each outcome using posterior probabilities for all treatments being at each possible rank for each intervention in the network. Publication bias was assessed using a funnel plot and eggers test.

Sensitivity analyses were conducted by restricting to studies reporting efficacy in children younger than five years and those conducted in West Africa. We assessed the effect of excluding one trial for which we approximated the treatment effect using cumulative risk rather than incidence rate, due to lack of person-time data (Table S3).[13] Network meta-regression was used to assess the effect of SMC supervision, risk of bias (high versus low), trial design (cluster versus individual randomisation), and the prevalence of known markers of resistance to SP on network heterogeneity. Resistance was characterised using time- and site-matched modelled median prevalences of *P. falciparum* dihydropteroate synthase (*Pfdhps*) A437G and K540E mutations.[7] The severe malaria NMA was also conducted using another contrast-based Bayesian model (post-hoc) using number of events and participants to evaluate different methodological approaches (Supplementary Appendix 3).

Analyses were conducted in R (version 4.5) using the gemtc (version 1.1), netmeta (version 3.3), and cmdstanr (version 0.9) packages. The data and R scripts used in this study are available on GitHub.



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## Results

The initial search identified 7,272 records, of which 150 studies were included in the WWARN ChemoMap (Figure S1). Of these, 69 (46%) were publications of SMC. The geographical distribution of SMC studies highlights limited evidence on the safety and efficacy of SMC from East and Southern Africa, with only six studies (9%) conducted in these regions (Figure S2). The mapping review also identified 34 studies of PMC, 17 studies of IPT in school-aged children, 8 studies of IPT in children with sickle cell disease, and 3 studies of post-discharge malaria chemoprevention. Summarised descriptions of all included studies are provided in Supplementary file 1 and on the WWARN ChemoMap surveyor.

Of the 69 SMC studies, 19 randomised trials were included in the NMA, comprising 14 individually randomised trials with 26,772 participants, four cluster randomised trials with 11,172 participants, and one stepped-wedge cluster randomised trial (Figure S3). Study-level characteristics are shown in Table 1, Table S4 (intervention characteristics) and Supplementary Appendix 2 (results of individual studies). All studies were conducted in West Africa, except one trial from Northeastern Uganda.[19] 13 trials enrolled children younger than five years, four included up to 10 years, and two recruited children aged 5-15 years. The number of monthly SMC cycles delivered ranged from one to six, with two trials delivering bimonthly cycles of SP and ASAQ. In 11 trials, SMC doses were administered under direct supervision (n=21,644) and in total, nine antimalarial regimens were assessed.

For uncomplicated malaria, most of the direct evidence came from pairwise comparisons of SPAQ, DHAPQ, and placebo/no SMC (Figure 1). For severe malaria, direct evidence was mostly from comparisons of SPAQ against placebo/no SMC, with no piperaquine-containing regimens represented.

For uncomplicated malaria, the combination of SPAQ plus seasonal RTS,S vaccination had the highest efficacy, with a 93% reduction (IRR 0·07 [95% CrI 0·06-0·09]) in the incidence of uncomplicated malaria compared to placebo/no SMC (Figure 2(a)). Notably, the efficacy of the combined intervention was approximately multiplicative when compared with the estimated individual effects of SPAQ alone (IRR 0·25 [95% CrI 0·24-0·27]) and seasonal RTS,S vaccination alone (IRR 0·26 [95% CrI 0·21-0·31]). SPPQ showed a considerably high protective efficacy of 84% (IRR 0·14 [95% CrI 0·04-0·22]), but with wide credible intervals due to only two trials with an SPPQ arm. DHAPQ and SPAQ reduced uncomplicated malaria by 88% (IRR 0·20 [95% CrI 0·16-0·23]) and 75% (IRR 0·25 [95% CrI 0·24-0·27]) compared with placebo/no SMC, respectively. The combined effect of SP plus AQ was sub-multiplicative compared to the effects of monthly SP alone (IRR 0·37 [95% CrI 0·31-0·44]) and AQ alone (IRR 0·33 [95% CrI 0·26-0·41]).

Comparing active antimalarials, piperaquine-containing SMC regimens (SPPQ and DHAPQ) showed better protective efficacies than amodiaquine-containing regimens (Table S5). Compared to SPAQ, SPPQ showed a 43% lower (IRR 0·57 [95% CrI 0·36-0·89]) and DHAPQ showed a 23% lower (IRR 0·77 [95% CrI 0·66-0·91]) rate of malaria. This was also reflected in comparisons of SPPQ vs ASAQ (IRR 0·44 [95% CrI 0·27-0·74]) and DHAPQ vs ASAQ (IRR 0·60 [95% CrI 0·45-0·81]). Treatment ranking showed that SPAQ plus seasonal RTS,S ranked highest, followed by SPPQ (second), while DHAPQ in third place outranked SPAQ (fourth), artesunate plus amodiaquine (ASAQ) (sixth), and monthly SP / SP plus artesunate (seventh) (Figure 3(a)).

For severe malaria, SPAQ plus RTS,S also showed the greatest protective efficacy (IRR 0·12 [95% CrI 0·06-0·28]) compared to placebo/no SMC, followed by SPAQ (IRR 0·42 [95% CrI 0·27-0·65]) and seasonal RTS,S alone (IRR 0·42 [95% CrI 0·22-0·79]) (Figure 2(b), again demonstrating a multiplicative effect of the combination. Notably for SPAQ (the most studied intervention across both outcomes), the reduction in severe malaria was less than the reduction in uncomplicated disease (58% reduction versus 75% reduction with non-overlapping credible intervals). There was no clear evidence of protection for monthly ASAQ and



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bimonthly SP or ASAQ. The treatment ranking for severe malaria was overall consistent with that observed for uncomplicated malaria (Figure 3(b)).

There was substantial within-design heterogeneity (p <0·001) for the uncomplicated malaria NMA (Figure 2(a)). Pairwise meta-analyses showed that comparison of SPAQ versus placebo/no SMC contributed most to this heterogeneity (Figure S4(a)). Network meta-regression showed that baseline parasite prevalence could partly explained the observed heterogeneity, with efficacy estimated to be 20% (95% CrI 9-30%) lower efficacy in studies with higher (24-61%) compared to lower (0·5-24%) parasitaemia (Table S8). Supervision of drug administration could also account for some variation between studies, as full (all three doses) versus partial (only first dose) supervision of SMC showed an 11% (95% CrI 0-21%) lower incidence of uncomplicated malaria, although this was not statistically significant. Other covariates, including study design, risk of bias, *Pfdhs* A437G mutant did not improve model fit nor explain the observed heterogeneity. The effect of the *Pfdhs* K540E mutant could not be assessed because of its very low prevalence amongst studies conducted in West Africa over the study period (Figure S11). For severe malaria, there was no significant within-design heterogeneity (p = 0.28), which may reflect the small number of studies in the meta-analysis. Node-splitting indicated serious inconsistency for DHAPQ versus placebo/no SMC (Figure S5), largely driven by two RCTs with opposing findings on the efficacy of DHAPQ compared to SPAQ (Figure S6).

Using the GRADE approach to assess the quality of evidence for uncomplicated malaria, most comparisons versus placebo/no SMC were rated as low quality. The network estimate for DHAPQ was further downgraded due to serious inconsistency (Table 2, Figure S7, and Supplementary Appendix 4). Our findings were consistent when analyses were restricted to children younger than five years (Figure S8). When evaluating RCTs conducted in West Africa, the relative efficacy of piperaquine-based regimens was lower than estimates including all RCTs (Figure S9), with DHAPQ achieving 66% (95% CrI 61-73%) and SPPQ 80% (95% CrI 69-88%). Upon excluding a three-arm trial comparing SPAQ, SPPQ, and DHAPQ[13] which did not report person-time, the uncertainty around the network estimate for SPPQ substantially increased (Figure S10), because very limited direct evidence remained for this intervention.

The tolerability NMA showed increased risk of vomiting after administration of SPAQ and SPPQ compared to no chemoprevention, however, the overall sample size for tolerability outcomes was small and the absolute number of events was low (Figures S15-S20). To explore different methodological approaches, we re-analysed the severe malaria data using only number of events and participants, however, there were fewer treatments in the network because two trials with adjusted treatment effects were not included in this analysis (Figure S12).[14, 20] The treatment ranking resulting from this method was identical to the main severe malaria analysis (Figure S14). However, there were differences in efficacy estimates (Figure S15), which could be biased due to exclusion of a large step-wedge cluster RCT.[20]



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## Discussion

SMC is an effective and scalable intervention in Africa, with over 50 million children receiving monthly SPAQ over the highest malaria transmission periods each year, likely preventing tens of thousands of deaths from malaria.[5, 6, 10] However, the efficacy of this intervention can still be improved. Our NMA shows that using piperaquine-based regimens and combining SMC with seasonal malaria vaccination could further improve its protective efficacy. To the best of our knowledge, this is the largest meta-analysis of SMC efficacy to date and the first NMA evaluating the relative efficacies of antimalarial regimens for SMC.

The studies included in this NMA were systematically identified from the WWARN ChemoMap. This annually updated library is designed to facilitate rapid systematic reviews and aggregate-level meta-analyses for chemoprevention interventions. WWARN ChemoMap is also relevant to the widening landscape of the SMC Alliance into the Malaria Chemoprevention Alliance, encompassing all forms of chemoprevention in children.[21] It therefore presents an opportunity to harmonise data from different chemoprevention interventions to enable comprehensive IPD meta-analyses that can better inform deployment strategies and resource allocation.

Our findings suggest that piperaquine-based regimens may have better chemopreventive efficacy than amodiaquine-based regimens This can be explained by the longer $t_{1/2}$ of piperaquine (20-30 days) compared to desethylamodiaquine (9-12 days), the active metabolite of amodiaquine.[22] However, piperaquine is currently only co-formulated with dihydroartemisinin, which is an expensive drug with a negligible chemoprophylactic effect (due to rapid elimination).[12] Of the currently available antimalarials with long $t_{1/2}$, SP is probably the only candidate that can safely be combined with piperaquine for mass deployment. The other 4-aminoquinoline drugs (chloroquine and amodiaquine) could result in substantial QT prolongation with piperaquine, making such regimens unsafe. Mefloquine is poorly tolerated, whereas tafenoquine would require testing for glucose-6-phosphate dehydrogenase deficiency.

The chemopreventive benefit of SP alone, however, remains unclear. A recent pooled parasitological efficacy analysis from Uganda, Mozambique, and Burkina Faso showed that desethylamodiaquine is the primary determinant of protection against malaria infection by day 28, with limited contributions from SP.[9] This was consistent across all study sites, irrespective of differences in anti-folate resistance profiles. In areas with high-level anti-folate resistance (high prevalence of quintuple mutant haplotypes), combining SP with other long-acting antimalarials is unlikely to provide any added antimalarial benefit, as shown in a Ugandan trial of IPTp.[23] Similarly, a pharmacometric analysis of SMC in the same region reported markedly reduced the efficacy of SPAQ against clinical malaria (60%, 95% CI 27-78%),[24] comparable to our network estimate for monthly ASAQ (67%, 95% CI 59-79%), likely reflecting the effect of amodiaquine alone. However, in regions where the quintuple mutant haplotypes remain less prevalent,[7] such as Sahelian West Africa, combining SP with piperaquine could have much better efficacy than SPAQ. This is demonstrated in our efficacy estimates for SPPQ (Table S5), despite the wide confidence intervals, which are informed by only two trials conducted in Senegal and The Gambia.[13, 25] Importantly, the dosage of piperaquine in these two studies was sub-optimal compared to the currently recommended weight-based dosing guidelines,[26] and this may have reduced the efficacy in some age groups, particularly infants, due to underdosing. In addition, there were no data on severe malaria for any piperaquine-based regimens in our analysis. Therefore, although SPPQ may provide greater protection than SPAQ, there is currently very limited randomised evidence to support its use in chemoprevention. Our findings support additional randomised trials comparing SP-piperaquine against SP-amodiaquine for SMC in West Africa.

SMC is delivered to healthy children, making safety and tolerability essential. Amodiaquine causes dose-dependent adverse effects, including vomiting and fever, which could reduce adherence and



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consequently its efficacy.[4, 27] Our tolerability NMA showed that piperaquine and amodiaquine similarly cause increased vomiting, consistent with findings from pooled IPTp tolerability analyses.[28] Although piperaquine causes a dose-dependent prolongation of the QT interval, its use has not been linked to sudden cardiac death.[29] Piperaquine is, therefore, unlikely to have a worse tolerability or safety profile than amodiaquine, particularly if overdosing is minimised. Piperaquine is currently dosed by bodyweight, but this is impractical for wide-scale deployment and optimal age-based regimens, achieving adequate drug exposure while minimising overdosing, should be developed to promote its use in chemoprevention.

SMC is delivered to healthy children, making safety and tolerability essential. Amodiaquine causes dose-dependent adverse effects, including vomiting and fever, which could reduce adherence and consequently its efficacy.[4, 27] Our tolerability NMA showed that piperaquine and amodiaquine similarly cause increased vomiting, consistent with findings from pooled IPTp tolerability analyses.[28] Although piperaquine causes a dose-dependent prolongation of the QT interval, its use has not been linked to sudden cardiac death.[29] Piperaquine is, therefore, unlikely to have a worse tolerability or safety profile than amodiaquine, particularly if overdosing is minimised. Piperaquine is currently dosed by bodyweight, but this is impractical for wide-scale deployment and optimal age-based regimens, achieving adequate drug exposure while minimising overdosing, should be developed to promote its use in chemoprevention.

This NMA also shows that seasonal vaccination has a multiplicative effect when given with SMC. Compared to no SMC, we estimate that seasonal vaccination with SPAQ results in more than a 90% reduction in the risk of clinical malaria, and more than a 70% reduction in the risk of severe malaria. This very high efficacy may partly reflect the timing of vaccination in the trial evaluating seasonal RTS,S vaccination, where the vaccine was administered just before the start of the peak transmission.[11] Whether similar protection could be achieved through more practical delivery modes, such as through Expanded Programme on Immunisation (EPI) clinics, remains unclear. A phase IV trial in Burkina Faso and Mali is currently evaluating EPI-based delivery of R21/Matrix-M alongside SMC.[30]

Our study had several limitations. All studies included in the NMA, except one conducted in Uganda, were from West Africa. Hence these findings, particularly concerning SP-based regimens, should be cautiously generalised beyond the Sahel, due to the differences in SP resistance profiles which we were unable to assess due to limited data. The overall quality of evidence from this NMA was low owing to substantial unexplained heterogeneity, largely driven by SPAQ trials. There was significant inconsistency in the efficacy estimates for DHAPQ across the two main trials contributing to this comparison in the network, indicating the need for more primary evidence on DHAPQ for SMC. Using aggregated data for the NMA, we were unable to fully characterise the effect of key contributors of heterogeneity, including age, transmission intensity or drug resistance. Additionally, we could not completely standardise the efficacy outcomes, which could have further contributed to heterogeneity. As a result, we will investigate the heterogeneity in treatment effect further through IPD meta-analyses using the WWARN SMC IPD repository.

This NMA provides a comprehensive assessment of optimal choices for long-acting antimalarials using the current evidence from randomised studies of SMC. Overall, our findings indicate that it is possible to substantially improve the efficacy of SMC either with a seasonal vaccine or with better drugs such as piperaquine, because chemopreventive efficacy with SPAQ is not currently saturated. Although vaccination can further enhance the effectiveness of SMC, the costs of large-scale vaccine deployment remain substantial. Therefore, optimising antimalarial drug regimens to achieve maximal benefit from SMC should remain a priority for funders and policy makers.



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## Contributions

DD, PD, PG, and JAW conceived and designed the study. DD, BEZ, and DSA selected the articles and extracted the data. DD and MS conducted the statistical analyses with supervision from JAW. DD, MS, AK, PD, PG, and JAW interpreted the results. DD, MS, and AK prepared the first draft of the manuscript. All authors had full access to all the data in this study, reviewed the drafts, and provided final approval to submit the manuscript for publication.


## Acknowledgments

We thank Elinor Harris from the Bodleian Health Care Libraries, University of Oxford, for all assistance related to the literature search. This study was funded by grant from Malaria Consortium. DD is funded by The Rhodes Trust. JAW is a Sir Henry Dale Fellow funded by the Wellcome Trust (223253/Z/21/Z). Generative AI (Chat GPT-5 model, available through University of Oxford's ChatGPT Edu) was used for writing assistance to improve the readability of this work.


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456 **Tables**

**Table 1. Characteristics of included studies in network meta-analysis**

| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Nuwa 2025 | Uganda | cRCT | 03-59 | 3881 | SP+AQ<br>DHA+PQ<br>No chemoprevention | 5 (monthly) | Partial | 31·5* | 60·9 |
| Traore 2024 | Mali | iRCT | 60-179 | 345 | SP+AQ<br>DHA+PQ<br>No chemoprevention | 4 (monthly) | Full | 15·6* | 98 |
| Chandramohan 2021 | Mali; Burkina Faso | iRCT | 05-17 | 6861 | SP+AQ + placebo vaccine<br>Seasonal RTS,S/AS01E vaccine + placebo chemoprevention<br>SP+AQ + Seasonal RTS,S/AS01E vaccine | 4 (monthly) | Full | 21·6* | 80·2 |
| Ndiaye 2019 | Senegal | cRCT | 03-119 | 4546 | SP+AQ<br>No chemoprevention | 5 (monthly) | Partial | 21·5 | 92·5 |
| Thera 2018 | Mali | iRCT | 60-179 | 200 | AS+AQ<br>No chemoprevention | 4 (monthly) | Full | 14* | 43.5 |



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**Table 1. Characteristics of included studies in network meta-analysis**

| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Tagbor 2016 | Ghana | iRCT | 03-59 | 2400 | SP+AQ | 5 (monthly) | Partial | 26·6 | 82.3 |
| | | | | | Placebo chemoprevention | | | | |
| Cisse 2016 | Senegal | Stepped-wedge cRCT | 03-119 | Year 1: 14000 | SP+AQ | 3 (monthly) | Partial | 5·1 | Year 1: 45-59 |
| | | | | Year 2: 90000 | No chemoprevention | | | | Year 2: 65-78 |
| | | | | Year 3: 160000 | | | | | Year 3: 67-77 |
| Zongo 2015 | Burkina Faso | iRCT | 03-59 | 1499 | SP+AQ | 3 (monthly) | Full | 44 | 26 |
| | | | | | DHA+PQ | | | | |
| Tine 2011 | Senegal | cRCT | 12-119 | 1000 | SP+AQ | 2 (monthly) | Full | 10·3 | 95·6 |
| | | | | | No chemoprevention | | | | |
| Dicko 2011 | Mali | iRCT | 03-59 | 3017 | SP+AQ | 3 (monthly) | Full | 13·2 | 99·5 |
| | | | | | Placebo chemoprevention | | | | |
| Konate 2011 | Burkina Faso | iRCT | 03-59 | 3014 | SP+AQ | 3 (monthly) | Full | 41·5 | 92·8 |
| | | | | | Placebo chemoprevention | | | | |

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**Table 1. Characteristics of included studies in network meta-analysis**

| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Sesay 2011 | The Gambia | iRCT | 06-59 | 1277 | SP+AQ<br>Placebo chemoprevention | 3 (monthly) | Partial | 0·5 | 93·3 |
| Bojang 2010 (a) | The Gambia | iRCT | 06-59 | 1008 | SP+AQ<br>DHA+PQ<br>SP+PQ | 3 (monthly) | Full | 2·1 | 68 |
| Bojang 2010 (b) | The Gambia | iRCT | 06-119 | 1200 | SP (monthly)<br>Placebo chemoprevention | 1-6 (monthly) | Full | 61·5 | <5 |
| Cisse 2009 | Senegal | cRCT | 02-59 | 1745 | SP+AQ<br>DHA+PQ<br>SP+PQ | 3 (monthly) | Partial | 4·8 | 28·9 |
| Sokhna 2008 | Mali | iRCT | 06-59 | 2102 | SP+AQ<br>SP+1AS<br>SP+3AS<br>AS+AQ | 3 (monthly) | Full | 27·3 | 18 |

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**Table 1. Characteristics of included studies in network meta-analysis**

| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Dicko 2008 | Ghana | iRCT | 06-119 | 262 | SP (bimonthly) | 2 (bimonthly) | Full | 35·5 | <5 |
| | | | | | No chemoprevention | | | | |
| Kweku 2008 | Senegal | iRCT | 03-59 | 2451 | SP (bimonthly) | 3 (bimonthly SP & AS+AQ) | Partial | 30 | 10·8 |
| | | | | | AS+AQ (monthly) | 6 (monthly AS+AQ) | | | |
| | | | | | AS+AQ (bimonthly) | | | | |
| | | | | | Placebo chemoprevention | | | | |
| Cisse 2006 | Senegal | iRCT | 02-59 | 1136 | SP+1AS | 3 (monthly) | Full | 60 | <1 |
| | | | | | Placebo chemoprevention | | | | |

Abbreviations: iRCT: individually randomised controlled trial; cRCT: cluster randomised controlled trial; DHA+PQ: dihydroartemisinin plus piperaquine; SP: sulphadoxine-pyrimethamine; SP+1AS: sulphadoxine-pyrimethamine plus artesunate (one dose); SP+3AS: sulphadoxine-pyrimethamine plus artesunate (three doses); SP+PQ: sulphadoxine-pyrimethamine plus piperaquine; SP+AQ: sulphadoxine-pyrimethamine plus amodiaquine; AS+AQ: artesunate plus amodiaquine.

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459 **Table 2. GRADE quality of evidence rating for network meta-analysis for uncomplicated malaria**

| **Intervention** (vs placebo/no SMC) | **Direct estimate** | Reason(s) for downgrading | **Indirect estimate** | Reason(s) for downgrading | **Network estimate** | Reason(s) for downgrading |
|---|---|---|---|---|---|---|
| **Seasonal RTS,S + SPAQ** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **SPPQ** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **DHAPQ** | Moderate | Some concerns: ROB | Low | Major concern: Within-design heterogeneity | Very Low | Major concern: Incoherence |
| **SPAQ** | Low | Major concern: Within-design heterogeneity | Moderate | Some concerns: ROB | Low | |
| **Seasonal RTS,S** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **ASAQ (monthly)** | Moderate | Some concerns: ROB | Low | Major concern: Within-design heterogeneity | Moderate | |
| **SPAS / SP (monthly)** | Moderate | Some concern: Within-design heterogeneity | Low | Major concern: Within-design heterogeneity | Moderate | |
| **SP (bimonthly)** | Moderate | Some concern: Within-design heterogeneity | n/a | | Moderate | |
| **ASAQ (bimonthly)** | Moderate | Some concern: Within-design heterogeneity | Low | Major concern: Within-design heterogeneity | Low | Some concerns: Imprecision |

460 Abbreviations: DHAPQ: dihydroartemisinin plus piperaquine; SP: sulphadoxine-pyrimethamine; SPAS: sulphadoxine-pyrimethamine plus artesunate; SPPQ: sulphadoxine-
461 pyrimethamine plus piperaquine; SPAQ: sulphadoxine-pyrimethamine plus amodiaquine; ASAQ: artesunate plus amodiaquine.

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462 **Figures**

463 Figure 1. Network graph of long-acting antimalarials used in SMC for (a) uncomplicated malaria and (b)
464 severe malaria.

465 Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal
466 malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin
467 plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal
468 malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus
469 artesunate; SP = sulphadoxine-pyrimethamine

470

471 Figure 2. Forest plot of network estimates for relative efficacies of long-acting antimalarials compared to
472 placebo/no chemoprevention in SMC for (a) uncomplicated malaria and (b) severe malaria.

473 Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal
474 malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin
475 plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal
476 malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus
477 artesunate; SP = sulphadoxine-pyrimethamine

478

479 Figure 3. Heat plot showing posterior ranking probabilities for all included treatments for (a)
480 uncomplicated malaria and (b) severe malaria

481 Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal
482 malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin
483 plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal
484 malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus
485 artesunate; SP = sulphadoxine-pyrimethamine

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**Table 1. Characteristics of included studies ordered by date of publication**

| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Nuwa 2025 | Uganda | cRCT | 03-59 | 3881 | SP+AQ<br>DHA+PQ<br>No chemoprevention | 5 (monthly) | Partial | 31·5* | 60·9 |
| Traore 2024 | Mali | iRCT | 60-179 | 345 | SP+AQ<br>DHA+PQ<br>No chemoprevention | 4 (monthly) | Full | 15·6* | 98 |
| Chandramohan 2021 | Mali; Burkina Faso | iRCT | 05-17 | 6861 | SP+AQ + placebo vaccine<br>Seasonal RTS,S/AS01E vaccine + placebo chemoprevention<br>SP+AQ + Seasonal RTS,S/AS01E vaccine | 4 (monthly) | Full | 21·6* | 80·2 |
| Ndiaye 2019 | Senegal | cRCT | 03-119 | 4546 | SP+AQ<br>No chemoprevention | 5 (monthly) | Partial | 21·5 | 92·5 |
| Thera 2018 | Mali | iRCT | 60-179 | 200 | AS+AQ<br>No chemoprevention | 4 (monthly) | Full | 14* | 43.5 |
| Tagbor 2016 | Ghana | iRCT | 03-59 | 2400 | SP+AQ | 5 (monthly) | Partial | 26·6 | 82.3 |

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| Study | Country | Study design | Age of participants (months) | No. randomized | Interventions | No. cycles (cycle frequency) | SMC supervision | Parasitaemia prevalence (baseline) (%) | ITN use (baseline) (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo chemoprevention | | | | |
| Cisse 2016 | Senegal | Stepped-wedge cRCT | 03-119 | Year 1: 14000 | SP+AQ | 3 (monthly) | Partial | 5·1 | Year 1: 45-59 |
| | | | | Year 2: 90000 | No chemoprevention | | | | Year 2: 65-78 |
| | | | | Year 3: 160000 | | | | | Year 3: 67-77 |
| Zongo 2015 | Burkina Faso | iRCT | 03-59 | 1499 | SP+AQ | 3 (monthly) | Full | 44 | 26 |
| | | | | | DHA+PQ | | | | |
| Tine 2011 | Senegal | cRCT | 12-119 | 1000 | SP+AQ | 2 (monthly) | Full | 10·3 | 95·6 |
| | | | | | No chemoprevention | | | | |
| Dicko 2011 | Mali | iRCT | 03-59 | 3017 | SP+AQ | 3 (monthly) | Full | 13·2 | 99·5 |
| | | | | | Placebo chemoprevention | | | | |
| Konate 2011 | Burkina Faso | iRCT | 03-59 | 3014 | SP+AQ | 3 (monthly) | Full | 41·5 | 92·8 |
| | | | | | Placebo chemoprevention | | | | |
| Sesay 2011 | The Gambia | iRCT | 06-59 | 1277 | SP+AQ | 3 (monthly) | Partial | 0·5 | 93·3 |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo chemoprevention | | | | |
| Bojang 2010 (a) | The Gambia | iRCT | 06-59 | 1008 | SP+AQ | 3 (monthly) | Full | 2·1 | 68 |
| | | | | | DHA+PQ | | | | |
| | | | | | SP+PQ | | | | |
| Bojang 2010 (b) | The Gambia | iRCT | 06-119 | 1200 | SP (monthly) | 1-6 (monthly) | Full | 61·5 | <5 |
| | | | | | Placebo chemoprevention | | | | |
| Cisse 2009 | Senegal | cRCT | 02-59 | 1745 | SP+AQ | 3 (monthly) | Partial | 4·8 | 28·9 |
| | | | | | DHA+PQ | | | | |
| | | | | | SP+PQ | | | | |
| Sokhna 2008 | Mali | iRCT | 06-59 | 2102 | SP+AQ | 3 (monthly) | Full | 27·3 | 18 |
| | | | | | SP+1AS | | | | |
| | | | | | SP+3AS | | | | |
| | | | | | AS+AQ | | | | |
| Dicko 2008 | Ghana | iRCT | 06-119 | 262 | SP (bimonthly) | 2 (bimonthly) | Full | 35·5 | <5 |
| | | | | | No chemoprevention | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| Kweku 2008 | Senegal | iRCT | 03-59 | 2451 | SP (bimonthly) | 3 (bimonthly SP & AS+AQ) | Partial | 30 | 10·8 |
| | | | | | AS+AQ (monthly) | 6 (monthly AS+AQ) | | | |
| | | | | | AS+AQ (bimonthly) | | | | |
| | | | | | Placebo chemoprevention | | | | |
| Cisse 2006 | Senegal | iRCT | 02-59 | 1136 | SP+1AS | 3 (monthly) | Full | 60 | <1 |
| | | | | | Placebo chemoprevention | | | | |

Abbreviations: iRCT: individually randomised controlled trial; cRCT: cluster randomised controlled trial; DHA+PQ: dihydroartemisinin plus piperaquine; SP: sulphadoxine-pyrimethamine; SP+1AS: sulphadoxine-pyrimethamine plus artesunate (one dose); SP+3AS: sulphadoxine-pyrimethamine plus artesunate (three doses); SP+PQ: sulphadoxine-pyrimethamine plus piperaquine; SP+AQ: sulphadoxine-pyrimethamine plus amodiaquine; AS+AQ: artesunate plus amodiaquine.

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**Table 2. GRADE quality of evidence rating for network meta-analysis for uncomplicated malaria**

| **Intervention** (vs placebo/no SMC) | **Direct estimate** | Reason(s) for downgrading | **Indirect estimate** | Reason(s) for downgrading | **Network estimate** | Reason(s) for downgrading |
|---|---|---|---|---|---|---|
| **Seasonal RTS,S + SPAQ** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **SPPQ** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **DHAPQ** | Moderate | Some concerns: ROB | Low | Major concern: Within-design heterogeneity | Very Low | Major concern: Incoherence |
| **SPAQ** | Low | Major concern: Within-design heterogeneity | Moderate | Some concerns: ROB | Low | |
| **Seasonal RTS,S** | n/a | | Low | Major concern: Within-design heterogeneity | Low | |
| **ASAQ (monthly)** | Moderate | Some concerns: ROB | Low | Major concern: Within-design heterogeneity | Moderate | |
| **SPAS / SP (monthly)** | Moderate | Some concern: Within-design heterogeneity | Low | Major concern: Within-design heterogeneity | Moderate | |
| **SP (bimonthly)** | Moderate | Some concern: Within-design heterogeneity | n/a | | Moderate | |
| **ASAQ (bimonthly)** | Moderate | Some concern: Within-design heterogeneity | Low | Major concern: Within-design heterogeneity | Low | Some concerns: Imprecision |

Abbreviations: DHAPQ: dihydroartemisinin plus piperaquine; SP: sulphadoxine-pyrimethamine; SPAS: sulphadoxine-pyrimethamine plus artesunate; SPPQ: sulphadoxine-pyrimethamine plus piperaquine; SPAQ: sulphadoxine-pyrimethamine plus amodiaquine; ASAQ: artesunate plus amodiaquine

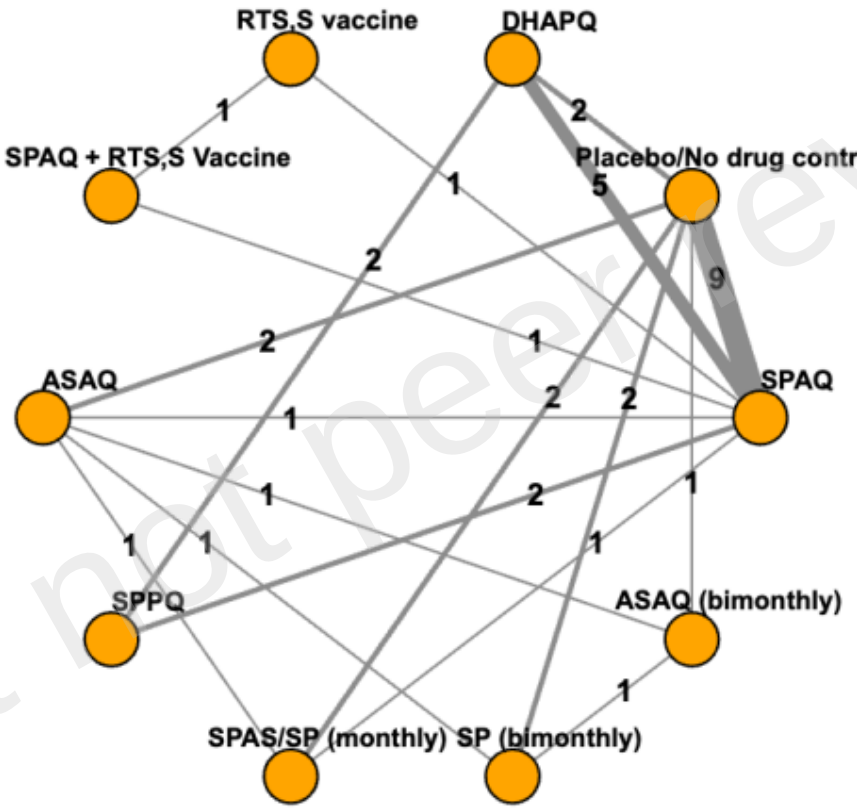
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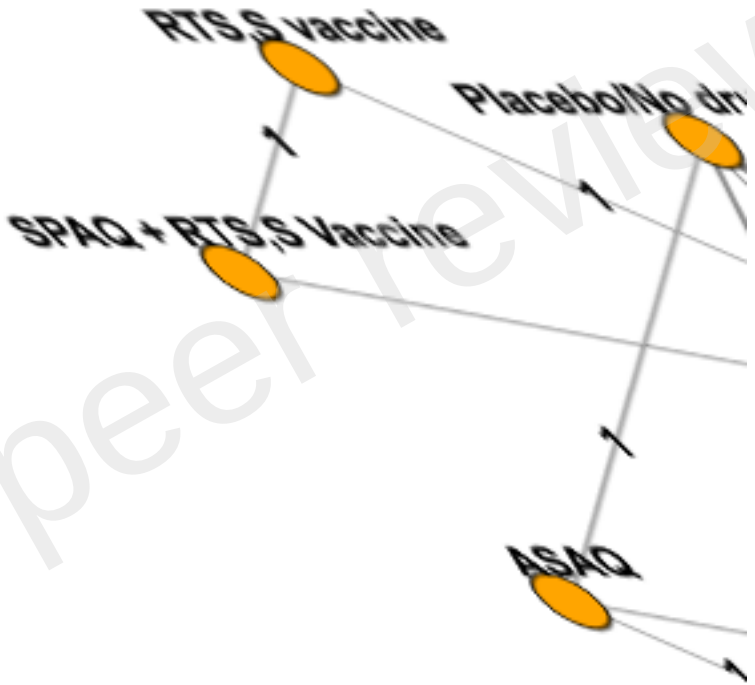
Figure 1(a) Uncomplicated malaria




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Figure 1(b) Severe malaria




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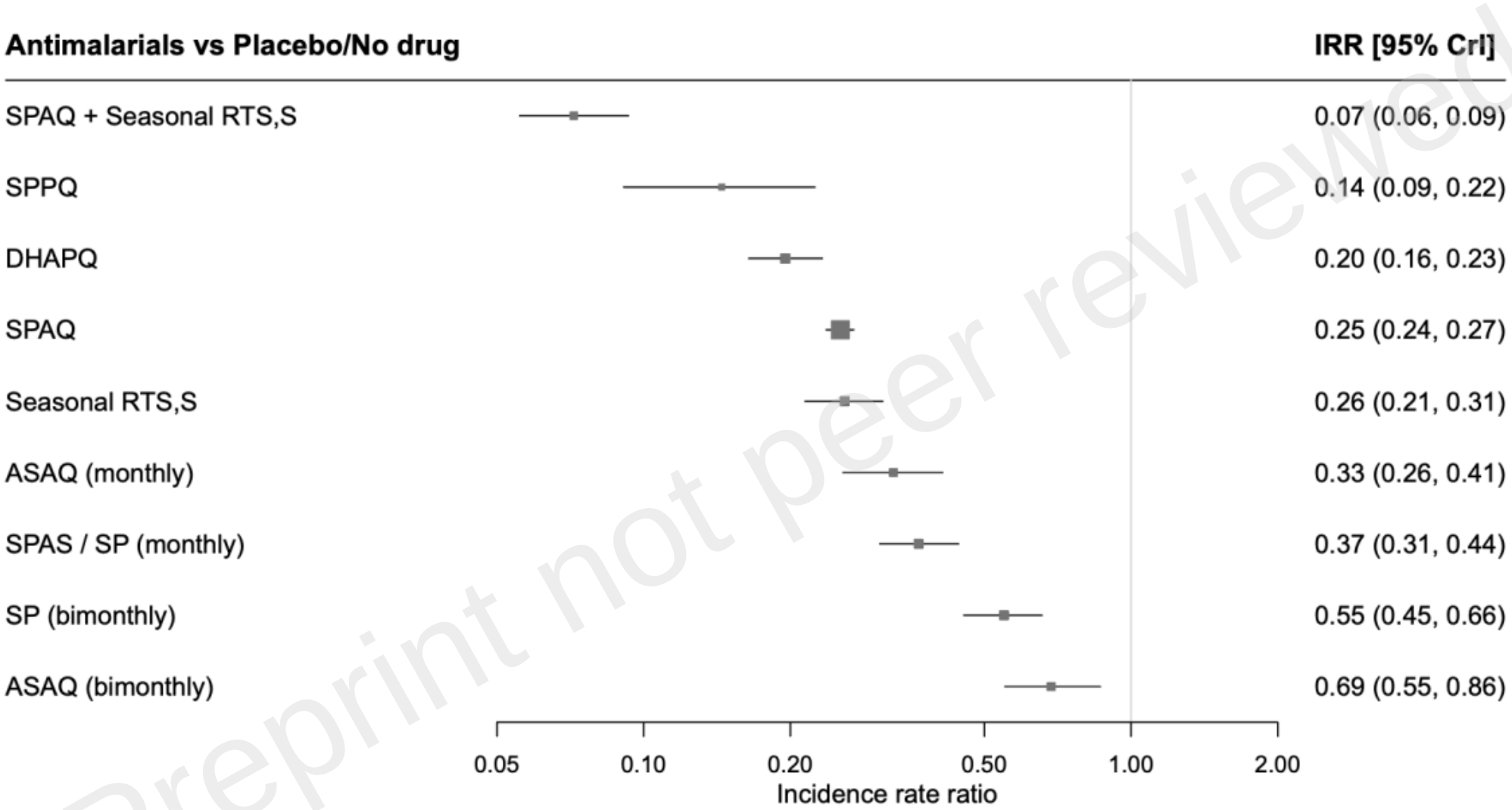
Figure 1. Network graph of long-acting antimalarials used in SMC for (a) uncomplicated malaria and (b) severe malaria. Each line represents a direct treatment comparison, and the thickness of the line reflects the relative amount direct evidence for that comparison.

Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus artesunate; SP = sulphadoxine-pyrimethamine

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Figure 2 (a) Uncomplicated malaria

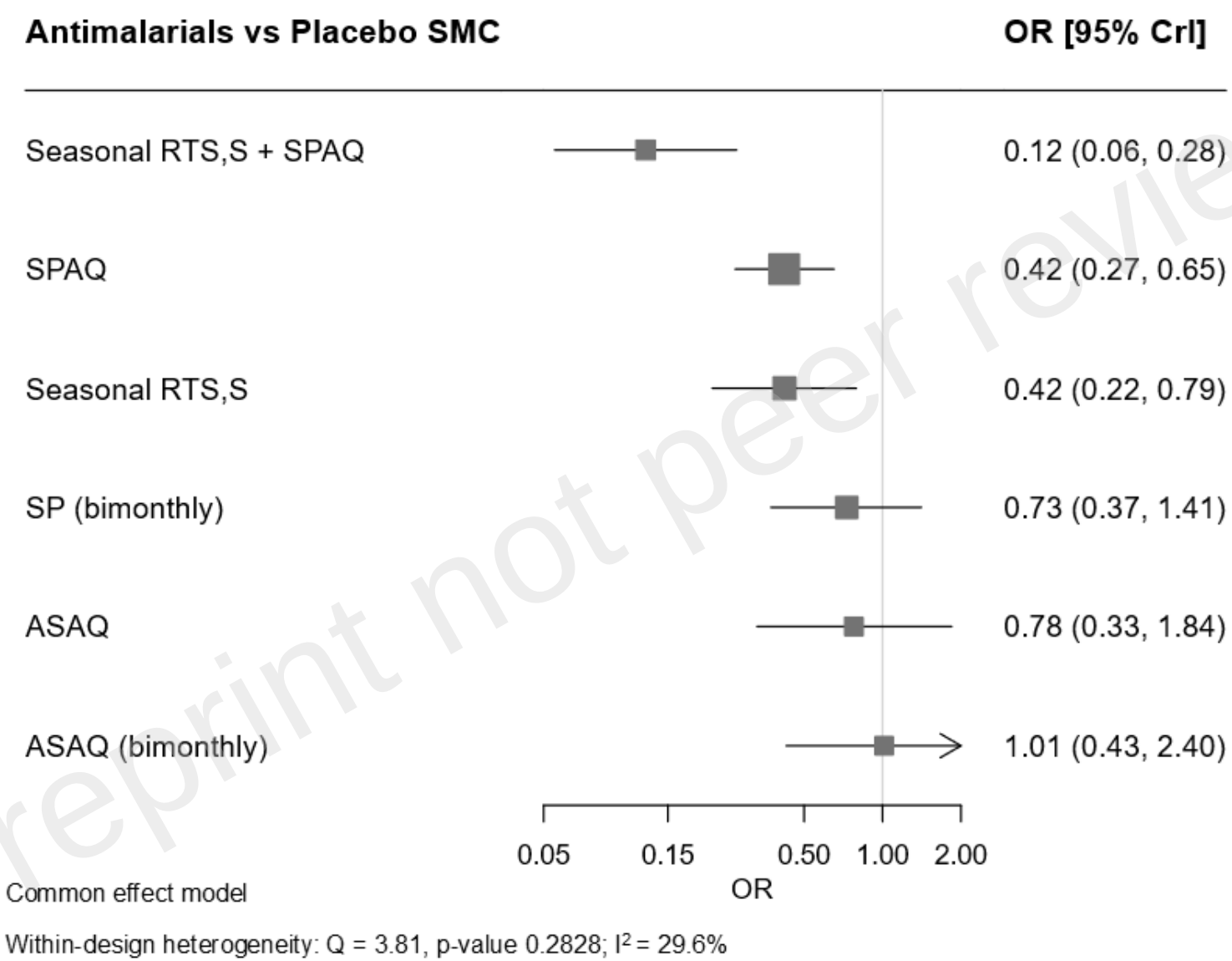



Common effect model
Within-design heterogeneity; Q = 107.12; p-value < 0.0001; $I^2$ = 95.4%

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Figure 2 (b) Severe malaria




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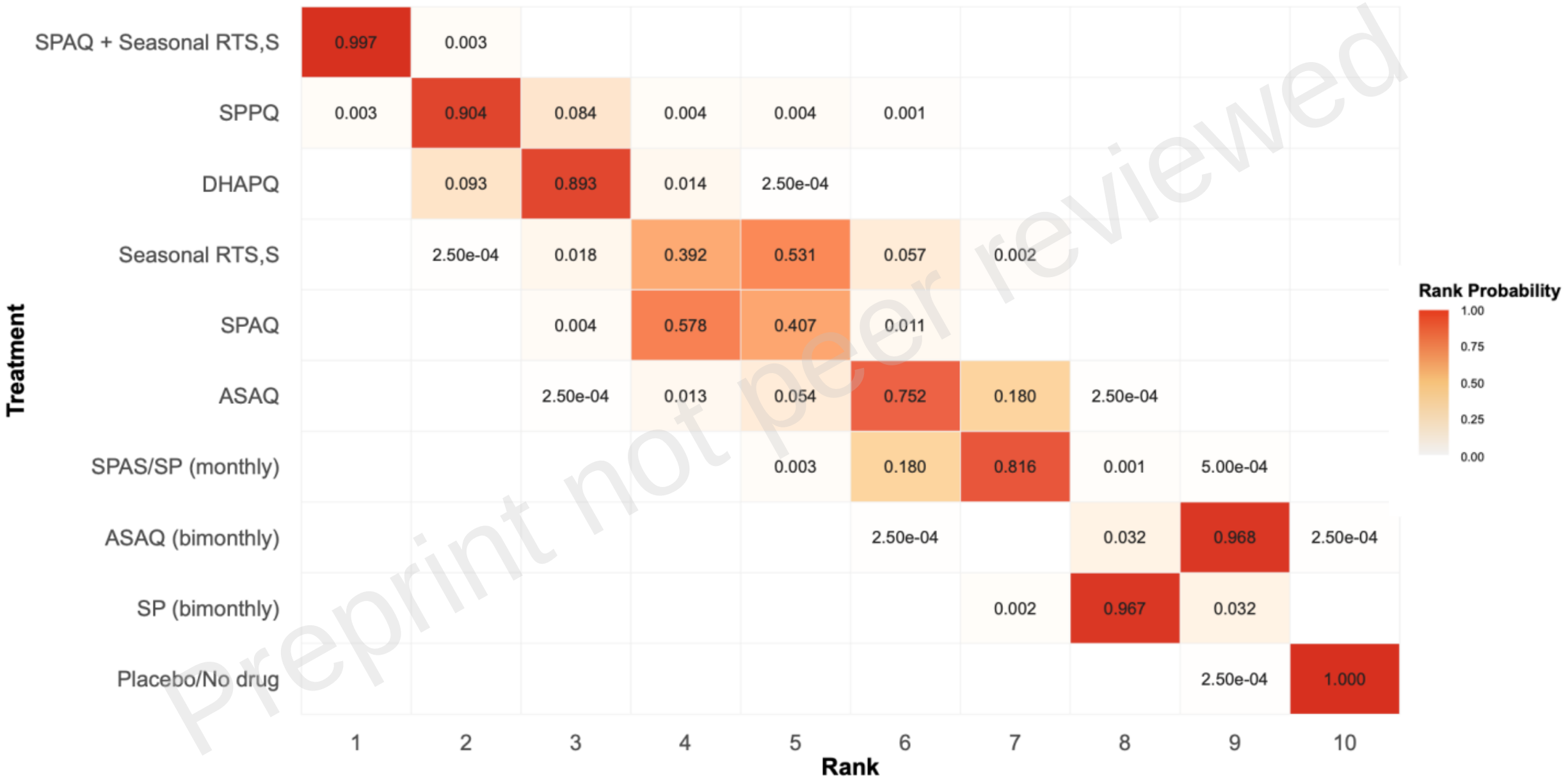
Figure 2. Forest plot of network estimates for relative efficacies of long-acting antimalarials compared to placebo/no chemoprevention in SMC for (a) uncomplicated malaria and (b) severe malaria.

Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus artesunate; SP = sulphadoxine-pyrimethamine

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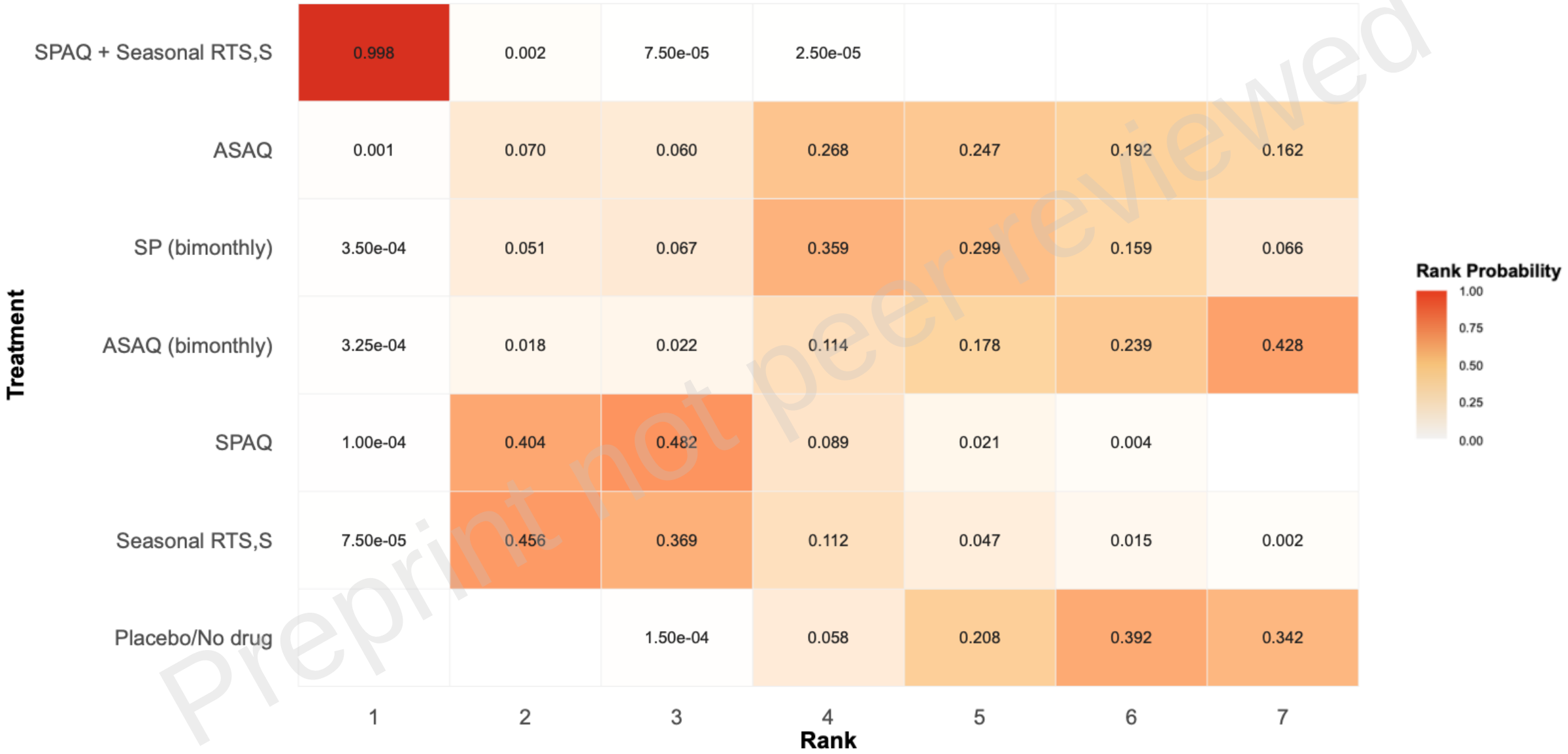
Figure 3 (a) Uncomplicated malaria




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Figure 3 (b) Severe malaria




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Figure 3. Heat plot showing posterior ranking probabilities for all included treatments for (a) uncomplicated malaria and (b) severe malaria

Abbreviations: SPAQ + Seasonal RTS,S = sulphadoxine-pyrimethamine plus amodiaquine plus seasonal malaria vaccination; SPPQ = sulphadoxine-pyrimethamine plus piperaquine; DHAPQ = dihydroartemisinin plus piperaquine; SPAQ = sulphadoxine-pyrimethamine plus amodiaquine; Seasonal RTS,S = seasonal malaria vaccination; ASAQ = artesunate plus amodiaquine; SPAS = sulphadoxine-pyrimethamine plus artesunate; SP = sulphadoxine-pyrimethamine

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