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Title

Post-discharge malaria chemoprevention in children admitted with severe anaemia in malaria-endemic settings in Africa: a systematic review and meta-analysis

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Post-discharge Malaria Chemoprevention in Children Admitted with Severe Anaemia in Malaria-Endemic Settings in Africa: A Systematic Review and Meta-Analysis

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Abstract

Background

Severe anaemia is associated with high in-hospital mortality among young children. In malaria-endemic areas, surviving children remain at an increased risk of mortality or readmission for at least six months after hospital discharge. Previous trials in Malawi, Kenya, Uganda and the Gambia have shown that monthly post-discharge malaria chemoprevention (PMC) substantially reduces this risk. We conducted a systematic review and meta-analysis to determine the efficacy of PMC for the post-discharge management of children recently discharged from hospital after recovery from severe anaemia.

Methods

Following PRISMA guidelines, we searched multiple databases for randomised controlled trials comparing monthly PMC regimens with placebo or standard of care among children admitted with severe anaemia in malaria-endemic Africa, conducted at any time. Fixed-effects meta-analysis was used to generate pooled effect estimates.

Findings

Three double-blind placebo-controlled PMC trials fulfilled the eligibility criteria, involving 3,663 children with severe anaemia. They received either monthly sulfadoxine-pyrimethamine (SP) until the end of the malaria transmission season (average: 3.1 doses per child) (N=1,200, the Gambia), monthly artemether-lumefantrine (AL) given at 4 and 8 weeks post-discharge (N=1,414, Malawi), or monthly dihydroartemisinin-piperaquine given at the start of the 3rd, 7th, and 10th week post-discharge (N=1,049, Uganda and Kenya). PMC was associated with a 77% (95% CI 30-92) reduction in mortality during the intervention period (primary outcome) (p=0.01, I^2=0%), a 58% (48-66) reduction in all-cause readmissions (p<0.001, I^2=87%), a 68% (54-78) reduction in readmissions due to severe malaria (p<0.001, I^2=93%), a 62% (44-74) reduction in readmissions due to severe anaemia (p<0.001, I^2=69%), a 24% (17-31) reduction in non-severe all-cause sick-child clinic visits (p<0.001, I^2=10%), and a 57% (50-64) reduction in uncomplicated clinical malaria (p<0.001, I^2=71%). The reduction was restricted to the intervention period and not sustained after protective drug levels had waned.

Interpretation

In malaria-endemic Africa, post-discharge malaria chemoprevention reduces mortality and readmissions in recently discharged children who have recovered from severe anaemia and can be a valuable strategy for the post-discharge management of this high-risk group. Future research should focus on methods of PMC delivery, options to prolong the duration of protection, for example, by combining chemoprevention with malaria vaccination or monoclonal antibody therapy, and options to include interventions targetting non-malarial causes of post-discharge morbidity.

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Introduction

Children hospitalised with severe anaemia in Africa are at high risk of readmission or death within six months after discharge.[1] However, no strategy specifically addresses this post-discharge period. Several trials in highly malaria-endemic areas of Africa have shown that post-discharge malaria chemoprevention (PMC) with monthly treatment courses of sulfadoxine-pyrimethamine[2] or artemisinin-based combination therapies (ACTs)[3,4] prevented a substantial number of post-discharge deaths and readmissions in recently discharged children who had recovered from severe anaemia. To review all available evidence, we conducted a systematic review and aggregated data meta-analysis of PMC trials to support policymakers in considering whether PMC should be considered for the post-discharge management of severe anaemia.

Methods

Search strategy and selection criteria

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[5] We identified eligible studies by performing a literature search using a combination of search terms (Supplement 1, page 2) in PubMed, SCOPUS, EMBASE, Web of Science, Cochrane CENTRAL and the WHO's clinical trial registry from inception to January 04, 2022. In addition, we identified other relevant studies by scanning reference lists of all identified articles and searching in Google and Google Scholar. Randomised controlled trials were eligible if they were conducted in a malaria-endemic area of Africa[6] among children <15 years of age recently discharged after hospitalisation for severe anaemia, and compared monthly malaria chemoprevention regimens after discharge against placebo or the current standard of post-discharge care. Trials using daily or weekly malaria prophylaxis were not eligible. The search was conducted in English but without language restrictions.

Data extraction and quality assessment

Two independent reviewers (TKK and FtK) screened titles, abstracts, and full texts of all identified citations and agreed on the final eligibility. Reviewers were unblinded to the authors of the source study. The two reviewers independently assessed the risk of bias for the included trials using the Cochrane risk-of-bias tool for randomised trials version 2 (RoB2)[7] (Supplement 2, page 2).

Outcomes

The primary outcome was all-cause mortality during the intervention period. Secondary outcomes included all-cause and cause-specific readmissions, non-severe all-cause sick-child clinical visits and episodes of uncomplicated clinical malaria during the intervention period and during the post-intervention follow-up period (see Statistical analysis, below). Definitions are provided in Supplement 3 (page 2).

Statistical analysis

Data were analysed using STATA/MP2 17.0 (StataCorp LP). Fixed-effects meta-analyses generated pooled relative risks (RR), incidence rate ratio (IRR) or hazard ratios (HR) depending on the effect measures presented by the sources studies. Results are also described as protective efficacy (PE) defined as either PE=100%x[1-RR], or PE=100%x[1-IRR], or PE=100%x[1-HR] depending on the effect measure that was available for each outcome across all three studies. Fixed effects (plural) models were preferred over fixed-effect (singular) models (common-effect models) because they do not assume one common true effect across all studies. A fixed-effects (plural) model assumes that different studies have different fixed effect sizes. The overall effect size was calculated as the weighted average of true study-specific effect sizes.[8,9] We did not consider random-effects models for the

primary analysis because the between-study variance cannot be reliably estimated with a small number of studies.[10-13]

The analysis was stratified *a priori* by the PMC-intervention period (starting from the first day of chemoprevention) (primary analysis) and a post-intervention period (evaluated in those who survived the intervention period), and 'overall', defined as the cumulative effect across both periods pooled. This was done to provide independent estimates of the direct effect of the intervention (PMC-intervention period) and to assess whether any rebound or delayed episodes occurred during the post-intervention period when the direct pharmacological protective effect of the antimalarial drugs had waned. It also allowed us to determine the overall cumulative effect at the end of the post-intervention follow-up (see Supplement 3, page 2 for definitions). The p-values for the differences in treatment effect during the intervention period vs the post-intervention period were obtained using inverse-variance weighted meta-regression with covariates for study and period to take the paired nature of the data into account. These are henceforth referred to a $P_{interaction}$.

We used P values <0.05 to indicate statistical significance (2-sided tests). The extent of heterogeneity was measured using the I^2 statistic,[6] which is a measure of the proportion of total variability explained by heterogeneity rather than chance, expressed as a percentage, with 0-40% representing no or little heterogeneity, 30-60% moderate heterogeneity, 50-90% substantial heterogeneity, and 75-100% considerable heterogeneity.[14]

The number-needed-to-treat (NNT) to prevent one all-cause death was computed as NNT=1/(ACR_{isk}x[1-RR]), where ACR is the assumed control risk,[15] calculated as the median risk of death by the end of the intervention period in the control arms of the three included trials and the control arm of one recent trial from Uganda with detailed post-discharge mortality data by 3 months.[16] ACR_{isk}x(1-RR) represents the absolute risk reduction. The number-needed-to-treat (NNT) to prevent one readmission was computed as NNT=1/(ACRatex[1-IRR]), where ACR_{ate} is the assumed control (incidence) rate per child,[15] calculated as the median risk of the incidence of all-cause readmission in the control arms of the included trials. ACR_{ate}x(1-IRR) represents the absolute rate reduction.

Role of the funding source
The funders of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Included studies
Our search identified 72 articles. After removing duplicates and screening titles and abstracts, ten full-text articles were further evaluated, including five RCTs evaluating post-discharge chemoprevention in children with severe anaemia. Three of the five trials were eligible (Figure 1 and Table 1). They were published between 2010 and 2020 and conducted in The Gambia (one[2]), Malawi (one[3]), Kenya and Uganda (one[4]). The Cochrane Collaboration tool for RCTs scored the three trials as low risk of bias (Table S1). The two excluded trials used daily or weekly chemoprophylaxis post-discharge instead of monthly administration of chemoprevention.[16,17]

All three included trials were double-blind and placebo-controlled. Combined, they included 3,663 children with severe anaemia.

The first trial was conducted in 2003-2004 in the Gambia and involved 1,200 children with severe anaemia (including children with non-malarial severe anaemia), defined as a Hb<7/g/dL.[2] This trial used monthly treatment courses with sulfadoxine-pyrimethamine (SP) or placebo provided until the

end of the malaria transmission season. The number of courses varied depending on the time of the transmission season at which the participants were recruited. The average number of PMC courses received was 3.1 (range 1 to 6). Approximately six months into the dry season, the caretakers were visited again to assess the vital status and the history of morbidity after the intervention period. Aggregated results were available for all outcomes during the intervention period (the transmission season) but only for mortality and clinical malaria during the post-intervention period (the six months during the dry season). At the time of the study, the quintuple dhfr/dhps haplotype associated with high-grade sulfonamide resistance was absent in the Gambia, and seasonal malaria chemoprevention (SMC) had not yet been introduced as national policy.

The second trial was conducted in 2006-2009 in four hospitals in southern Malawi involving 1,414 children with severe malaria anaemia (Hb<5g/dL).[3] Children in both arms received artemether-lumefantrine (AL) at discharge and then AL or placebo at 1 and 2 months post-discharge, providing about 11 to 12 weeks of protection.[13] Children were followed for six months. Results were available by the intervention period (1-3 months), post-intervention period (4-6 months) and overall (1-6 months post-discharge).

The third trial was conducted in 2016-2018 in nine hospitals in Uganda and Kenya and involved children with severe anaemia (Hb<5g/dL), including severe non-malarial anaemia.[4] All children in both arms received presumptive courses of AL at discharge and then either monthly dihydroartemisinin-piperaquine (DHA-PiP) or placebo at the start of week 3 (14 days post-discharge), 7, and 11 weeks post-discharge, providing a total of 14 weeks of prophylaxis (N=1,049). Children were followed for a total of 26 weeks, and results were available by the intervention period (2-14 weeks post-discharge), post-intervention period (15-26 weeks) and overall (2-26 weeks) for all outcomes.

Efficacy

Primary outcome

During the intervention period, children in the PMC arms were less likely to die post-discharge than in the placebo arms (RR=0.23 [95% CI 0.08-0.70], p=0.01, I^2=0%, Figure 2), corresponding to a protective efficacy of 77% [95% CI 30-92] and an absolute risk reduction of 1.2% [95% CI 0.5-1.4] from an assumed control risk of 1.6% in the control group to 0.4% in the PMC group. The NNT was 83 (95% CI 70-213). The protective effect was only evident during the intervention period and not sustained during the post-intervention period (RR=1.61 [95% CI 0.81-3.19], p=0.17, I^2=0%). There was no evidence of a cumulative beneficial effect on mortality at the end of the follow-up period (RR=0.77 [95% CI 0.47-1.28], p=0.32, I^2=0%). This difference in effect between the two periods was not statistically significant ($p_{interaction}$ =0.16) (Figure-3).

Secondary outcomes

Children in the PMC arms also had fewer all-cause readmissions during the intervention period (IRR=0.42 [95% CI 0.34-0.52], p<0.001, I^2=87%, Figure-2), corresponding to a protective efficacy of 58% [48-66]. The absolute rate reduction was 40 [95% CI 33-45] per 100 child-years from an assumed control risk of 68 per 100 child-years in the control group to 29 per 100 child years in the PMC group. The NNT to prevent one readmission was 11 (95% CI 9-13).

During the intervention period, readmissions due to severe malaria were reduced by 68% but this data was only available from two studies (HR=0.32 [95% CI 0.22-0.46], P<0.001, I^2=93%) and by 62% for readmissions due to severe anaemia (HR=0.38 [95% CI 0.26-0.56], p<0.001, I^2=69%). PMC was also associated with a 24% reduction in non-severe all-cause sick-child clinic visits (HR=0.76 [95% CI 0.69-0.83], p<0.001, I^2=10%), and a 57% reduction in uncomplicated clinical malaria (HR=0.43 [95% CI 0.36-0.50], p<0.001, I^2=71%) (Figure-2).

The data on clinical malaria for the post-intervention period were available for all three trials (unlike the other secondary outcomes, see below). PMC had no effect on clinical malaria during the post-intervention period (HR=0.96 [95% CI 0.83-1.11), P=0.58, I^2=32%). This was not significantly less than the 57% reduction in clinical malaria during the intervention period ($p_{interaction}$=0.09). The cumulative effect by the end of the follow-up period was 36% (HR=0.64 [95% CI 0.58-0.72], p<0.001, I^2=77%) (Figure 3).

The assessment of the treatment effect by intervention period for other secondary outcomes could only be assessed in the trials by Phiri et al. and Kwambai et al., as details for the post-intervention period were not available for the study by Bojang et al. beyond mortality and clinical malaria. The stratified analysis by study period using the data from these two trials showed that the rate of readmissions due to severe anaemia were 26% lower in the PMC arm during the post-intervention period, but this effect was not significant (HR=0.74, [95% CI 0.52-1.05], p=0.09, I^2=0%). There was no effect on all-cause re-admissions during the post-intervention period (HR=1.04, [95% CI 0.83-1.30], p=0.74, I^2=0%). Similarly, PMC had no effect on severe malaria re-admissions or non-severe all-cause sick visits. These differences in treatment effect between the intervention period and the post-intervention period were only statistically significant for non-severe all-cause sick child clinic visits and malaria, the two most frequent outcomes (Figure 4).

Other subgroup analysis

Further subgroup analysis was conducted to determine whether the presence of malaria during the initial hospital admission was a determinant of the magnitude of the effect of PMC. This was only possible in the study by Kwambai et al. in Kenya and Uganda, which enrolled both children with severe malarial anaemia (85% of the study population) and non-malarial anaemia (the remaining 15%). The protective efficacy for the composite of all-cause mortality and readmission (the primary outcome of that trial) was greater in children with severe malarial anaemia (41% vs 9%), but this difference in effect size was not significant ($p_{interaction}$=0.26).[4]

Tolerance and safety

Monthly SP was well tolerated. In the study by Bojang et al., no severe cutaneous reactions suggestive of the Stevens-Johnson syndrome were seen. Minor symptoms recorded during the 30 days after the administration of each treatment were similar in the SP and placebo groups.[2] No drug-related serious adverse events were reported in the study by Phiri et al. in the study arm receiving monthly AL.[3] ECG monitoring was conducted in a nested cardiac monitoring study involving 66 children in the study by Kwambai et al., which used dihydroartemisinin-piperaquine.[4] This showed that dihydroartemisinin-piperaquine (n=33) was associated with an 18.6ms (95% CI 15.6-21.8) increase in the QTc interval (Fridericia's method) after the third dose of each course (all asymptomatic), whereas placebo (n=33) was not (-1.8ms, -5.3-1.7) (p<0.001). The mean QTcF prolongation decreased with each subsequent course and was lower after the third compared to the first courses of PMC with dihydroartemisinin-piperaquine (p=0.02). None of the 33 children in the dihydroartemisinin-piperaquine arm experienced QTcF values >480ms. The proportion of participants who vomited the study medication at least once within 60 minutes after drug intake was higher with PMC (12.4%) than placebo (3.8%), but this did not result in any children having to stop the study medication. Overall, monthly dihydroartemisinin-piperaquine was well tolerated.[4]

Discussion

This is the first meta-analysis of monthly malaria chemoprevention trials for the efficacy of post-discharge management of African children who survived hospital admission for severe anaemia. The combined data show that approximately three months of PMC has the potential to prevent three out

of every four deaths and 60% of all-cause hospital readmissions during this period. The number needed to treat with PMC to avert one death was 83 and to avert one readmission was 11. PMC also halved the number of clinic visits needed because of uncomplicated malaria. The direction of the effect was consistent across all three trials in the four countries. Reduced readmissions were primarily due to severe malaria or severe malaria anaemia. These results show that PMC is a highly effective intervention that can have a high impact per child treated in preventing death or readmissions post-discharge in highly or perennial malaria transmission areas in Africa.

All three drugs used in these trials were well tolerated. AL provided the shortest post-treatment prophylaxis, judging by the sharp increase in clinical malaria cases seen 21 days after completion of each course.[3] Ideally, this would have required a 3-weekly regimen. AL may not be suitable as chemoprevention in settings where AL is used as first-line treatment for malaria case management. Still, it was chosen because, at the time, insufficient safety experience was available with monthly courses of dihydroartemisinin-piperaquine. The combination of SP plus amodiaquine, widely used for SMC, could be an alternative in areas of West Africa where SMC is not being implemented.

In settings with high-grade SP resistance, as is the case in most of east and southern Africa, dihydroartemisinin-piperaquine is currently the most suitable candidate for chemopreventive strategies. There is now significant experience corroborating the safety of monthly prophylaxis with dihydroartemisinin-piperaquine from studies in pregnant women,[18-24] adults,[25] children aged 6 to 24 months[26] and as SMC.[27-29] In the PMC trial by Kwambai et al.,[4] which included nested cardiac monitoring, monthly courses of dihydroartemisinin-piperaquine for PMC were well tolerated. No serious adverse events attributable to the study drug were observed. Asymptomatic corrected QT interval prolongation on the electrocardiogram was, as expected, significantly higher with dihydroartemisinin-piperaquine than placebo. However, no episode of QT prolongation was associated with arrhythmias or clinical adverse events. Furthermore, QT prolongation decreased significantly with each monthly course, consistent with previous trials in pregnancy.[22,24,30] Up to 18 monthly treatment courses of dihydroartemisinin-piperaquine have been safely given to children aged less than two years who received monthly courses from 6 months onwards.[26] Other options include weekly dosing post-discharge following a loading dose with a full treatment course at discharge. However, trials with weekly regimens of dihydroartemisinin-piperaquine are yet to be completed.

The protective effect was restricted to the intervention period and was not sustained after the direct pharmacodynamic effect of the drugs had waned. There was some indication that all-cause mortality during the post-intervention period was higher in the PMC group (RR=1.61, p=0.17), consistent with an increased risk of uncomplicated clinical malaria seen in previous seasonal malaria chemoprevention studies in children.[31,32] This could reflect an effect on premunition. However, in the PMC trials, there was no evidence for an increase in uncomplicated or severe malaria post-intervention. Another explanation could be that this reflects an artifactual increase due to frailty effects because, unlike the placebo arm, a higher proportion of the vulnerable children in the PMC arm survive to contribute to the post-intervention period. This was observed in the trial by Kwambai et al., where among those who died in the post-intervention period, 73% in the PMC arm had a history of previous hospital admissions before the initial hospitalisation.[4] However, overall, the initial 77% reduction in mortality conferred by PMC during the intervention period in this meta-analysis outweighed the 61% increase during the post-intervention follow-up period. The overall cumulative protective efficacy by the end of six months was still in favour of PMC in all three studies, although this effect was not significant (23% [-28, 53]).

Interventions that protect for longer than 3 to 4 months may further boost the magnitude of the effect of PMC. The studies by Kwambai and Phiri et al. showed that after these three months of PMC, the

rates of re-admissions and out-patient clinic visits increased again to similar levels as seen in the control arms. As many as one in six surviving children were either readmitted or died in the three months after the protective drug levels had waned. There is some indication that adherence to courses may be limited beyond three post-discharge courses of PMC (which provide four months of protection). The study by Bojang et al., which provided monthly PMC with SP for the rest of the transmission season, showed that adherence was initially high but decreased progressively with subsequent courses in study subjects scheduled to take more than three courses.[2] This suggests that PMC regimens containing four courses, including one course at discharge and three courses spaced monthly after discharge, may provide the right pragmatic balance. It would allow for monthly spacing of PMC courses, unlike in the trial by Kwambai et al., where the children received AL at discharge (the standard of care) followed by dihydroartemisinin-piperaquine two weeks later. It would also allow facility staff to instruct caregivers on the concept of PMC and how to administer the drug while the child is still in the hospital. Longer courses could be considered when delivery platforms are created to deliver chemoprevention in communities, such as for perennial malaria chemoprevention (an extension of intermittent preventive treatment (IPT) in infants, and similar to the experience with monthly SMC, which is now given up to five times in some parts of west Africa.

Other options to prolong the duration of protection may involve combining chemoprevention with vaccination as the effects of the malaria vaccine may persist after the protective drug levels have waned.[33] A recent trial conducted in young children in Burkina Faso and Mali showed that a combination of the RTS,S/AS01E malaria vaccine and SMC provided markedly superior protection compared to SMC or RTS,S/AS01E alone.[34] Depending on the child's vaccination status, the vaccine could be provided either as three monthly priming doses in the first months post-discharge or as a single booster dose at discharge. Another option that could be available soon is monoclonal antibody therapy, which can potentially provide at least six months of protection against malaria.[35] Ideally, children should also receive a long-lasting insecticide-treated net at discharge.

Should PMC be restricted to children with severe malaria anaemia, or also offered to children with non-malarial causes of severe anaemia? Subgroup analyses suggested that the most significant reductions were observed in children admitted for severe malarial anaemia. This group comprised 62% of initial admissions with severe anaemia in the Gambia and 85% in Uganda and Kenya. In the trial in Kenya and Uganda, PMC was associated with a 36% reduction in the composite of readmissions or deaths in children surviving admittance for non-malarial causes of severe anaemia and 74% in those with severe malarial anaemia.[4] This latter group may have benefitted more from PMC, a malaria-specific intervention, as most of them return to the same high-risk environment where they acquired their initial infections. In contrast, children admitted with other causes of severe anaemia may have more complex, multifactorial aetiologies in which malaria plays a smaller part. As a result, they are at increased risk of receiving inadequate diagnoses and therefore care during initial hospitalisation, resulting in continued disease progression and a poor prognosis after discharge.[36,37] However, these children also obtained some benefit from the near-complete chemoprevention of malaria provided by PMC after discharge, although less than in those with malarial anaemia. Furthermore, many children receive parenteral antimalarial treatment presumptively, regardless of confirmation of malaria diagnosis, either because laboratory facilities are not available or because of the difficulty of interpreting diagnostic test results if children received antimalarials before reaching the hospital.[38] Providing PMC to all children with severe anaemia in highly malaria-endemic areas, regardless of whether they have malaria during the initial hospitalisation, could be a pragmatic solution, provided they are not already scheduled to receive malaria chemoprevention for other reasons such as SMC or sickle cell disease.

The pros and cons of introducing PMC in areas where SMC is implemented would require careful consideration. PMC and SMC both provide monthly prophylaxis, and there could be an increased risk of toxicity when courses are given close to each other. For example, there could be a potential increased risk for cardiotoxicity due to the provision of two QT-prolonging drugs like piperaquine and amodiaquine, or severe cutaneous adverse reaction associated with the frequent administration of SP and intervals shorter than one month as was seen in travellers taking weekly or bi-weekly prophylaxis with SP.[39,40] However, many cases of severe malarial anaemia are seen towards the end of the transmission season and early into the dry season when some residual transmission is ongoing. Thus, a child who is discharged in the month after SMC is stopped could potentially benefit from PMC.

With large-scale drug administration, there is always a concern about the spread of drug resistance. Although none of the studies was powered to address this issue, the fraction of the population targeted by PMC and the corresponding selective drug pressure on the parasite population is much smaller than with SMC, IPT in pregnancy (IPTp) or infants (IPTi), which includes all members of a target population regardless of health status.

Health services research has shown that PMC is highly cost-effective[41] and highly acceptable to caregivers and community health volunteers.[42,43] Unlike SMC, IPTp or IPTi, there is currently no healthcare delivery platform designated to support PMC delivery. PMC is directed at a small, seriously ill population with an ongoing risk that is already connected to the healthcare system (i.e., they were recently admitted to hospital).[44] This in-hospital period provides an opportunity to engage with the caregivers and provide clear and context-specific health education messages to ensure adequate coverage of all PMC courses under programmatic conditions. A recent delivery mechanism trial showed that provision of all three post-discharge PMC courses to the caregivers at discharge (i.e. while the child was still in-hospital) achieved better coverage than facility-based delivery that required caregivers to return to the facility to collect their next course of PMC.[45] This could be combined with mobile-phone text reminders or home visits by village health workers.[45]

This meta-analysis has several limitations. First, the number of trials was limited to three, and each trial used a different drug and slightly different regimens. Further subgroup and sensitivity analyses to explore the determinants of heterogeneity in effect size and influence of malaria transmission intensity, intervention regimen and study quality on results was not possible due to the small number of studies. For similar reasons, the assessment of publication and small-study bias was not possible. There were also variations in the measures of associations reported by the studies and between outcomes. Other limitations include limited available diagnostic data for the non-malaria causes of post-discharge readmissions or deaths. Furthermore, the absolute difference in mortality may have been underestimated because the mortality in the control arm in all three trials was lower than that in the post-discharge community at large.[37] This may have reflected the enhanced access to standard care from participating in a trial, including the early diagnosis of events requiring re-admission.

The strengths of this review include the high quality of the trials and the robustness of the findings in favour of PMC across the trials.

Future research should focus on methods of PMC delivery to prolong the duration of protection, for example, by combining chemoprevention with malaria vaccination or monoclonal antibody therapy. Other interventions, such as anthelmintics or those that address additional nutritional factors or recurrent bacterial infections, could also be considered but may be less generalisable and requires tailoring to local modifiable risk factors.

In conclusion, this review confirms that children recently discharged from hospital after recovery from severe anaemia are at high risk of dying or being readmitted in the first six months after discharge.

For malaria control in areas of high malaria transmission, monthly malaria chemoprevention with long-acting antimalarials represents a valuable new strategy for the post-discharge management of children with severe anaemia.

Article information

Contributors

FtK and KP conceived the idea of this meta-analysis. CK wrote the protocol with input from FtK. TKK and FTK developed search terms and applied them to electronic databases. TKK and FtK reviewed all abstracts, selected full-text articles, and assigned bias scores; CK served as a tiebreaker. CK abstracted all the data and conducted the meta-analysis. KP, TK, KB, AD, RI, RO and BG, BR, and FtK provided source data. KP, CK and FtK wrote the first draft of the manuscript. All authors reviewed, revised and approved the final version of the manuscript.

Declaration of interest

There are no conflicts of interest to declare.

Data sharing

Individual patient data for studies contributing to this analysis are available from the Worldwide Antimalarial Resistance Network (WWARN) data repository.

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Ethics

The original studies were approved by the relevant local and international partner ethics committees and institutional review boards.

References

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Figures

Figure 1: PRISMA Flow Diagram

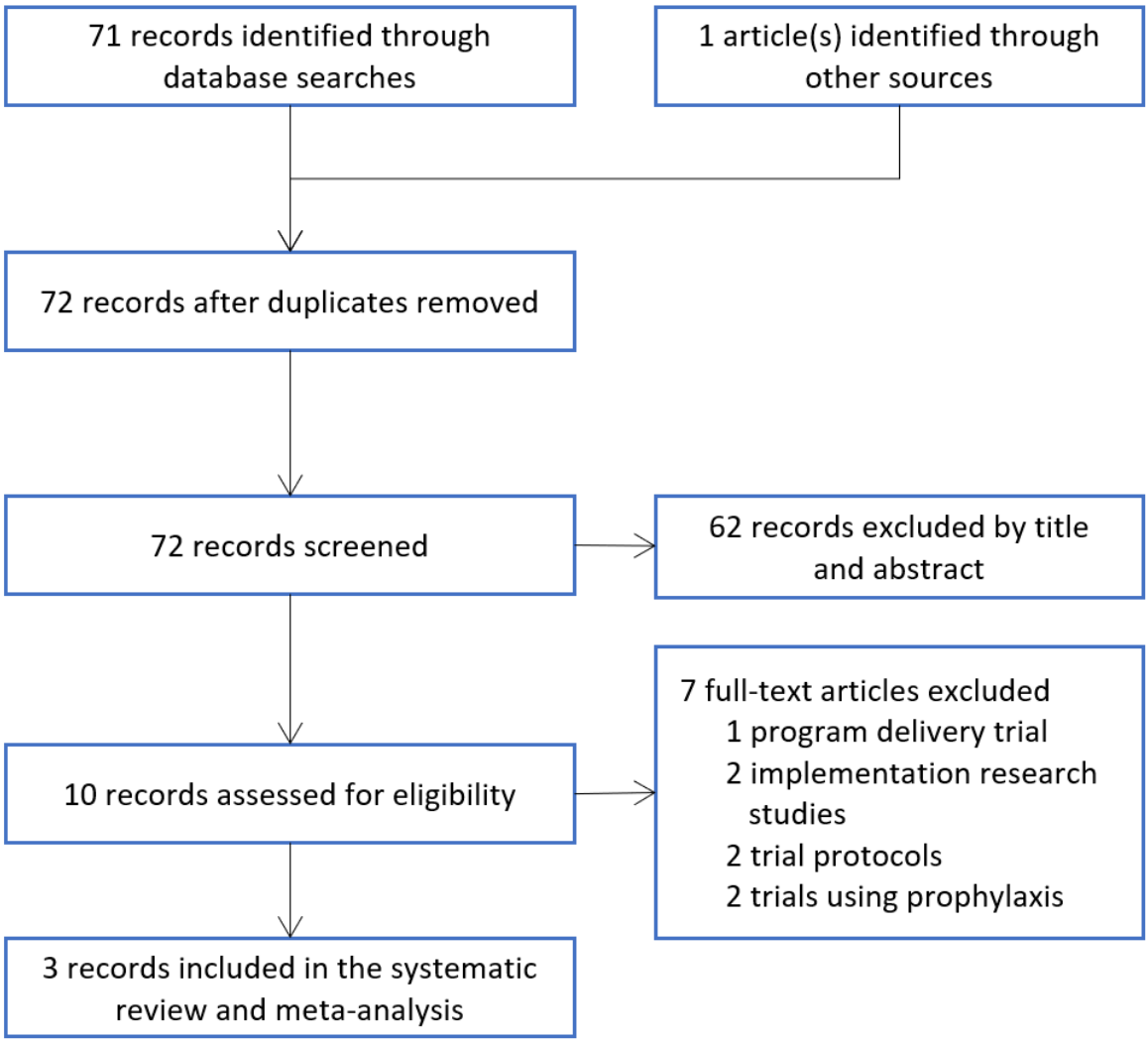
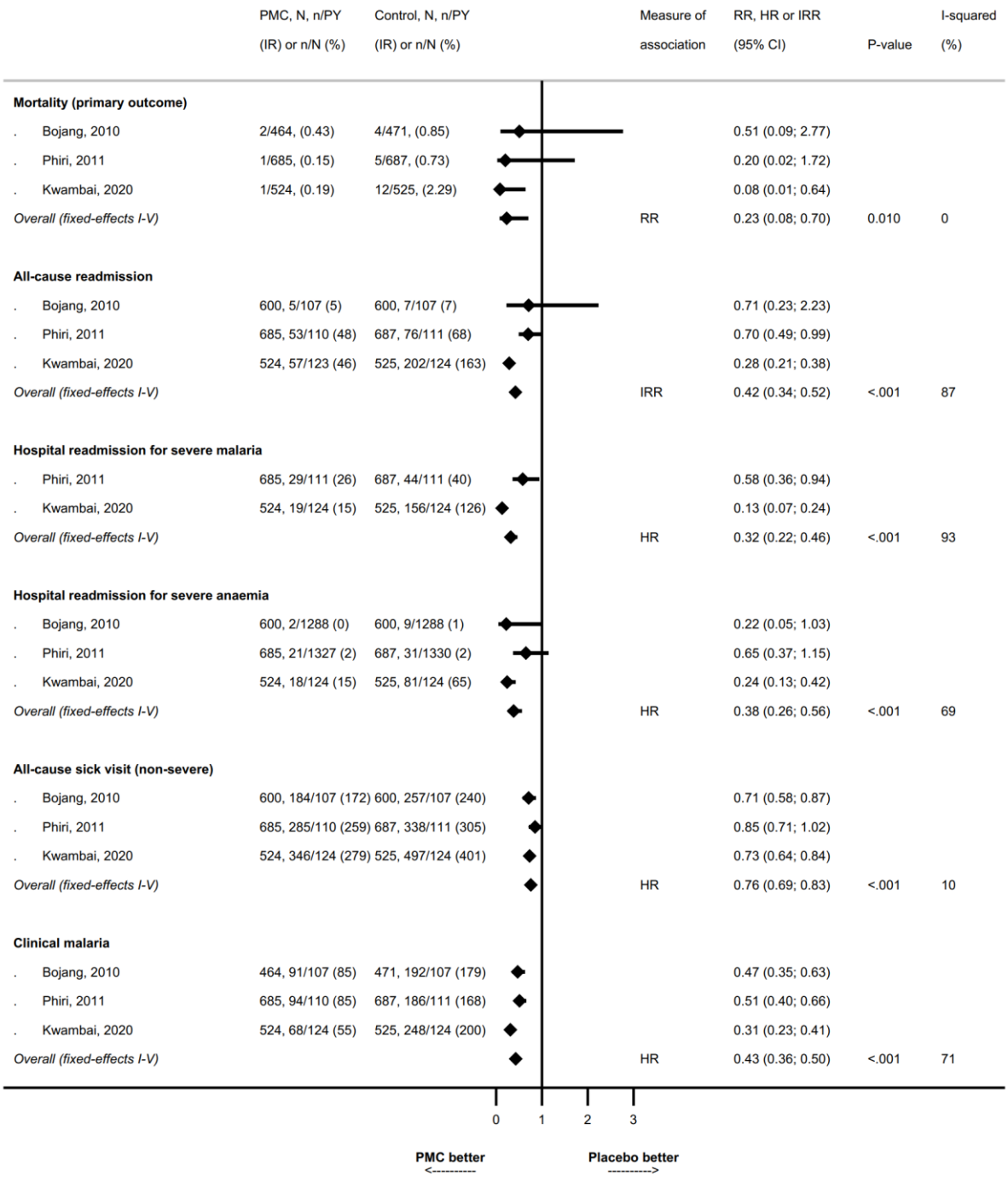


Figure 2: Effect of PMC versus standard or care on readmissions or death during the intervention period (primary analysis)



N=number of children contributing, n=number of children with events or number of events. PY=person-years, IR=incidence rate per 100 person-years. RR=relative risk. HR=hazard ratio. IRR=Incidence rate ratio. I-V=Inverse variance fixed effects. References to source studies include Bojang, 2010[2]; Phiri, 2020[3]; Kwambai, 2020[4]

Figure 3: Efficacy outcomes by study period (3 trials)

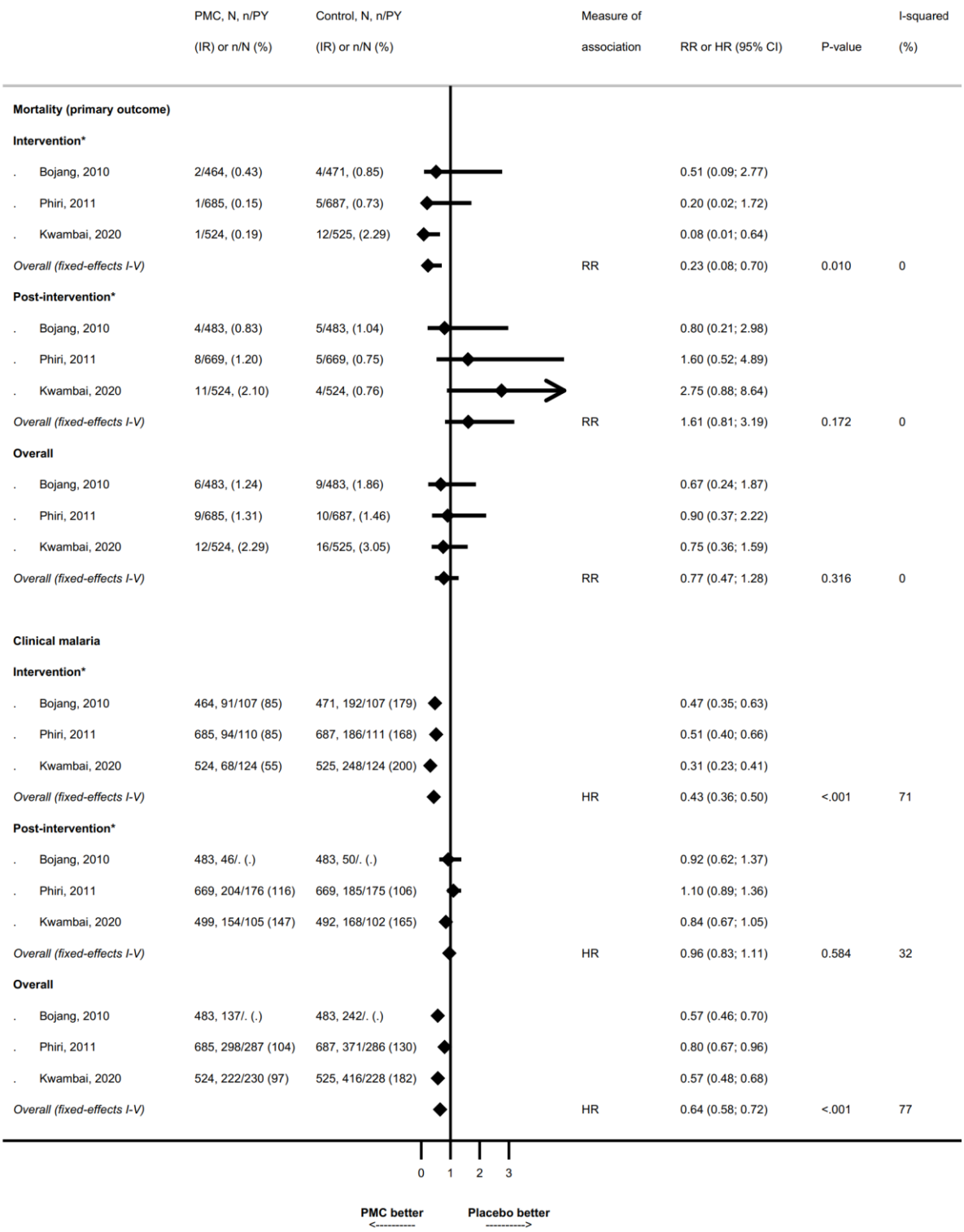
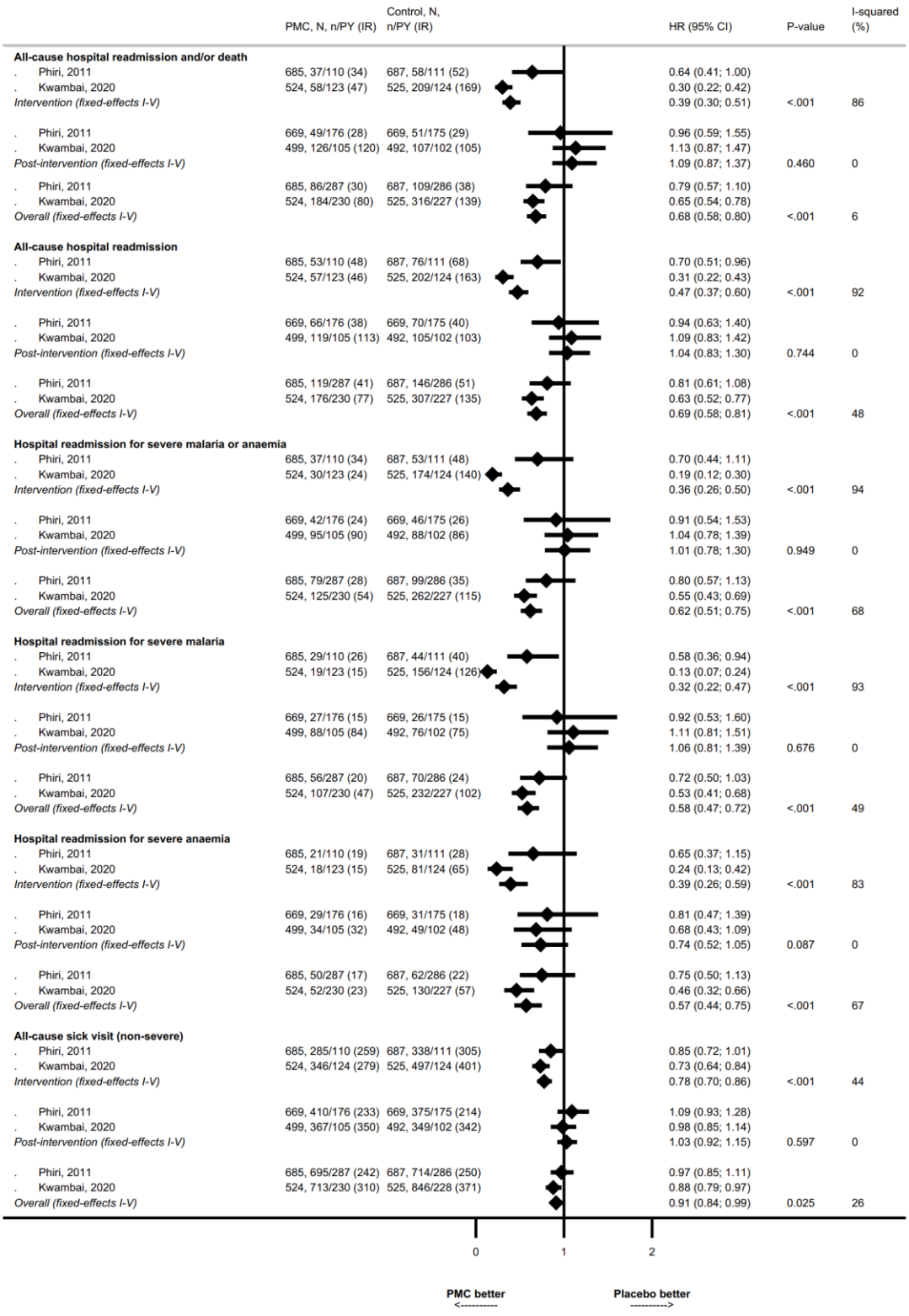


Figure 4: Efficacy outcomes by intervention period for other secondary outcomes (2 trials)



HR=hazard ratio. CI=confidence interval. I-V=Inverse variance fixed-effects. The p-values for the differences in treatment effect between the intervention period and the post-intervention period ($p_{interaction}$) were p=0.002 for non-severe all-cause sick visits, p=0.037 for the composite of all-cause readmission and/or death, p=0.07 for all-cause hospital admission, p=0.09 for readmissions for severe malaria, p=0.09 readmission for severe anaemia, and also p=0.09 for the composite of readmisisons due to severe malaria or anaemia. References to source studies include Phiri, 2020[3]; Kwambai, 2020[4]

Tables

Table 1: Characteristics of included trials

First author	Bojang[2]	Phiri[3]	Kwambai[4]
Year published	2010	2012	2020
Country	The Gambia	Malawi	Kenya and Uganda
Years of study	2003-04	2006-09	2016-18
Enrolled (PMC:control)	1,200 (600:600)	1,414 (706:708)	1049 (524:525)
Design	Placebo controlled	Placebo controlled	Placebo controlled
Admission Health-condition	Severe anaemia (Hb< 7.0/g/dL) regardless of the presence of malaria parasites	Severe malarial anaemia (Hb<5.0 g/dL and parenteral malarial treatment given)	Severe anaemia (Hb< 5.0/g/dL) regardless of the presence of malaria parasites
Initial case-management in-hospital provided to both study arms	Blood transfusion if clinically indicated, intramuscular quinine or parenteral chloroquine followed by SP (for those with malaria)	Blood transfusion, parenteral quinine or artesunate, followed by AL	Blood transfusion, parenteral artesunate (for those with malaria), followed by AL regardless of malaria
Post-discharge Intervention arms	Monthly SP for the rest of the malaria transmission season, starting at day-7 post-discharge. The average number of PMC courses was 3.1 and varied depending upon the time of the year at which they were recruited.	Monthly AL at the start of the 2nd and 3rd month post-discharge providing about 11 to 12 weeks of chemoprevention	Monthly DHA-PiP at the start of week 3 (about 14 days after discharge), 7, and 11 weeks post-discharge.
Control arm	Placebo SP	Placebo AL	Placebo DHA-PiP
Intervention period	Average of 3.1 monthly courses starting on day 7 post-discharge until the end of the malaria transmission season.	2 months (month 1 to 3 post-discharge)	12 weeks (weeks 3-14 post-discharge)
Post-intervention follow-up period	Approximately five months into the dry season (Jan-May)	13-26 weeks post-discharge	15-26 weeks post-discharge
Key inclusion criteria for age and Hb	3m to 9y, Hb<7.0 g/dL	4m-59m, Hb<5.0 g/dL	<5 years, bodyweight ≥5.0 kg, Hb<5.0 g/dL
The primary method of analysis to obtain measures of association	Mortality: RR based on the number died/number enrolled; Count outcomes: Cox regression for repeated events with robust standard error estimation methods to account for correlation between episodes within children All-cause readmission: crude number of events and person-time (IRR)	Mortality: RR based on the number died/number enrolled; Count outcomes: Hazard ratios calculated by Cox regression for repeated events with robust standard error estimation methods to account for correlation between episodes within children All-cause readmission: IRR (instead of HR) based on the crude number of events and person-time when used in pooled analysis with Bojang et al[2]	Mortality: RR based on the number died/number enrolled; Count outcomes: Hazard ratios calculated by Cox regression for repeated events with robust standard error estimation methods to account for correlation between episodes within children All-cause readmission: IRR (instead of HR) based on the crude number of events and person-time when used in pooled analysis with Bojang et al[2]

SP=sulfadoxine-pyrimethamine; AL=artemether-lumefantrine; DHA-PiP=dihydroartemisinin-piperaquine; Hb=haemoglobin concentration; PMC=post-discharge malaria chemoprevention

Supplementary appendix

Supplement to: Phiri et al., Post-discharge Malaria Chemoprevention in Children Admitted with Severe Anaemia in Malaria-Endemic Settings in Africa: A Systematic Review and Meta-Analysis

Table of Contents

Supplemental methods

Supplement 1: Search terms used in PubMed

(child OR childhood OR infant OR pediatric OR paediatric) AND (malaria OR plasmodium) AND ("severe anaemia" OR "severe anemia" OR transfusion) AND (recurrence OR discharge OR postdischarge OR post-discharge)

Supplement 2: Quality and risk of bias assessment of trials

The risk of bias assessment for each included trial was conducted by two investigators (TKK and FtK) using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2).[1,2] RoB2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting. A judgement about the risk of bias arising from each domain is proposed by an algorithm and can be overwritten by the authors with justification. Judgements can be a 'low' or 'high' risk of bias or expressed as 'some concerns'. Where disagreement occurred, a joint review of the study was conducted until agreement was reached by consensus. Studies were not excluded *a priori* on the basis of their quality score.

Supplement 3: Definition of outcomes

Primary outcome

All-cause death during the intervention period

Secondary outcomes (by intervention period and overall)

- All-cause deaths during the post-intervention follow-up period and overall
- All-cause readmissions
- All-cause death or readmissions (composite)
- Cause-specific readmissions
- All-cause non-severe sick-child visits
- Unomplicated clinical malaria, defined according to the data reported in the source studies as as a non-severe sick-child clinic visit resulting in receipt of oral antimalarials for confirmed or presumptive malaria infections.

Where data was available, outcomes were to be assessed during three time periods: the intervention period and post-intervention follow-up period and overall (intervention and post-intervention follow-up period pooled). The intervention period was considered the primary period for analysis.

The intervention period was defined as the period starting from the first dose of the first course of post-discharge malaria chemoprevention until four weeks after the first dose of the last course of PMC.

The post-intervention period was defined as the period starting the day after the completion of the intervention period (see above) up to six months post-discharge in the trial in Malawi,[3] Kenya and Uganda,[4] or until the assessment approximately six months into the dry season in the trial from the Gambia [5].

Supplemental tables

Table S1: Cochrane collaboration tool for quality assessment of randomised controlled trials

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Bojang, 2010[5]	+	+	+	+	+	+	+
Phiri, 2012[3]	+	+	+	+	+	+	+
Kwambai, 2020[4]	+	+	+	+	+	+	+

+	Low Risk of Bias	?	Unclear Risk of Bias	-	High Risk of Bias

Risk of bias assessment for included studies with the authors' judgements for each included trial. Adapted from the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[2]

Table S2: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review=meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving a rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3 and S2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in a systematic review, and, if applicable, included in the meta-analysis).	3

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3 and S2 and Table S1
Summary measures	13	State the principal summary measures (e.g., risk ratio, the difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure-2 Figure-3 Figure-4

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure-2 Figure-3 Figure-4
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15).	Table S1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	6 to 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., the supply of data); the role of funders for the systematic review.	2 and 10

Supplemental references

1. Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R, 2020. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. J Clin Epidemiol 126: 37-44.
2. Higgins J, Savović J, Page MJ, Elbers RG, Sterne JAC, 2021. Chapter 8: Assessing risk of bias in randomized trials. Available at: https://training.cochrane.org/handbook/current. Accessed.
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4. Kwambai TK, Dhabangi A, Idro R, Opoka R, Watson V, Kariuki S, Kuya NA, Onyango ED, Otieno K, Samuels AM, Desai MR, Boele van Hensbroek M, Wang D, John CC, Robberstad B, Phiri KS, Ter Kuile FO, 2020. Malaria Chemoprevention in the Postdischarge Management of Severe Anemia. N Engl J Med 383: 2242-2254.
5. Bojang KA, Milligan PJ, Conway DJ, Sisay-Joof F, Jallow M, Nwakanma DC, Abubakr I, Njie F, Greenwood B, 2010. Prevention of the recurrence of anaemia in Gambian children following discharge from hospital. PLoS One 5: e11227.