Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention in the postdischarge management of severe anemia. N Engl J Med 2020;383:2242-54. DOI: 10.1056/NEJMoa2002820

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Investigators

Titus K Kwambai, MD, PhD[1-3]; Aggrey Dhabangi, MD, PhD[4]; Richard Idro, MD, PhD[4]; Robert Opoka, MD[4]; Victoria Watson, BSc[3,5]; Simon Kariuki, PhD[1]; Nickline A Kuya, Dip ClinMed[1]; Eric D Onyango, BSc[1]; Kephas Otieno, MPH[1]; Aaron M Samuels, MD, MHS[6]; Meghna Desai, PhD[6]; Michael Boele van Hensbroek, MD, PhD[7]; Duolao Wang, PhD[3]; Chandy C John, MD[8]; Bjarne Robberstad, PhD[9] ; Kamija S Phiri, MD, PhD[10]; Feiko O ter Kuile, MD, PhD[1,3]

Institutional affiliations

1 Kenya Medical Research Institute/Centre for Global Health Research (KEMRI/CGHR), Kisumu, Kenya
2 Kisumu County Department of Health, Kenya Ministry of Health, Kisumu, Kenya
3 Department of Clinical Sciences, Liverpool School of Tropical Medicine (LSTM), Liverpool, United Kingdom
4 Makerere University College of Health Sciences, Kampala, Uganda.
5 Department of Biostatistics, University of Liverpool, Liverpool, Merseyside, United Kingdom
6 Malaria Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States
7 Emma Children's Hospital, Academic Medical Centre, University of Amsterdam, the Netherlands
8 Ryan White Center for Pediatric Infectious Disease and Global Health, Indiana University School of Medicine, Indianapolis, IN, USA
9 Section for Ethics and Health Economics and Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
10 School of Public Health and Family Medicine, College of Medicine, University of Malawi, Blantyre, Malawi

Supplemental methods

Eligibility criteria

Children aged <5 years, weighing ≥5 kg, who had been admitted with severe anemia (hemoglobin <5g/dL/hematocrit <15% or clinical indication for blood transfusion) and had received the standard in-hospital care were eligible during their convalescence period if their post-transfusion hemoglobin concentration was ≥5g/dL, they were clinically stable and able to take oral medication, and if their caretakers agreed to the follow-up schedule. Exclusion criteria were admission with severe anemia due to blood loss/trauma, malignancy, known bleeding disorders or sickle cell disease, known hypersensitivity to study drug, known heart conditions or need for drugs that may be associated with QTc prolongation, non-resident in the study area, enrolled into another clinical trial or previous participation in this trial.

Outcomes

Efficacy outcomes

Primary efficacy outcome

The primary outcome was a composite of the time to one or more all-cause hospital readmissions or death determined by the time from randomization around two weeks post-discharge until week-26 inclusive. A composite outcome was chosen to increase the power of the study and because the two components were expected to follow a similar biological pathway and relative risk reductions.

Secondary efficacy outcomes

- Composite primary outcome of the time to all-cause hospital readmissions or death by study period (PMC-intervention period and post-intervention period)
- All-cause hospital readmissions (overall and by study period)
- Hospital readmissions due to severe anemia or malaria (composite) (overall and by study period)
- All-cause mortality (overall and by study period)
- All-cause sick clinic visits (overall and by study period)
- Uncomplicated clinical malaria (overall and by study period)

Tertiary efficacy outcomes

- Hospital readmissions due to severe anemia (overall and by study period)
- Hospital readmissions due to severe malarial anemia, defined as severe anemia plus RDT or microscopy confirmed malaria or, if no diagnostic test result is available, any treatment with parenteral or oral antimalarial treatment (overall and by study period)
- Hospital readmissions due to severe malaria (overall and by study period)
- Hospital readmission due to severe malaria-specific anemia (severe anemia plus parenteral or oral antimalarial treatment and parasite density >5000/microliter) (overall and by study period)
- Hospital readmission due to severe disease other than severe anemia and severe malaria
- Primary outcome that excludes hospital admissions due to trauma and malignancies (overall and by study period)
- All-cause hospital admissions that exclude admissions due to trauma and malignancies (overall and by study period)
- Non-severe all-cause sick-child clinic visits (overall and by study period)
- Non-malaria sick child clinic visits (overall and by study period)
- Malaria infection (overall and by study period)
- Antibiotic use (overall and by study period)
- Malaria infection (at 26 weeks)
- Hb (at 26 weeks)
- Any anemia (Hb<11.0 g/dL), mild anemia (Hb 8.0-10.99 g/dL) moderate anemia (Hb 5.0-7.99 g/dL) and severe anemia (Hb<5.0 g/dL) (at 26 weeks)
- Weight-for-age, height-for-age, and height-for-weight z-scores (standard deviation [SD] scores of reference population) and as categories <2SD and <3SD from references population (at 26 weeks).

Tolerability and safety outcomes

- Treatment emerging serious adverse events, excluding primary and secondary efficacy outcomes (overall and by study period)
- Treatment emerging serious adverse events within 4 days after the start of each course of PMC, excluding primary and secondary efficacy outcomes.

- Treatment emerging adverse events (overall and by study period)
- Treatment emerging adverse events within 4 days after the start of each course of PMC
- Mean QTc and mean increase in QTc prolongation measured by electrocardiogram (ECG) 4-6 hours after 3rd dose of each course (mean SD) and QTC prolongation >480ms and >500ms and >60ms increase in QTc at any course (binary; yes/no)

Cardiac monitoring

A nested cardiac monitoring study was conducted among 66 children enrolled at the Jinja site in Uganda to determine whether previously documented transient QTc prolongation associated with dihydroartemisinin-piperaquine[1,2] increases in magnitude with subsequent courses. The primary endpoint was the difference in QTc prolongation between the first and last PMC course, where QTc prolongation was defined as the increase in QTcF values between the first and last dose of each course. Following randomization, 33 children per arm had an ECG taken before the first dose and again 4-6 hours after the third dose of each course of dihydroartemisinin-piperaquine, when both the maximum concentration of piperaquine and the maximum prolongation of the QT interval were expected.[4] All ECGs were done in triplicate, and the mean values were used for the analysis. All ECGs were read on-site by the study team, and again by a cardiologist in Jinja. It was estimated that 33 children in the dihydroartemisinin-piperaquine arm were required to detect a mean of paired difference of 20ms between courses in the increase in QTc per course, assuming an estimated standard deviation of 30ms, with 90% power, at a significance level 0.05 using a paired t-test, and allowing for 20% loss to follow-up. Because the study was placebo-controlled, 66 children were recruited. Analyses were first conducted to determine the best correction method to obtain heart rate corrected QTc intervals; Fridericia's (observed QT interval divided by the cube root of RR interval, in seconds [QT / $(RR)^{0.33}$]) or Bazett's method (observed QT interval divided by the square root of RR interval, in seconds [QT / $(RR)^{0.5}$]). Fridericia's method resulted in better rate correction and was used in subsequent analyses. Paired t-tests were used to compare QTc intervals pre vs. post-dose for each course and to compare the mean QTc prolongation after the first and third courses.

Sample Size

Original sample size

As described in the published protocol,[1] the initial sample size was 2212 children (1106 per arm) across both countries pooled, and the study was designed to detect a 30% reduction in the incidence rate of the composite primary outcome (death or all-cause readmission) from 469 per 1000 child years in the control arm to 328 per 1000 child years in the intervention arm (IRR=0.70, power 90%, α=0.05). This allowed for one interim analysis and a 15.7% loss to follow-up. For these estimations, we assumed an average pooled event rate of 399 per 1000 child years across the two arms. We based this assumption on observations in western Kenya (Desai et al., unpublished) and Malawi.[2] However, the observed event rate, pooled across both arms, during the first year of the study was 1,120 per 1000 child years, which was almost three times higher than the assumed event rates. Recruitment was competitive between sites.

Blinded interim sample size re-estimation

Following recommendations from the Data Monitoring and Ethics Committee (DMEC) and The Trial Steering Committee (TSC), a blinded interim sample size re-estimation was conducted to take into account a lower than expected rate of loss to follow-up and the higher than expected pooled incidence

rate of the composite primary outcome (death or all-cause readmission). The revised sample size calculations showed that a total sample size of 1040 children (520 per arm) was required to detect a 25% reduction in the incidence of the composite primary outcome from 1,152 per 1000 child years (530 events per 1000 children) in the control arm to 864 per 1000 child years (398 per 1000 children) in the intervention arm (power 80%, α=0.05), allowing for 10% loss to follow-up.

Statistical Analysis

Definition of analysis populations

The intention-to-treat (ITT) population included all randomized participants regardless of whether they received the intervention. The per-protocol population included participants who received all possible scheduled courses. The safety population included participants who received at least one dose of the first course.

PWP-TT extended Cox proportional hazard model for recurrent events

Because it was anticipated that PMC would have an impact on recurrent events, and because the order and time to each event were considered important, we used an extension of the Cox proportional hazards model for recurrent events (multiple-failure survival analysis). Preference was given to the Prentice-Williams-Peterson (PWP) models over the Andersen-Gill (AG) model because PWP models consider the order of events[3] and stratify on the number of previous events (in this case hospital admissions) and thus account for an increase in the baseline risk of readmission with the number of previous admissions.[4] It is reasonable to expect that risk of admission will increase with the accumulated number of previous admissions as has been illustrated previously.[4] The Andersen-Gill (AG) model is a non-stratified model which does not consider the order of events and thus the underlying risk of failure is regarded as the same for each event within an individual.[3-5] Both PWP and AG models account for the within-subject correlation of failure times.[6] So no gap time independence is assumed, but the length of the gap time is assumed to be dependent on the covariates at baseline. We considered two PWP models; Total Time (PWP-TT) and Gap Time (PWP-GT). The risk interval for the first event is the same with both models, but with Total-Time, the interval for the next event starts at the time at which the previous event ends and ends when the next event occurs. The risk intervals with Gap-Time are of the same length as with total time, but each interval restarts at zero.[6] Comparison of the model fit for PWP-TT and PWP-GT using the blinded data while recruitment was still ongoing showed a slightly better fit for the PWP-TT model based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores. Preference was therefore given to the PWP-TT model, which has also previously been recommended for the analysis of multiple-failure survival datasets, which detail recurrent hospital admissions.[4] PWP techniques assume proportional hazards. Graphical examination of plots of the relationship between the scaled Schoenfeld residuals and functions of time showed that this assumption was not violated.

Definition of study time intervals

Participants were randomized about 14 (11-28) days after discharge. This was delayed if the child was readmitted before day 14 or was found to be acutely ill on the scheduled day of randomization. The survival or incidence data analysis cut-off date for a participant was the date of the last study visit if no follow-up contact was available after that or last known survival status date or end of study visit at 182 days (26 weeks) post-discharge (i.e., enrolment).

The study period was divided into three periods: 1) pre-randomization period of approximately two weeks from the time the participant was formally enrolled (day 0) until the day of randomization when the first dose of the first course of PMC or PMC-placebo was given approximately two weeks later, 2) PMC-intervention period (week 3-14) of approximately 12 weeks starting from the date of randomization and ending four weeks (28 days inclusive) after the date of the first dose of the last 3-day course of PMC or 14 weeks from enrolment (98 days inclusive), whichever came last and 3) Post-PMC extended follow-up period (weeks 15-26) of approximately 12 weeks from the end date of the subject's PMC intervention period plus one day until 26 weeks after enrolment (182 days).

The analysis for each outcome was presented as the overall effect during the entire on-study period (3-26 weeks) and stratified by the study period (the PMC intervention period and the post-PMC extended follow-up period).

Covariate adjusted analysis

Secondary covariate-adjusted analysis of the primary outcome was conducted to determine whether the treatment effect estimates or standard errors were affected by the inclusion of covariates. In addition to stratification factor, site and weight, the following pre-specified covariates were included: previous hospital admissions, the syndrome on admissions (non-malaria severe anemia vs. severe malarial anemia, age, Hb level at randomization, distance to hospital, readmission during the pre-randomization screening period, and socioeconomic status). The same covariates were used in the sub-group analysis of the primary outcome defined *a priori*.

Subgroup analysis of the primary outcome

Subgroup analysis of the primary outcome using the PWP-TT model was conducted to determine the extent to which the study effect varied by sub-groups. The treatment, subgroup variable, and their interaction term were used as predictors. The ratio of hazard ratios and corresponding confidence intervals for models involving interaction with the period of assessment were obtained using Altman and Bland's method.[7] Sub-group variables considered *a priori* included; period of assessment, adherence to the number of courses taken, malarial season on admission based on microscopy or RDT positivity among participants, country, dose in mg/kg received, the severity of anemia on initial admission, blood transfusion status on initial admission, Hb level at randomization, distance to nearest study hospital and socioeconomic status.

Adjustment for multiplicity

Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, p-values are omitted, and results are only reported as point estimates and 95% confidence intervals. The widths of the confidence intervals for these outcomes have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. Furthermore, for the subgroup analyses, the interaction tests for the primary outcomes have not been adjusted for multiple testing and are, therefore, exploratory in nature. P-values are therefore not shown, except for one pre-specified subgroup analysis of the primary outcome by the period of assessment. However, for safety analysis, p-values are reported to avoid missing any safety signals.

Missing data

All children contributed person-time to the primary outcome. Missing baseline covariates were imputed using multiple imputation methods with ten imputations in STATA using the 'mi impute' command. The

seed for the imputation was set as 128 to allow for reproducibility. 'Unknown' was not considered to be missing if this was a valid category (e.g., HIV status: positive, negative, unknown).

Proportional hazard assumption

The proportional hazards assumption was tested for the time until the first event analyses using the Schonfeld residuals and plotting the observed vs. predicted, and the assumption did not appear to be seriously violated. Due to the baseline hazard not being constant, we could not formally check the proportional hazards assumption for the primary analysis for recurrent events.

Cause of death

Data on cause of deaths was collected at least one month after the death had occurred using standardized WHO verbal autopsy forms to gather information on symptoms and any treatments or care sought before death.[8] The forms were reviewed independently by two clinical officers and a probable cause of death assigned.[9] The number (%) of participants with cause-specific death was summarized by treatment group.

Supplemental results

Predictors of mortality during the post-intervention period

A *post-hoc* analysis was conducted of the baseline predictors of mortality during the post-intervention period (15-26 weeks post-discharge). Predictor variables with a p-value of less than 0.2 in the univariate analysis were included in the full model (previous hospitalization, severe acute malnutrition, Hb at randomization, bednet use, and socioeconomic status of the household). Of these, a history of previous hospitalizations was the only predictor significantly associated with post-intervention mortality (HR=4.25, 95% 1.30-13.84) in the final model that also included treatment arm, and site and weight category as covariates to adjust for stratification factors. Of the 15 children who died in the post-intervention period, 8 out of 11 had a history of previous hospitalizations in the PMC arm. This was 2 out of 4 in the placebo arm.

Post-hoc analysis of heterogeneity in effect size between study sites

To explore the source of heterogeneity in effect size between study sites (Figure-S3), we conducted further sub-group analysis and meta-regression to examine the potential modifying effects of malaria transmission intensity *post-hoc*. A site-level variable for malaria transmission intensity was computed, defined as the average prevalence of malaria infection in children <5 years of age during the study. The prevalence data were obtained from pediatric in-hospital patients screened for malaria at their hospital admission, and the out-patient sick-child clinic visits among study participants in the control arm. The pooled data were used to calculate the average prevalence of malaria over 26 weeks following each day that study enrolment was ongoing. This site-specific estimate of the rolling daily 26-week average prevalence was merged with the trial data by day of enrolment and study site. The overall site-specific malaria prevalence during the study was then calculated as the average 26-week prevalence of all children enrolled in that site.

Random-effects meta-analysis stratified by malaria transmission intensity terciles showed that PMC was associated with a 48% lower hazard of the primary outcome by 26 weeks in the three sites with the highest malarial transmission (HR=0.52, 95% CI 0.39-0.65). The corresponding estimates in the sites with

the middle and the lowest malaria transmission were 29% (HR=0.71, 0.28-1.14) and 15% (HR=0.03-1.68), respectively (Figure S6). Random-effects meta-regression using the log-transformed effect size showed a significant linear trend towards an increase in the protective efficacy of PMC on the primary outcome with an increasing site prevalence of malaria infection (expressed as a percentage on a continuous scale) (slope 0.92, 95% CI 0.86-0.99).

Results of cardiac monitoring

A total of 66 children were recruited; 33 per arm. All 66 received three courses of PMC. A total of 1,188 ECGs were taken consisting of 396 timepoints in triplicate, 2 per course for three courses each. There were no clinical cardiac adverse events.

The Fridericia's method resulted in a better rate correction than the Bazett's method in the PMC arm. In the PMC arm, the mean (SD) QTcF was 400ms (14) at baseline and increased to 422ms (15), 4-6 hours after the last dose of the first course (Table-S8), representing a mean (SD) increase of 22ms (14) (95% CI 20 to 24) (range -6 to 54), $p<0.0001$ (paired t-test). No increase in mean QTcF interval was seen in the placebo arm.

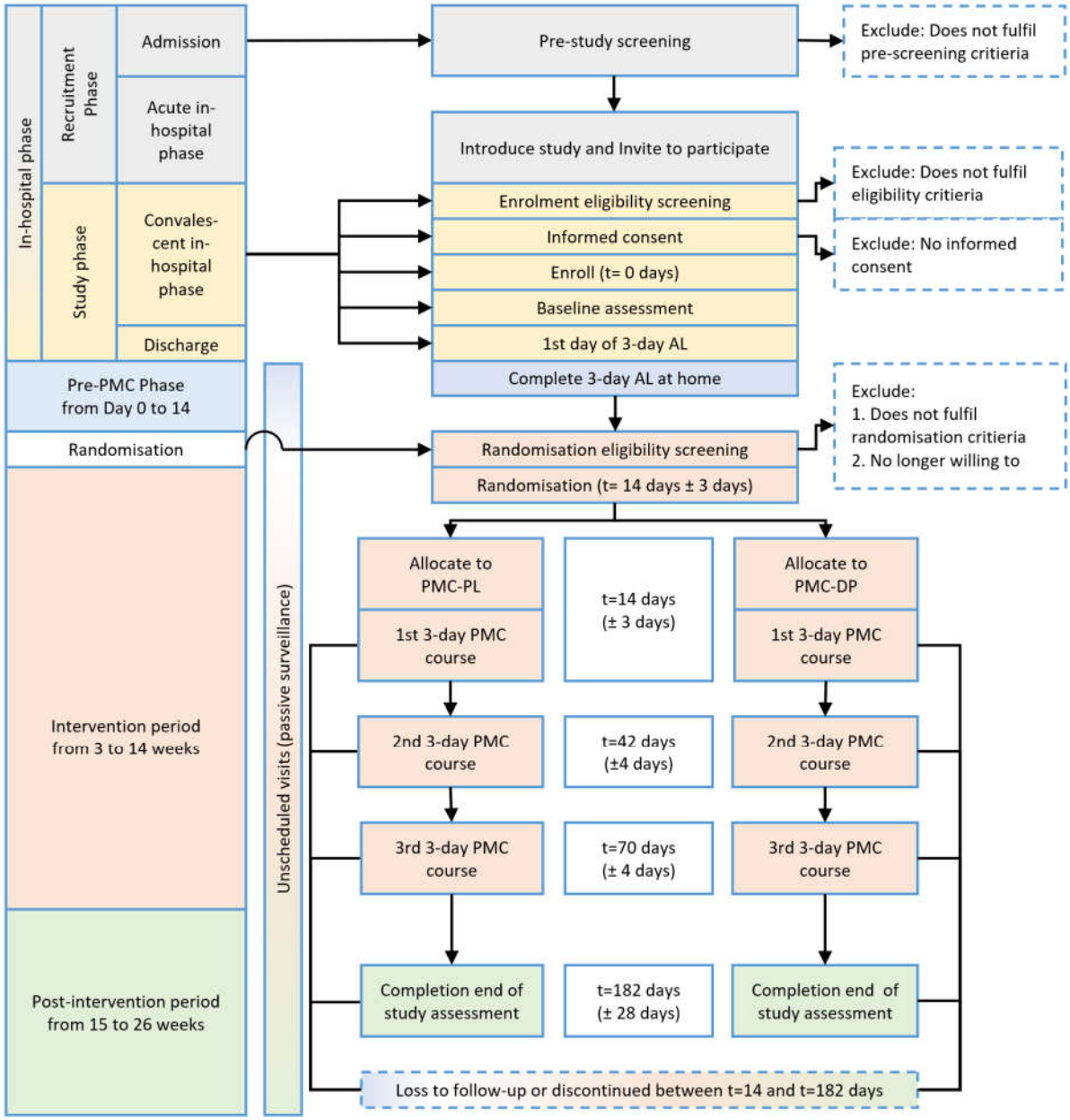
Significant increases were also seen after the second and third courses. Comparison of the delta QTc between the courses suggested a significant decline in QTcF prolongation from a mean (SD) of 22ms (14) prolongation after the first course to 14ms (17) after the third course (mean difference [MD], 8ms, 95% CI 1-15). None of the children had QTcF values exceeding 480ms.

Differences between manuscript, trial protocol, and trial registration

- The study protocol and trial registration included several secondary outcomes that were collected as part of nested studies. Specifically, these include health economic measures as part of the cost-effectiveness analysis of PMC, which will be reported elsewhere.
- Because of funding restrictions, no assays to determine phenotypic or molecular host genetics were conducted as part of this trial. The exception was the assessment of the sickle cell status, which was determined by Hb electrophoresis as this was part of the exclusion criteria because children with sickle cell disease already receive malaria prophylaxis in Kenya and Uganda as per national policy.

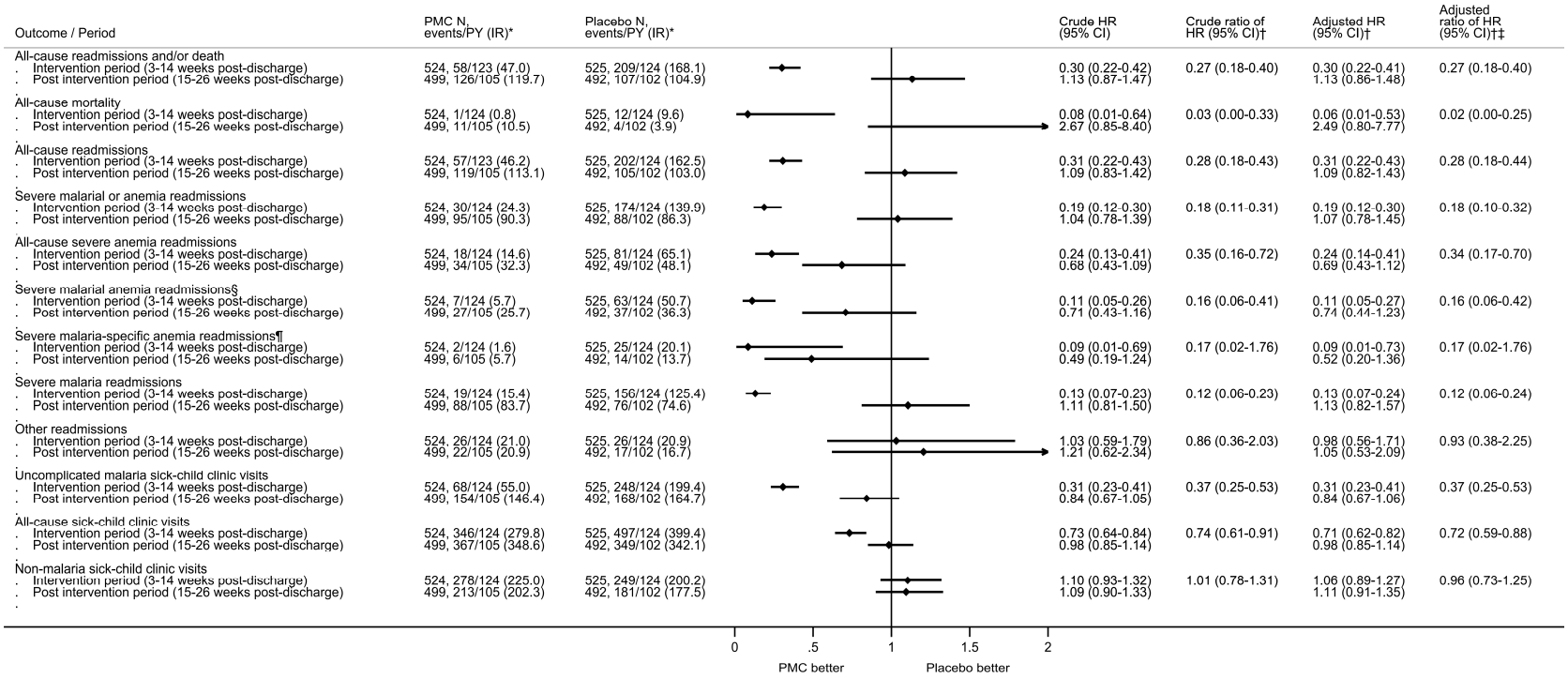
Supplemental figures

Figure S1: Overview study flow and periods of assessment{Kwambai, 2018 #1136}



PMC=post-discharge malaria chemoprevention, DP=dihydroartemisinin-piperaquine, PL=placebo.

Figure S2: interaction terms for period and treatment



N=total number contributing per period, PMC=post-discharge malaria chemoprevention, IR=incidence rate per 100 person-years, PY=person years, HR=hazard ratio, CI=confidence interval.

* Incidence rates obtained from two separate models, one per period.

† Ratio of the hazard ratio in the intervention period and the post-intervention period obtained using the method described by Altman and Bland.[4]

‡ Adjusted for site, bodyweight, previous hospital admissions, the syndrome on admissions, age, hemoglobin level at randomization, distance to hospital, number of previous admissions, and socioeconomic status.

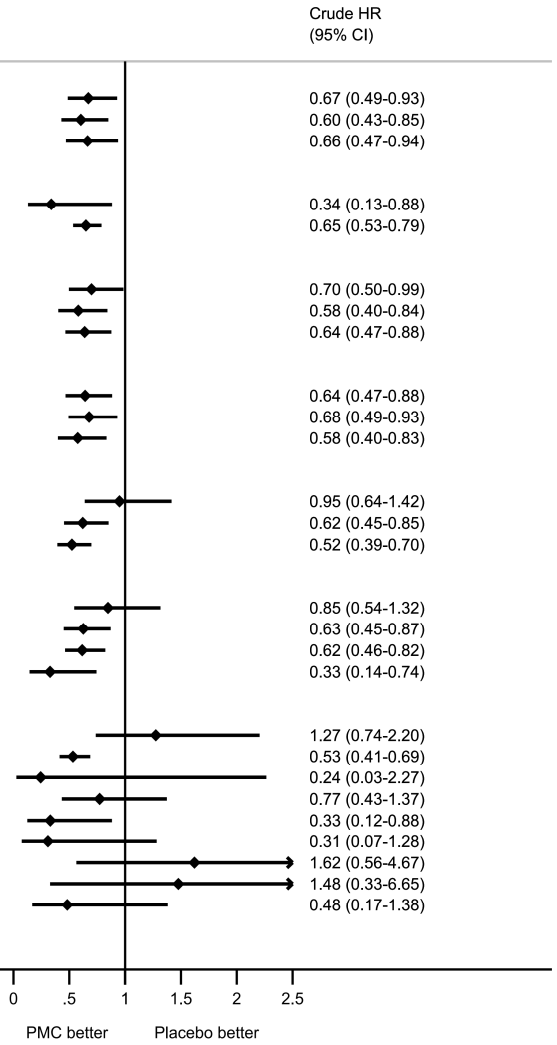
§ Severe anemia in the presence of any evidence of malaria infection detected by rapid diagnostic tests or malaria microscopy.

¶ Severe anemia in the presence of malaria infection detected by microscopy with >5,000 parasites per microliter.

The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects or differences between subgroups.

Figure S3: Sub-group analysis of the primary outcome by other pre-specific participant or site characteristics

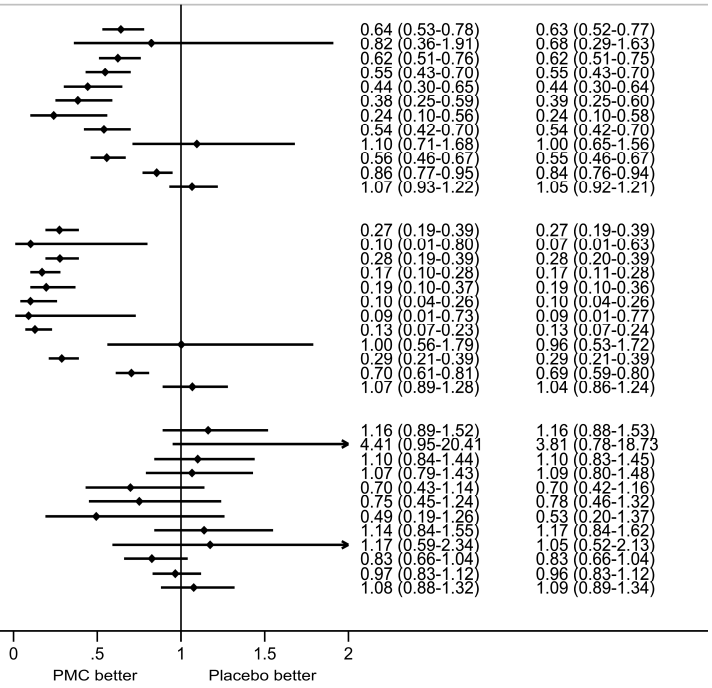
Subgroup	PMC N, events/PY (IR)*	Placebo N, events/PY (IR)*	Crude HR (95% CI)
Haemoglobin (g/dL) at randomization			
. Lowest Tercile	177, 61/76 (80.7)	181, 106/75 (141.4)	0.67 (0.49-0.93)
. Middle Tercile	167, 59/74 (79.7)	173, 111/76 (146.7)	0.60 (0.43-0.85)
. Highest Tercile	178, 63/80 (79.2)	168, 99/76 (129.7)	0.66 (0.47-0.94)
.			
Re-admission during pre-randomization period			
. Yes	14, 9/6 (151.1)	18, 18/7 (244.7)	0.34 (0.13-0.88)
. No	510, 175/224 (78.1)	507, 298/220 (135.3)	0.65 (0.53-0.79)
.			
Socioeconomic status (SES)			
. Lowest Tercile	187, 68/81 (83.5)	159, 97/69 (140.9)	0.70 (0.50-0.99)
. Middle Tercile	164, 52/73 (71.7)	189, 116/82 (141.1)	0.58 (0.40-0.84)
. Highest Tercile	173, 64/76 (84.0)	177, 103/77 (134.4)	0.64 (0.47-0.88)
.			
Travel time to study hospital			
. Lowest Tercile	176, 67/77 (87.4)	163, 111/72 (153.2)	0.64 (0.47-0.88)
. Middle Tercile	171, 65/76 (85.0)	168, 103/74 (138.3)	0.68 (0.49-0.93)
. Highest Tercile	161, 48/72 (66.7)	177, 100/77 (129.7)	0.58 (0.40-0.83)
.			
Malaria transmission season			
. Lowest Tercile	175, 47/73 (64.7)	177, 55/74 (74.6)	0.95 (0.64-1.42)
. Middle Tercile	175, 59/79 (75.1)	173, 103/75 (136.7)	0.62 (0.45-0.85)
. Highest Tercile	174, 78/79 (98.9)	175, 158/79 (201.1)	0.52 (0.39-0.70)
.			
Weight band at randomization			
. 5 to <8 kg	91, 33/39 (83.9)	97, 44/41 (107.6)	0.85 (0.54-1.32)
. 8 to <11 kg	186, 56/81 (69.2)	183, 91/78 (115.9)	0.63 (0.45-0.87)
. 11 to <17 kg	224, 88/100 (88.2)	222, 163/98 (166.8)	0.62 (0.46-0.82)
. 17 to <25 kg	23, 7/10 (69.3)	23, 18/11 (170.5)	0.33 (0.14-0.74)
.			
Study site, country			
. Hoima, Uganda	95, 32/43 (74.6)	95, 25/42 (59.4)	1.27 (0.74-2.20)
. Jinja, Uganda	133, 99/60 (165.3)	134, 206/60 (343.4)	0.53 (0.41-0.69)
. Kamuli, Uganda	27, 1/12 (8.1)	28, 5/13 (39.9)	0.24 (0.03-2.27)
. Masaka, Uganda	59, 27/26 (102.3)	57, 33/25 (132.6)	0.77 (0.43-1.37)
. Mubende, Uganda	33, 4/15 (26.5)	31, 16/14 (114.1)	0.33 (0.12-0.88)
. Siaya, Kenya	30, 3/14 (22.2)	31, 12/13 (92.5)	0.31 (0.07-1.28)
. Kisumu, Kenya	52, 9/20 (45.5)	51, 5/19 (26.1)	1.62 (0.56-4.67)
. Homabay, Kenya	43, 5/17 (28.9)	46, 4/19 (21.2)	1.48 (0.33-6.65)
. Migori, Kenya	52, 4/23 (17.5)	52, 10/23 (43.2)	0.48 (0.17-1.38)
.			



PMC=post-discharge malaria chemoprevention; IR=incidence rate per 100 person-years; PY=person-years; HR=hazard ratio; CI=confidence interval. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

Figure S4: Per protocol analysis

Outcome	PMC N, events/PY (IR)*	Placebo N, events/PY (IR)*	Crude HR (95% CI)	Adjusted HR (95% CI)†
Overall (3-26 weeks post-discharge)				
All-cause readmissions and/or death (primary outcome)	470, 172/214 (80.4)	472, 299/213 (140.6)	0.64 (0.53-0.78)	0.63 (0.52-0.77)
All-cause mortality	470, 10/214 (4.7)	472, 12/213 (5.6)	0.82 (0.36-1.91)	0.68 (0.29-1.63)
All-cause readmissions	470, 165/214 (77.1)	472, 294/213 (138.3)	0.62 (0.51-0.76)	0.62 (0.51-0.75)
Severe malarial or anemia readmissions	470, 120/214 (56.1)	472, 252/213 (118.5)	0.55 (0.43-0.70)	0.55 (0.43-0.70)
All-cause severe anemia readmissions	470, 47/214 (22.0)	472, 121/213 (56.9)	0.44 (0.30-0.65)	0.44 (0.30-0.64)
Severe malarial anemia readmissions‡	470, 33/214 (15.4)	472, 93/213 (43.7)	0.38 (0.25-0.59)	0.39 (0.25-0.60)
Severe malaria-specific anemia readmissions§	470, 8/214 (3.7)	472, 38/213 (17.9)	0.24 (0.10-0.56)	0.24 (0.10-0.58)
Severe malaria readmissions	470, 106/214 (49.5)	472, 224/213 (105.3)	0.54 (0.42-0.70)	0.54 (0.42-0.70)
Other readmissions	470, 43/214 (20.1)	472, 40/213 (18.8)	1.10 (0.71-1.68)	1.00 (0.65-1.56)
Uncomplicated malaria sick-child clinic visits	470, 206/214 (96.3)	472, 398/213 (187.1)	0.56 (0.46-0.67)	0.55 (0.46-0.67)
All-cause sick-child clinic visits	470, 666/214 (311.3)	472, 813/213 (382.2)	0.86 (0.77-0.95)	0.84 (0.76-0.94)
Non-malaria sick-child clinic visits	470, 460/214 (215.0)	472, 415/213 (195.2)	1.07 (0.93-1.22)	1.05 (0.92-1.21)
Intervention period (3-14 weeks post-discharge)				
All-cause readmissions and/or death	470, 50/113 (44.4)	472, 198/114 (173.0)	0.27 (0.19-0.39)	0.27 (0.19-0.39)
All-cause mortality	470, 1/113 (0.9)	472, 10/114 (8.7)	0.10 (0.01-0.80)	0.07 (0.01-0.63)
All-cause readmissions	470, 49/113 (43.5)	472, 193/114 (168.6)	0.28 (0.19-0.39)	0.28 (0.20-0.39)
Severe malarial or anemia readmissions	470, 26/113 (23.1)	472, 167/115 (145.8)	0.17 (0.10-0.28)	0.17 (0.11-0.28)
All-cause severe anemia readmissions	470, 14/113 (12.4)	472, 75/115 (65.5)	0.19 (0.10-0.37)	0.19 (0.10-0.36)
Severe malarial anemia readmissions‡	470, 6/113 (5.3)	472, 58/115 (50.7)	0.10 (0.04-0.26)	0.10 (0.04-0.26)
Severe malaria-specific anemia readmissions§	470, 2/113 (1.8)	472, 24/115 (21.0)	0.09 (0.01-0.73)	0.09 (0.01-0.77)
Severe malaria readmissions	470, 18/113 (16.0)	472, 150/115 (131.0)	0.13 (0.07-0.23)	0.13 (0.07-0.24)
Other readmissions	470, 23/113 (20.4)	472, 24/114 (21.0)	1.00 (0.56-1.79)	0.96 (0.53-1.72)
Uncomplicated malaria sick-child clinic visits	470, 60/113 (53.2)	472, 235/114 (205.2)	0.29 (0.21-0.39)	0.29 (0.21-0.39)
All-cause sick-child clinic visits	470, 317/113 (281.0)	472, 474/115 (413.9)	0.70 (0.61-0.81)	0.69 (0.59-0.80)
Non-malaria sick-child clinic visits	470, 257/113 (227.8)	472, 239/115 (208.7)	1.07 (0.89-1.28)	1.04 (0.86-1.24)
Post intervention period (15-26 weeks post-discharge)				
All-cause readmissions and/or death	469, 122/100 (122.1)	462, 101/97 (104.2)	1.16 (0.89-1.52)	1.16 (0.88-1.53)
All-cause mortality	469, 9/100 (9.0)	462, 2/97 (2.1)	4.41 (0.95-20.41	3.81 (0.78-18.73
All-cause readmissions	469, 116/100 (116.1)	462, 101/97 (104.2)	1.10 (0.84-1.44)	1.10 (0.83-1.45)
Severe malarial or anemia readmissions	469, 94/100 (94.1)	462, 85/97 (87.8)	1.07 (0.79-1.43)	1.09 (0.80-1.48)
All-cause severe anemia readmissions	469, 33/100 (33.0)	462, 46/97 (47.5)	0.70 (0.43-1.14)	0.70 (0.42-1.16)
Severe malarial anemia readmissions‡	469, 27/100 (27.0)	462, 35/97 (36.1)	0.75 (0.45-1.24)	0.78 (0.46-1.32)
Severe malaria-specific anemia readmissions§	469, 6/100 (6.0)	462, 14/97 (14.5)	0.49 (0.19-1.26)	0.53 (0.20-1.37)
Severe malaria readmissions	469, 88/100 (88.1)	462, 74/97 (76.4)	1.14 (0.84-1.55)	1.17 (0.84-1.62)
Other readmissions	469, 20/100 (20.0)	462, 16/97 (16.5)	1.17 (0.59-2.34)	1.05 (0.52-2.13)
Uncomplicated malaria sick-child clinic visits	469, 146/100 (146.2)	462, 163/97 (168.2)	0.83 (0.66-1.04)	0.83 (0.66-1.04)
All-cause sick-child clinic visits	469, 349/100 (349.4)	462, 339/97 (349.7)	0.97 (0.83-1.12)	0.96 (0.83-1.12)
Non-malaria sick-child clinic visits	469, 203/100 (203.2)	462, 176/97 (181.7)	1.08 (0.88-1.32)	1.09 (0.89-1.34)



* N=total number contributing per period, PY=person years, IR=Incidence rate per 100 person-years.

† HR=hazard ratio, adjusted for site, bodyweight, previous hospital admissions, the syndrome on admissions, age, hemoglobin level at randomization, distance to hospital, number of previous admissions, and socioeconomic status.

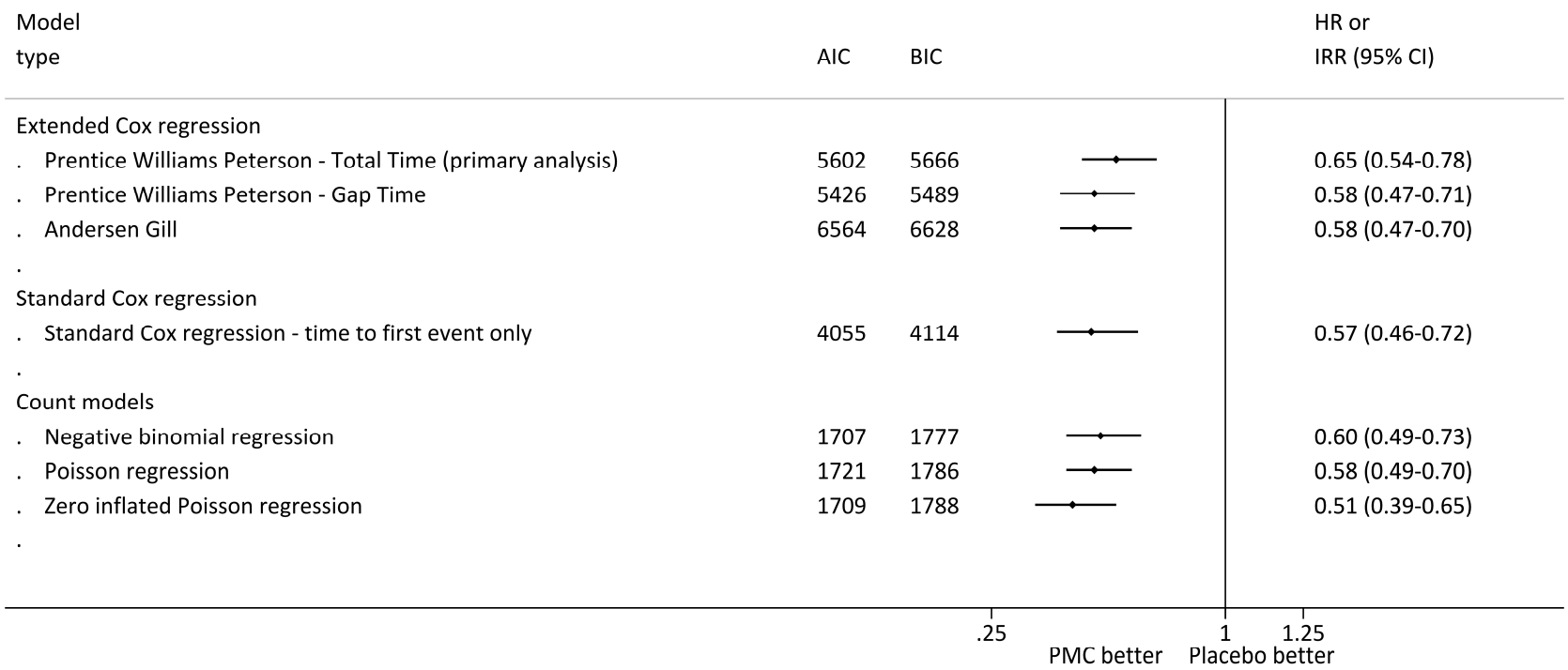
‡ Severe anemia in the presence of any evidence of malaria infection detected by rapid diagnostic tests or malaria microscopy.

§ Severe anemia in the presence of malaria infection detected by microscopy with >5,000 parasites per microliter.

PMC=Post-discharge malaria chemoprevention.

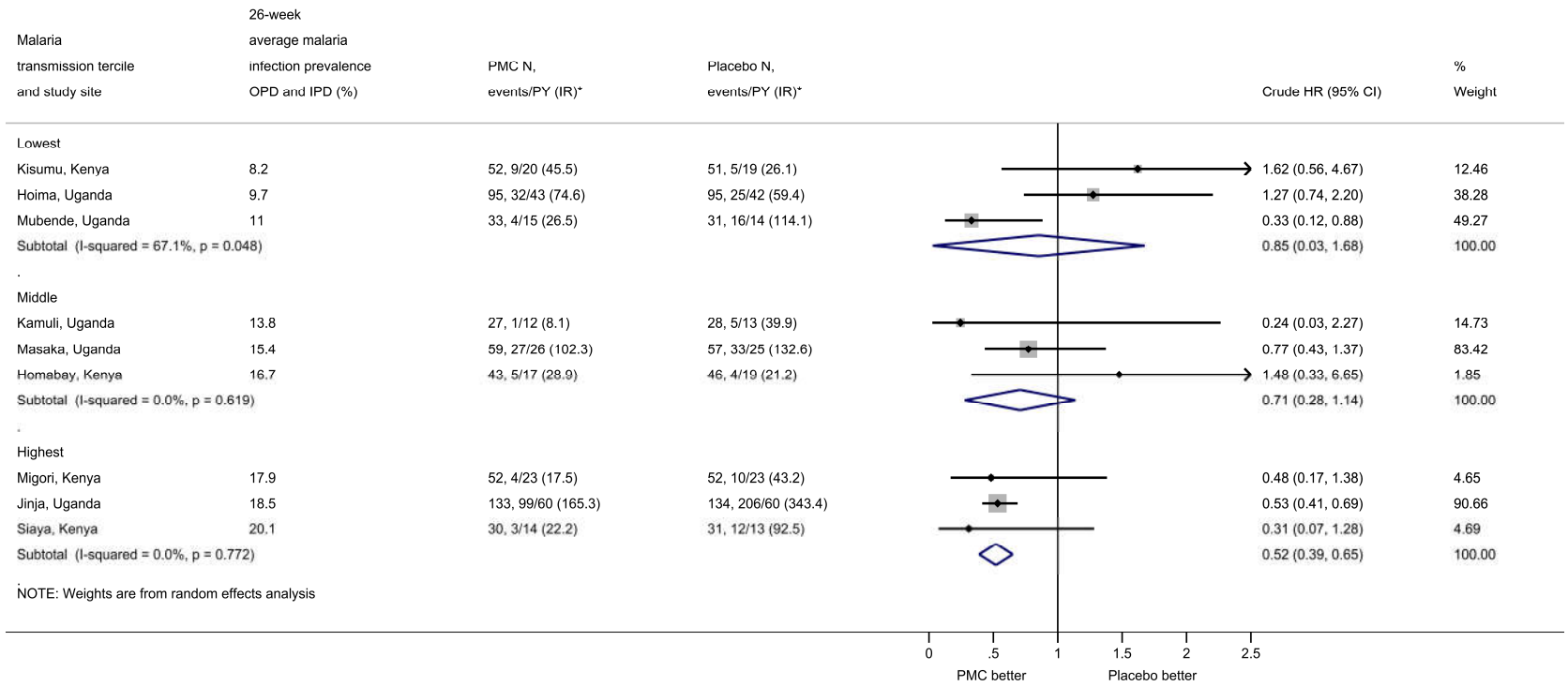
The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

Figure S5: Sensitivity analysis of the primary outcome using alternative models



HR=hazard rate, IRR=incidence rate ratio, AIC=Akaike information criterion, BIC=Bayesian information criterion. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

Figure S6: Random-effects meta-analysis of the treatment effect on the primary outcome by malaria transmission intensity



* N=total number contributing, PY=person years, IR=Incidence rate per 100 person-years.
OPD=out-patient department; IPD=in-patient department; PMC=post-discharge malaria chemoprevention; HR=hazard ratio; CI=confidence interval.
The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.
Random-effects meta-regression using the log-transformed effect size showed a significant linear trend towards an increase in the protective efficacy of PMC on the primary outcome with an increasing site prevalence of malaria infection (expressed as a percentage on a continuous scale) (slope 0.92, 95% CI 0.86-0.99).

Supplemental tables

Table S1: Dihydroartemisinin-piperaquine* weight-based dosing schedule

Weight in Kg	Daily dose (mg)		Tablet strength and number of tablets per dose
	Piperaquine	DHA	
5 to <8	160	20	1 x 160 mg / 20 mg tablet or ½ x 320 mg / 40 mg tablet
8 to <11	240	30	1.5 x 160 mg / 20 mg tablet or ¾ x 320 mg / 40 mg tablet
11 to <17	320	40	1 x 320 mg / 40 mg tablet
17 to <25	480	60	1.5 x 320 mg / 40 mg tablet
25 to<36	640	80	2 x 320 mg / 40 mg tablet

* Alfasigma, Bologna, Italy.
DHA=dihydroartemisinin

Table S2: Artemether-lumefantrine* weight-based dosing schedule

Weight in Kg	Number of pediatric tablets of artemether (20 mg)-and lumefantrine (120 mg) per dose					
	Day 1		Day 2		Day 3	
	1st dose	8 hours	24 hours	36 hours	48 hours	60 hours
5 to <15	1	1	1	1	1	1
15 to<25	2	2	2	2	2	2
25 to ≤34	3	3	3	3	3	3
>34	4	4	4	4	4	4

* Coartem®, Novartis Pharmaceuticals Corporation, Switzerland
The first dose to first three doses of the 3-day course of artemether-lumefantrine was typically given in hospital as directly observed therapy. Most children were discharged after that, and the remaining doses for day-2 and day-3 were given to the caretaker to give to the child at home.

Table S3: Participant adherence to the study schedule

	PMC N=524	Placebo N=525	Pooled N=1049
Achieved/expected (%) *			
PMC1	524/524 (100.0)	525/525 (100.0)	1049/1049 (100.0)
PMC2	516/524 (98.5)	515/524 (98.3)	1031/1048 (98.4)
PMC3	509/523 (97.3)	499/518 (96.3)	1008/1041 (96.8)
Total person-days			
Overall (week 3-26)	83,191	84,111	16,7302
PMC intervention period (week 3-14)	45,445	45,162	90,607
Post intervention period (week 15-26)	37,264	38,456	75,720
Median (IQR) person-days			
Overall (week 3-26)	168 (163-168)	168 (159-168)	168 (161-168)
PMC intervention period (week 3-14)	84 (84-87)	84 (82-88)	84 (83-88)
Post intervention period (week 15-26)	81 (75-83)	80 (71-83)	81(73-83)
Lost/withdrawn by 26 weeks (%)			
Overall (week 3-26)	44 (8.4)	36 (6.9)	80 (7.6)
PMC intervention period (week 3-14)	24 (4.6)	21 (4.0)	45 (4.3)
Post intervention period (week 15-26)	20 (3.8)	15 (2.9)	35 (3.3)

PMC=post-discharge malaria chemoprevention, IQR=interquartile range.
PMC1, PMC2, and PMC3 are the first, second, and third PMC courses respectively provided at approximately 2, 6, and 10 weeks post-discharge.
*Number of participants who received the PMC courses/number expected to receive the PMC course after taking any deaths into account that occurred before the next scheduled course.

Table S4: Number of primary outcome events by study arm

		PMC	Placebo	Pooled
Events	Number of events	n (%)	n (%)	n (%)
	1st	138 (75.0)	177 (56.0)	315 (63.0)
	2nd	38 (20.7)	76 (24.1)	114 (22.8)
	3rd	8 (4.3)	38 (12.0)	46 (9.2)
	4th	0 (0.0)	17 (5.4)	17 (3.4)
	5th	0 (0.0)	6 (1.9)	6 (1.2)
	6th	0 (0.0)	2 (0.6)	2 (0.4)
	total	184 (100)	316 (100)	500 (100)
Children	Total events/child			
	0	386 (73.7)	348 (66.3)	734 (70.0)
	1	100 (19.1)	101 (19.2)	201 (19.2)
	2	30 (5.7)	38 (7.2)	68 (6.5)
	3	8 (1.5)	21 (4.0)	29 (2.8)
	4	0 (0.0)	11 (2.1)	11 (1.0)
	5	0 (0.0)	4 (0.8)	4 (0.4)
	6	0 (0.0)	2 (0.4)	2 (0.2)
	total	524 (100)	525 (100)	1049 (100)

PMC=post-discharge malaria chemoprevention

Table S5: End of study cross-sectional survey*

Characteristics	PMC (N=473)	Placebo (N=472)	RR or MD (95% CI)*
Fever†	67/470 (14.3)	80/471 (17.0)	0.84 (0.62, 1.13)
Malaria RDT positivity	116/461 (25.2)	137/464 (29.5)	0.85 (0.69, 1.05)
Anemia (Hb <11.0 g/dL)	197/458 (43.0)	188/463 (40.6)	1.06 (0.91, 1.23)
Moderate anemia (Hb≥5.0 and <8.0 g/dL)	48/458 (10.5)	39/463 (8.4)	1.24 (0.83, 1.86)
Hemoglobin in g/dL, mean (SD)	11.0 (2.1)	11.0 (2.2)	-0.03 (-0.31, 0.24)
HAZ, mean (SD)	-1.0 (3.0)	-1.0 (3.2)	0.07 (-0.34, 0.48)
WAZ, mean (SD)	-0.6 (1.6)	-0.7 (1.4)	0.05 (-0.14, 0.25)
WHZ, mean (SD)	-0.1 (1.3)	0.0 (1.4)	-0.09 (-0.27, 0.09)
HAZ, Z-score <-2	146/448 (32.6)	157/452 (34.7)	0.94 (0.78, 1.13)
HAZ, Z-score <-3	60/448 (13.4)	73/452 (16.2)	0.83 (0.60, 1.14)
WAZ, Z-score <-2	64/448 (14.3)	59/452 (13.1)	1.09 (0.79, 1.52)
WAZ, Z-score <-3	18/448 (4.0)	12/452 (2.7)	1.51 (0.74, 3.10)
WHZ, Z-score <-2	28/446 (6.3)	20/446 (4.5)	1.40 (0.80, 2.45)
WHZ, Z-score <-3	8/446 (1.8)	6/446 (1.3)	1.33 (0.47, 3.81)

Numbers denote n/N 9%) unless otherwise indicated.

SD=standard deviations, SES=socioeconomic status, RDT=rapid diagnostic test, Hb=hemoglobin, HAZ=height (or length) for age z score, WAZ=weight for age z score, WHZ=weight for height (or length) age z score, CI=confidence interval.

* RR=relative risk for binary variables, MD=mean difference for continuous variables. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

† Fever=documented fever or a history of fever in the last 48 hours (*post-hoc*).

Table S6: Vomiting within 1 hour after drug intake of the PMC or placebo course

	PMC	Placebo	RR (95% CI)	P-value
1st course	45/524 (8.6%)	14/525 (2.7%)	3.22 (1.79-5.79)	<0.001
2nd course	15/516 (2.9%)	4/515 (0.8%)	3.74 (1.25-11.20)	0.011
3rd course	13/509 (2.6%)	2/499 (0.4%)	6.37 (1.45-28.09)	0.005
At least once	65/524 (12.4%)	20/525 (3.8%)	3.26 (2.00-5.30)	<0.001

PMC=post-discharge malaria chemoprevention, RR=relative risk

Table S7: Serious adverse events within 4 days of following each PMC or placebo course

	PMC (N=524)	Placebo (N=525)	
MedDRA System organ class	No of participants with an event (%)	No of participants with an event (%)	P†
Overall*	12 (2.3)	30 (5.7)	0.007
Blood and lymphatic system disorders	6 (1.1)	11 (2.1)	0.33
Cardiac disorders	0 (0.0)	0 (0.0)	1.00
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1.00
Gastrointestinal disorders	1 (0.2)	0 (0.0)	0.50
General disorders and administration site conditions	0 (0.0)	1 (0.2)	1.00
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1.00
Immune system disorders	0 (0.0)	0 (0.0)	1.00
Infections and infestations	8 (1.5)	29 (5.5)	0.001
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1.00
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1.00
Nervous system disorders	0 (0.0)	1 (0.2)	1.00
Renal and urinary disorders	0 (0.0)	0 (0.0)	1.00
Respiratory, thoracic and mediastinal disorders	2 (0.4)	2 (0.4)	1.00
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1.00

MedDRA Medical Dictionary for Regulatory Activities

* One hospital admission in the overall category could contribute to events in multiple MedDRA system organ classes.

† Unadjusted p-value from two-sided Fisher exact test.

PMC=post-discharge malaria chemoprevention

Table S8: Cardiac monitoring; mean and mean change in QTcF at baseline and 4 to 6 hours after the third dose of each course

Dihydroartemisinin-piperaquine			QTcF in ms				Change in QTcF from baseline* in ms				
PMC course	Day + time ECG	No	Mean (SD)	Range	>480ms n (%)	>500ms n (%)	Mean (SD)	Range	95% CI	p	>60 ms
1st	0	33	400 (14)	377-431	0 (0)	0 (0)	Ref				
	2+4h	33	422 (15)	396-456	0 (0)	0 (0)	22 (14)	-6, 54	17, 27	<0.001	0 (0)
2nd	0	33	401 (16)	363-431	0 (0)	0 (0)	Ref				
	2+4h	33	420 (17)	388-460	0 (0)	0 (0)	20 (15)	-18, 44	14, 25	<0.001	0 (0)
3rd	0	33	402 (15)	369-431	0 (0)	0 (0)	Ref				
	2+4h	33	416 (20)	384-458	0 (0)	0 (0)	14 (16)	-14, 55	8, 20	<0.001	0 (0)

Placebo			QTcF in ms				Change in QTcF from baseline* in ms				
PMC course	Day + time ECG	No	Mean (SD)	Range	>480ms n (%)	>500ms n (%)	Mean (SD)	Range	95% CI	p	>60 ms
1st	0	33	401 (14)	370-439	0 (0)	0 (0)	Ref				
	2+4h	33	401 (14)	376-431	0 (0)	0 (0)	0 (13)	-27, 31	-4, 5	0.87	0 (0)
2nd	0	33	400 (13)	373-420	0 (0)	0 (0)	Ref				
	2+4h	33	395 (16)	367-420	0 (0)	0 (0)	-4 (17)	-46, 27	-10, 2	0.18	0 (0)
3rd	0	33	400 (19)	358-433	0 (0)	0 (0)	Ref				
	2+4h	33	398 (20)	320-425	0 (0)	0 (0)	-2 (22)	-82, 47	-9, 6	0.68	0 (0)

PMC=post-discharge malaria chemoprevention, ECG=Electrocardiogram, QTcF=QT interval on ECG corrected using the Fridericia method, ms=milliseconds, SD=standard deviation, 2+4h=Day 2 plus 4 to 6 hours after the third (last) dose of each course of dihydroartemisinin-piperaquine (Tmax), CI=confidence interval

* Change in QTcF from baseline in ms. Baseline was the QTcF interval taken just before the first dose of each course of PMC.

Supplemental references

1. Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention with monthly dihydroartemisinin-piperaquine for the post-discharge management of severe anaemia in children aged less than 5 years in Uganda and Kenya: study protocol for a multi-centre, two-arm, randomized, placebo-controlled, superiority trial. Trials 2018;19:610.
2. Phiri K, Esan M, van Hensbroek MB, Khairallah C, Faragher B, ter Kuile FO. Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomized, placebo-controlled trial. The Lancet Infectious diseases 2012;12:191-200.
3. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. Annals of Statistics 1982;10:1100-20.
4. Westbury LD, Syddall HE, Simmonds SJ, Cooper C, Sayer AA. Identification of risk factors for hospital admission using multiple-failure survival models: a toolkit for researchers. BMC Med Res Methodol 2016;16:46.
5. Villegas R, Julia O, Ocana J. Empirical study of correlated survival times for recurrent events with proportional hazards margins and the effect of correlation and censoring. BMC Med Res Methodol 2013;13:95.
6. Smedinga H, Steyerberg EW, Beukers W, van Klaveren D, Zwarthoff EC, Vergouwe Y. Prediction of Multiple Recurrent Events: A Comparison of Extended Cox Models in Bladder Cancer. Am J Epidemiol 2017;186:612-23.
7. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. Bmj 2003;326:219.
8. World Health Organization. Verbal Autopsy Standards: 2012 WHO Verbal Autopsy lnstrument. Geneva: World Health Organization; 2012.
9. Van Eijk A, Adazu K, Ofware P, Vulule J, Hamel M, Slutsker L. Causes of deaths using verbal autopsy among adolescents and adults in rural western Kenya. Tropical Medicine & International Health 2008;13:1314-24.