

ORIGINAL ARTICLE

Malaria Chemoprevention in the Postdischarge Management of Severe Anemia

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ABSTRACT

BACKGROUND

Children who have been hospitalized with severe anemia in areas of Africa in which malaria is endemic have a high risk of readmission and death within 6 months after discharge. No prevention strategy specifically addresses this period.

METHODS

We conducted a multicenter, two-group, randomized, placebo-controlled trial in nine hospitals in Kenya and Uganda to determine whether 3 months of malaria chemoprevention could reduce morbidity and mortality after hospital discharge in children younger than 5 years of age who had been admitted with severe anemia. All children received standard in-hospital care for severe anemia and a 3-day course of artemether–lumefantrine at discharge. Two weeks after discharge, children were randomly assigned to receive dihydroartemisinin–piperaquine (chemoprevention group) or placebo, administered as 3-day courses at 2, 6, and 10 weeks after discharge. Children were followed for 26 weeks after discharge. The primary outcome was one or more hospital readmissions for any reason or death from the time of randomization to 6 months after discharge. Conditional risk-set modeling for recurrent events was used to calculate hazard ratios with the use of the Prentice–Williams–Peterson total-time approach.

RESULTS

From May 2016 through May 2018, a total of 1049 children underwent randomization; 524 were assigned to the chemoprevention group and 525 to the placebo group. From week 3 through week 26, a total of 184 events of readmission or death occurred in the chemoprevention group and 316 occurred in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.54 to 0.78; $P < 0.001$). The lower incidence of readmission or death in the chemoprevention group than in the placebo group was restricted to the intervention period (week 3 through week 14) (hazard ratio, 0.30; 95% CI, 0.22 to 0.42) and was not sustained after that time (week 15 through week 26) (hazard ratio, 1.13; 95% CI, 0.87 to 1.47). No serious adverse events were attributed to dihydroartemisinin–piperaquine.

CONCLUSIONS

In areas with intense malaria transmission, 3 months of postdischarge malaria chemoprevention with monthly dihydroartemisinin–piperaquine in children who had recently received treatment for severe anemia prevented more deaths or readmissions for any reason after discharge than placebo. (Funded by the Research Council of Norway and the Centers for Disease Control and Prevention; ClinicalTrials.gov number, NCT02671175.)

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SEVERE ANEMIA CONTRIBUTES SUBSTANTIALLY to childhood mortality and is a leading cause of hospital admissions in areas of Africa in which malaria is endemic.¹⁻⁵ In the past few decades, most research on severe anemia in Africa has focused on improving in-hospital care.^{4,6,7} However, in areas with intense malaria transmission, a substantial, potentially preventable component of the burden occurs in the first few months after discharge,⁸⁻¹² with more deaths occurring during this time than during the in-hospital period.^{9,10} Strategies that reduce the risk during this postdischarge period may offer substantial public health gains.

A previous study from Malawi performed in areas in which malaria is endemic showed that children who were admitted with severe anemia did not have full hematologic recovery until at least 2 to 3 months after discharge.⁹ In areas with intense malaria transmission, a delay in hematologic recovery because of new or recurrent malaria infection is common and may contribute to the high burden of adverse health outcomes after discharge.^{10,13} Currently, other than hematinic agents, no routine preventive strategies are provided after hospital discharge in areas in which malaria is endemic. We hypothesized that administration of malaria prophylaxis during a limited period after transfusion would allow the bone marrow sufficient time to recover, resulting in a more sustained hematologic recovery.¹⁴ Our previous trial in Malawi showed that 3 months of postdischarge malaria chemoprevention with monthly treatment courses of artemether-lumefantrine prevented 21% of deaths or readmissions within 6 months after discharge in children younger than 5 years of age who had been admitted with severe malarial anemia and had been successfully treated with blood transfusion and parenteral antimalarial drugs.¹¹

In this trial, we aimed to confirm these promising findings. We assessed the efficacy of 3 months of postdischarge malaria chemoprevention with monthly 3-day treatment courses of the long-acting antimalarial drug combination of dihydroartemisinin-piperaquine in preventing readmission or death after discharge in children younger than 5 years of age with severe anemia.

METHODS

DESIGN AND OVERSIGHT

We conducted a parallel, two-group, individually randomized, double-blind, placebo-controlled, superiority trial in nine hospitals in Kenya and Uganda that were located in areas with moderate-to-intense perennial malaria transmission.¹⁵ The trial was approved by the ethics committees at the Kenya Medical Research Institute, Makerere University School of Medicine, the Western Norway Regional Committee for Medical and Health Research Ethics, and the Liverpool School of Tropical Medicine. This article is published with the permission of the director of the Kenya Medical Research Institute. The Liverpool School of Tropical Medicine oversaw the trial, with support from its Global Health Trials Unit. The collaboration of the Centers for Disease Control and Prevention with the Center for Global Health Research, Kenya Medical Research Institute, in western Kenya provided infrastructural support for the trial in Kenya as well as centralized data management. The Makerere University School of Medicine provided oversight and technical and infrastructural support for the trial in Uganda. Written informed consent was obtained from the parents or guardians of the children. Dihydroartemisinin-piperaquine and placebo were supplied free of charge by Alfasigma (Bologna, Italy), which had no role in the design, conduct, analysis, or reporting of the trial. The funders had no role in the design or execution of the trial, the analysis or interpretation of the data, or the decision to submit the manuscript for publication. The protocol,¹⁵ with the statistical analysis plan, is available with the full text of this article at NEJM.org. Three of the authors vouch for the accuracy and completeness of the data, and all the authors vouch for the fidelity of the trial to the protocol.

RANDOMIZATION AND MASKING

Children younger than 5 years of age who had been admitted with severe anemia (at enrollment, severe anemia was defined as a hemoglobin level of <5 g per deciliter, a hematocrit of <15%, or clinical indication for blood transfusion not caused by sickle cell disease, cancer, trauma, or elective surgery) and who fulfilled other eligibility criteria underwent randomiza-

tion 2 weeks after discharge and were assigned in a 1:1 ratio to receive either postdischarge malaria chemoprevention (the chemoprevention group) or placebo. Full eligibility criteria are listed in the Supplementary Appendix, available at NEJM.org. Randomization was performed by means of a computer-generated randomization schedule prepared by an independent statistician with the use of permuted blocks of random size, stratified according to trial site and five body-weight categories (additional details are provided in the Supplementary Appendix).

Sequentially numbered, sealed, opaque, identical envelopes were used to conceal trial-group assignments. The envelopes contained three other envelopes, each of which contained the trial drug or placebo for each course. Trial staff enrolled the children and performed the follow-up. The investigators, caregivers, and trial staff were unaware of the trial-group assignments.

INTERVENTIONS

All children received standard in-hospital care for severe anemia and any other conditions; parenteral artesunate was administered if the child had severe malaria (on the basis of the treatment guidelines of the ministries of health of Kenya and Uganda). All children also received a 3-day course of artemether–lumefantrine at the time of discharge, regardless of their malaria status at admission, as soon as they were able to take oral medication. Two weeks after discharge, surviving children were randomly assigned to receive a standard 3-day treatment course of dihydroartemisinin–piperaquine or placebo at 2, 6, and 10 weeks after enrollment.¹⁵ Children received iron supplementation (2 mg per kilogram of body weight per day) for 28 days after randomization as monotherapy or combined with folic acid (130 to 520 μ g per day). Caregivers were encouraged to ensure that children slept under an insecticide-treated bed net. The dihydroartemisinin–piperaquine and artemether–lumefantrine doses were determined on the basis of guidelines of the World Health Organization (Tables S1 and S2 in the Supplementary Appendix).

Adherence to administration of dihydroartemisinin–piperaquine or placebo by the caregiver was assessed by trial staff who directly observed administration of the first dose of each course during home visits. Daily telephone contact with caregivers and random home visits were used to verify that the second and third doses of each

course were administered. If children vomited within 30 minutes after taking a full dose of dihydroartemisinin–piperaquine or placebo, they received a second full dose. If the child vomited within 30 to 60 minutes after taking a full dose, an additional half dose was administered. If vomiting occurred after administration of any of the repeated doses, the child received artemether–lumefantrine. If a child vomited after taking a dose at home, caregivers were instructed to inform the trial team on the same day to obtain a replacement dose.

OUTCOMES

All children were followed from the time of randomization (day 14 after enrollment) through week 26 (Fig. S1). The primary outcome was one or more hospital readmissions for any reason or death from the time of randomization to 6 months after discharge. Key secondary outcomes included the individual components of the primary outcome, hospital readmissions because of severe anemia or malaria, and outpatient clinic visits for any reason or for malaria-related reasons (see the Supplementary Appendix for additional outcomes). Safety outcomes included adverse events reported by trial clinicians, interruption of the trial regimen because of side effects, and prolongation of the corrected QT interval (QTc), measured by means of electrocardiography before the first dose of each course and at 4 to 6 hours after the third dose of each course.

STATISTICAL ANALYSIS

We calculated that a total of 1040 children (520 per group) would be required to give the trial 80% power to detect a 25% lower incidence of readmissions or deaths in the chemoprevention group than in the placebo group (1152 events vs. 864 events per 1000 person-years), with a two-sided P value of 0.05, assuming a 10% loss to follow-up.¹⁵

Analyses were performed with the use of Stata software, version 15.1 (StataCorp). The primary outcome was analyzed as recurrent time-to-event data with the use of the Prentice–Williams–Peterson total-time approach,¹⁶ and results are reported as hazard ratios with 95% confidence intervals and P values. Data were censored at the date of the last contact (if children were lost to follow-up) or at the end of the trial (at the end of week 26). Models included site and weight category as covariates to adjust

for stratification factors. The primary analysis was performed in the intention-to-treat population and included new events occurring from the day of randomization (day 14 after enrollment) through week 26. We also prespecified the analysis to be stratified according to the period in the trial (intervention period [week 3 through week 14] or postintervention period [week 15 through week 26]); the postintervention period would be the time when the direct pharmacologic protective effect of dihydroartemisinin-piperazine would have waned.

Similar analyses were used for secondary time-to-event outcomes. Supportive analyses of the primary outcome with adjustment for covariates and a per-protocol analysis were also performed. Further sensitivity analyses to assess the robustness of the primary analysis were conducted with the use of alternative time-to-event models and count models. All children contributed person-time to the primary analysis, and no imputation for missing outcome data was used. See the Supplementary Appendix for additional details regarding statistical methods and imputation methods used for missing covariable values.

RESULTS

TRIAL POPULATION

From May 2016 through May 2018, a total of 1366 children were screened, and 1125 were assessed for eligibility; 1049 children underwent randomization and were included in the intention-to-treat population (524 in the chemoprevention group and 525 in the placebo group) (Fig. 1). The baseline characteristics were similar in the two groups (Table 1). Overall, 96.8% of children received the prespecified number of courses (97.3% in the chemoprevention group and 96.3% in the placebo group), and 7.6% of children were withdrawn or were lost to follow-up (8.4% in the chemoprevention group and 6.9% in the placebo group) (Table S3).

PRIMARY OUTCOME

Overall, 500 events of readmission or death occurred in 315 of 1049 children (30.0%); 184 events in the chemoprevention group and 316 events in the placebo group. Readmission or death occurred in 138 of 524 children (26.3%) in the chemoprevention group and in 177 of 525 (33.7%) in the placebo group. A total of 46 children (8.8%) in the chemoprevention group and 139 (26.5%) in

the placebo group had multiple events (Table S4). At the end of week 26, the risk of readmission or death was 35% lower in the chemoprevention group than in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.54 to 0.78; $P < 0.001$). During the intervention period (week 3 through week 14 after randomization), the risk of death or readmission was 70% lower in the chemoprevention group than in the placebo group (hazard ratio, 0.30; 95% CI, 0.22 to 0.42; $P < 0.001$); during the postintervention period (week 15 through week 26), the risk was 13% lower in the placebo group than in the chemoprevention group (hazard ratio, 1.13; 95% CI, 0.87 to 1.47; $P = 0.35$) (Fig. 2). The difference in effect between the intervention and the postintervention periods was significant (Fig. S2). Similar results were seen in covariate-adjusted, subgroup, per-protocol, and sensitivity analyses (Figs. 2 and 3 and Figs. S3 through S5). The effect size of chemoprevention was larger in areas in which malaria transmission was higher (Fig. S6). The incidence of readmission or death was higher among children with severe malarial anemia at the initial hospitalization than among children with nonmalarial anemia (41% vs. 9%), but this difference was not significant (Fig. 3). Children with nonmalarial anemia made up 15% of the population with severe anemia. Postdischarge malaria chemoprevention delayed the time to the first event of readmission or death (hazard ratio, 0.58; 95% CI, 0.47 to 0.73); the 20th percentile of the time to the first event was 135 days (95% CI, 123 to 149) in the chemoprevention group and 55 days (95% CI, 43 to 66) in the placebo group.

SECONDARY OUTCOMES

Chemoprevention resulted in a 37% lower incidence than placebo in the number of hospital readmissions for any reason at the end of week 26 (hazard ratio, 0.63; 95% CI, 0.52 to 0.77). The hazard ratio was 0.31 (95% CI, 0.22 to 0.43) during the intervention period and 1.09 (95% CI, 0.83 to 1.42) during the postintervention period (Fig. 2). The incidences of hospital readmission because of severe malaria, severe anemia, severe malarial anemia, and other severe diseases were also significantly lower in the chemoprevention group than in the placebo group and were also lower during the intervention period than during the postintervention period. The hazard ratio for death from any cause was 0.74 at week 26 (95%

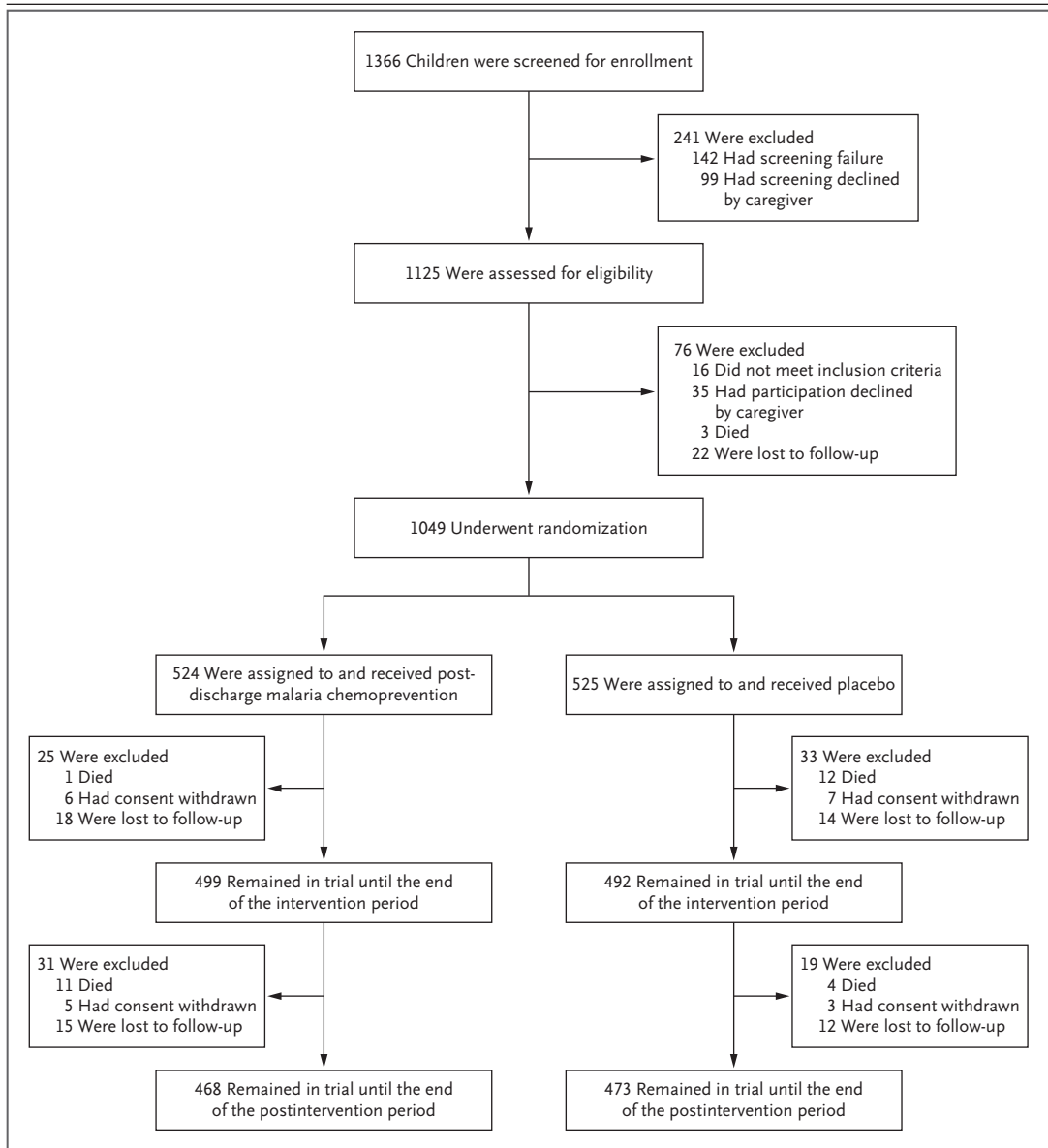


Figure 1. Screening, Randomization, and Follow-up.

All 1049 children who underwent randomization were included in the intention-to-treat analysis. Among the children who had screening failure, 2 children were older than 59.5 months at the time of screening (i.e., about 2 weeks before randomization), 1 had a history of hypersensitivity to a trial drug, 6 had sickle cell disease, 14 were receiving a prohibited medication or were enrolled in another study that used a prohibited medication, 79 were unable to adhere to the follow-up schedule, 2 had a history of cardiac disorders, and blood transfusion had not yet been completed in 38.

CI, 0.35 to 1.56), 0.08 during the intervention period (95% CI, 0.01 to 0.64), and 2.67 during the postintervention period (95% CI, 0.85 to 8.40).

In the analyses of the nonsevere outcomes, the hazard ratio for clinic visits for any illness was 0.88 (95% CI, 0.79 to 0.97), mainly reflecting the treatment effect on uncomplicated ma-

laria (hazard ratio, 0.57; 95% CI, 0.48 to 0.69). The hazard ratio for clinic visits for illnesses unrelated to malaria was 1.09 (95% CI, 0.96 to 1.24). At 26 weeks, there was no substantial effect on malaria infection (relative risk, 0.85; 95% CI, 0.69 to 1.05) and no substantial difference in mean hemoglobin levels (11.0 g per deciliter in

Table 1. Baseline Characteristics of the Children and Parents.*

Characteristic	Chemoprevention (N=524)	Placebo (N=525)
Children		
Trial site — no. (%)		
Uganda	347 (66.2)	345 (65.7)
Kenya	177 (33.8)	180 (34.3)
Male sex — no. (%)	280 (53.4)	265 (50.5)
Age — mo	26.8±15.5	26.3±14.8
Distance to clinic — km	27.5±22.6	29.1±14.8
Socioeconomic status level — no. (%)		
Poor	173 (33.0)	177 (33.7)
Poorer	164 (31.3)	189 (36.0)
Poorest	187 (35.7)	159 (30.3)
Hemoglobin level before transfusion — g/dl	4.1±1.1	4.2±1.2
Hemoglobin level at randomization — g/dl	8.1±4.5	8.0±2.0
Body weight at randomization — kg	11.1±3.2	11.0±3.1
Severe malarial anemia — no. (%)†	436 (83.2)	454 (86.5)
Sleeps under a bed net — no./total no. (%)	317/380 (83.4)	318/385 (82.6)
Previous hospitalizations — no./total no. (%)		
0	339/521 (65.1)	330/522 (63.2)
1	94/521 (18.0)	98/522 (18.8)
≥2	88/521 (16.9)	94/522 (18.0)
Readmitted after discharge, before randomization — no. (%)	14 (2.7)	18 (3.4)
Parents		
Marital status of mother — no. (%)		
Single	41 (7.8)	29 (5.5)
Married	425 (81.1)	435 (82.9)
Other	58 (11.1)	61 (11.6)
Father unemployed — no./total no. (%)	32/134 (23.9)	22/117 (18.8)
Education level of mother — no./total no. (%)		
None	36/349 (10.3)	33/366 (9.0)
Primary	224/349 (64.2)	248/366 (67.8)
Secondary	84/349 (24.1)	72/366 (19.7)
Postsecondary or higher	5/349 (1.4)	13/366 (3.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

† Severe malarial anemia was defined as severe anemia in the presence of any evidence of malaria infection detected by means of rapid diagnostic tests or microscopic examination or, if no diagnostic test result was available, any treatment with parenteral antimalarial drugs in the hospital.

each group) (Table S5). The number of children who vomited at least once within 60 minutes after taking the trial medication or placebo was higher in the chemoprevention group (65 of 524 [12.4%]) than in the placebo group (20 of 525 [3.8%]) (Table S6).

SAFETY OUTCOMES

There were 284 serious adverse events in the chemoprevention group and 534 in the placebo group ($P<0.001$) (Table 2). In 12 children (2.3%) in the chemoprevention group and 30 (5.7%) in the placebo group, these events occurred within

Outcome	Chemoprevention no. of children	Placebo no. of children	Chemoprevention no. of events/no. of events per yr (incidence rate per 100 person-yr)	Placebo no. of events/no. of events per yr (incidence rate per 100 person-yr)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Overall, 3–26 wk after discharge	524	525	184/230 (80.0)	316/228 (138.8)	0.65 (0.54–0.78)	0.64 (0.53–0.78)
Primary outcome: readmission or death from any cause	524	525	12/230 (5.2)	16/228 (7.0)	0.74 (0.35–1.56)	0.65 (0.30–1.38)
Death from any cause	524	525	176/230 (76.5)	307/228 (134.8)	0.63 (0.52–0.77)	0.63 (0.52–0.76)
Readmission for any reason	524	525	125/230 (54.3)	262/228 (115.1)	0.55 (0.43–0.69)	0.55 (0.44–0.70)
Readmission for severe malaria anemia or severe anemia	524	525	52/230 (22.6)	130/228 (57.1)	0.46 (0.32–0.66)	0.46 (0.32–0.66)
Readmission for severe anemia of any cause	524	525	34/230 (14.8)	100/228 (43.9)	0.37 (0.24–0.57)	0.38 (0.25–0.57)
Readmission for severe malaria anemia	524	525	8/230 (3.5)	39/228 (17.1)	0.23 (0.10–0.54)	0.23 (0.10–0.55)
Readmission for severe malaria-specific anemia	524	525	107/230 (46.5)	232/228 (101.9)	0.53 (0.41–0.68)	0.53 (0.41–0.68)
Readmission for severe malaria	524	525	48/230 (20.9)	43/228 (18.9)	1.13 (0.75–1.70)	1.02 (0.67–1.55)
Readmission for other reasons	524	525	222/230 (96.5)	416/228 (182.7)	0.57 (0.48–0.69)	0.57 (0.48–0.69)
Clinic visit for uncomplicated malaria	524	525	713/230 (309.6)	846/228 (371.4)	0.88 (0.79–0.97)	0.86 (0.78–0.96)
Clinic visit for any illness	524	525	491/230 (213.3)	430/228 (188.9)	1.09 (0.96–1.24)	1.08 (0.94–1.23)
Clinic visit for illness unrelated to malaria	524	525	58/123 (47.0)	209/124 (168.1)	0.30 (0.22–0.42)	0.30 (0.22–0.41)
Intervention period, 3–14 wk after discharge	524	525	1/124 (0.8)	12/124 (9.6)	0.08 (0.01–0.64)	0.06 (0.01–0.53)
Readmission or death from any cause or both	524	525	57/123 (46.2)	202/124 (162.5)	0.31 (0.22–0.43)	0.31 (0.22–0.43)
Death from any cause	524	525	30/124 (24.3)	174/124 (139.9)	0.19 (0.12–0.30)	0.19 (0.12–0.30)
Readmission for any reason	524	525	18/124 (14.6)	81/124 (65.1)	0.24 (0.13–0.41)	0.24 (0.14–0.41)
Readmission for severe malaria anemia or severe anemia	524	525	7/124 (5.7)	63/124 (50.7)	0.11 (0.05–0.26)	0.11 (0.05–0.27)
Readmission for severe anemia of any cause	524	525	2/124 (1.6)	25/124 (20.1)	0.09 (0.01–0.69)	0.09 (0.01–0.73)
Readmission for severe malaria anemia	524	525	19/124 (15.4)	156/124 (125.4)	0.13 (0.07–0.23)	0.13 (0.07–0.24)
Readmission for other reasons	524	525	26/124 (21.0)	26/124 (20.9)	1.03 (0.59–1.79)	0.98 (0.56–1.71)
Readmission for severe malaria	524	525	68/124 (55.0)	248/124 (199.4)	0.31 (0.23–0.41)	0.31 (0.23–0.41)
Clinic visit for uncomplicated malaria	524	525	346/124 (279.8)	497/124 (399.4)	0.73 (0.64–0.84)	0.71 (0.62–0.82)
Clinic visit for any illness	524	525	278/124 (225.0)	249/124 (200.2)	1.10 (0.93–1.32)	1.06 (0.89–1.27)
Clinic visit for illness unrelated to malaria	524	525	126/105 (119.7)	107/102 (104.9)	1.13 (0.87–1.47)	1.13 (0.86–1.48)
Postintervention period, 15–26 wk after discharge	499	492	11/105 (10.5)	4/102 (3.9)	2.67 (0.85–8.40)	2.49 (0.80–7.77)
Readmission or death from any cause	499	492	119/105 (113.1)	105/102 (103.0)	1.09 (0.83–1.42)	1.09 (0.82–1.43)
Death from any cause	499	492	95/105 (90.3)	88/102 (86.3)	1.04 (0.78–1.39)	1.07 (0.78–1.45)
Readmission for any reason	499	492	34/105 (32.3)	49/102 (48.1)	0.68 (0.43–1.09)	0.69 (0.43–1.12)
Readmission for severe malaria anemia or severe anemia	499	492	27/105 (25.7)	37/102 (36.3)	0.71 (0.43–1.16)	0.74 (0.44–1.23)
Readmission for severe anemia of any cause	499	492	6/105 (5.7)	14/102 (13.7)	0.49 (0.19–1.24)	0.52 (0.20–1.36)
Readmission for severe malaria anemia	499	492	88/105 (83.7)	76/102 (74.6)	1.11 (0.81–1.50)	1.13 (0.82–1.57)
Readmission for severe malaria-specific anemia	499	492	22/105 (20.9)	17/102 (16.7)	1.21 (0.62–2.34)	1.05 (0.53–2.09)
Readmission for other reasons	499	492	154/105 (146.4)	168/102 (164.7)	0.84 (0.67–1.05)	0.84 (0.67–1.06)
Clinic visit for uncomplicated malaria	499	492	367/105 (348.6)	349/102 (342.1)	0.98 (0.85–1.14)	0.98 (0.85–1.14)
Clinic visit for any illness	499	492	213/105 (202.3)	181/102 (177.5)	1.09 (0.90–1.33)	1.11 (0.91–1.35)
Clinic visit for illness unrelated to malaria	499	492				



Figure 2 (facing page). Primary Outcome and Other Efficacy Outcomes.

The primary outcome was one or more hospital readmissions for any reason or death from the time of randomization to 6 months after discharge. The adjusted hazard ratios were adjusted for site, body weight, number of previous hospital admissions, syndrome at the time of admission (severe malarial anemia or severe nonmalarial anemia), age, hemoglobin level at randomization, distance to the hospital, and socioeconomic status. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. The bars and the point estimates for the confidence intervals correspond to the crude hazard ratios. Severe anemia was defined as a hemoglobin level of less than 5 g per deciliter, a hematocrit of less than 15%, or a clinical indication for blood transfusion. Severe malarial anemia was defined as severe anemia in the presence of any evidence of malaria infection detected by means of rapid diagnostic tests or microscopic examination. Severe malaria-specific anemia was defined as severe anemia in the presence of malaria infection detected by means of microscopic examination, with more than 5000 parasites per microliter. A secondary analysis of the primary outcome that excluded death or readmission due to trauma or cancer showed similar results because only one event in the chemoprevention group and no event in the placebo group was due to trauma or cancer.

4 days after administration of dihydroartemisinin–piperaquine or placebo ($P=0.007$) (Table S7). None of the events were judged by the site investigator to be related to the trial regimen. Data obtained with the use of the World Health Organization verbal autopsy questionnaire^{17,18} and clinical notes suggested that of the 28 deaths, 8 were due to severe malarial anemia, 9 to severe anemia, and 11 to other causes.

Electrocardiographic monitoring in 66 children (33 in each group) showed that dihydroartemisinin–piperaquine was associated with an 18.6 msec (95% CI, 15.6 to 21.8) increase in the QT interval corrected for heart rate according to Fridericia's formula (QTcF) after the third dose of each course (all events of QTcF prolongation were asymptomatic), whereas placebo was not associated with an increase in the QTcF interval (change in QT interval, -1.8 msec; 95% CI, -5.3 to 1.7). The mean QTcF prolongation was 8 msec less (95% CI, 1 to 15) after the third course than after the first course of dihydroartemisinin–piperaquine. No QTcF values greater than 480 msec were observed (Table S8).

DISCUSSION

A course of 3 months of postdischarge malaria chemoprevention with monthly dihydroartemisinin–piperaquine in children with severe anemia was highly effective and resulted in a 35% lower incidence of death or readmission for any reason than placebo. About one third of children in the placebo group died or were readmitted at least once during the 24 weeks after randomization, and many of the children were readmitted multiple times, findings that are consistent with the high postdischarge burden seen in previous studies in similar settings.^{9,10,19,20} The lower incidence of readmission in the chemoprevention group than in the placebo group was mostly the result of the dihydroartemisinin–piperaquine treatment preventing events of severe malaria or severe malarial anemia, and the greatest reductions in the incidence of readmissions were observed after a child had been hospitalized for severe malarial anemia and then discharged. Severe malarial anemia made up the majority (85%) of all initial admissions for severe anemia.

The beneficial effect of chemoprevention was restricted to the 12-week intervention period; during this time, the incidence of readmission or death in the chemoprevention group was 70% lower than that in the placebo group, the incidence of readmission for severe malaria was 87% lower, and the incidence of readmission for severe malarial anemia was 89% lower. The results observed in the extended follow-up period, starting 4 weeks after the third course, indicated that the beneficial effect was not sustained after about 14 weeks, when the protective piperaquine levels had waned. There was a nonsignificant increase in death from any cause (hazard ratio, 2.67; 95% CI, 0.85 to 8.40) after 14 weeks — a result consistent with previous seasonal malaria chemoprevention studies in children.^{21,22} This could reflect a delay in the acquisition of protective immunity to malaria or a loss of protective immunity, but the result may also be artificial because of factors relating to frailty; in contrast to the placebo group, more of the vulnerable children in the chemoprevention group survived to contribute data to the postintervention period (e.g., of those who died during the postintervention period, 8 of 11 children in the chemoprevention group and 2 of 4 children in the placebo group had had a previous hospitalization before

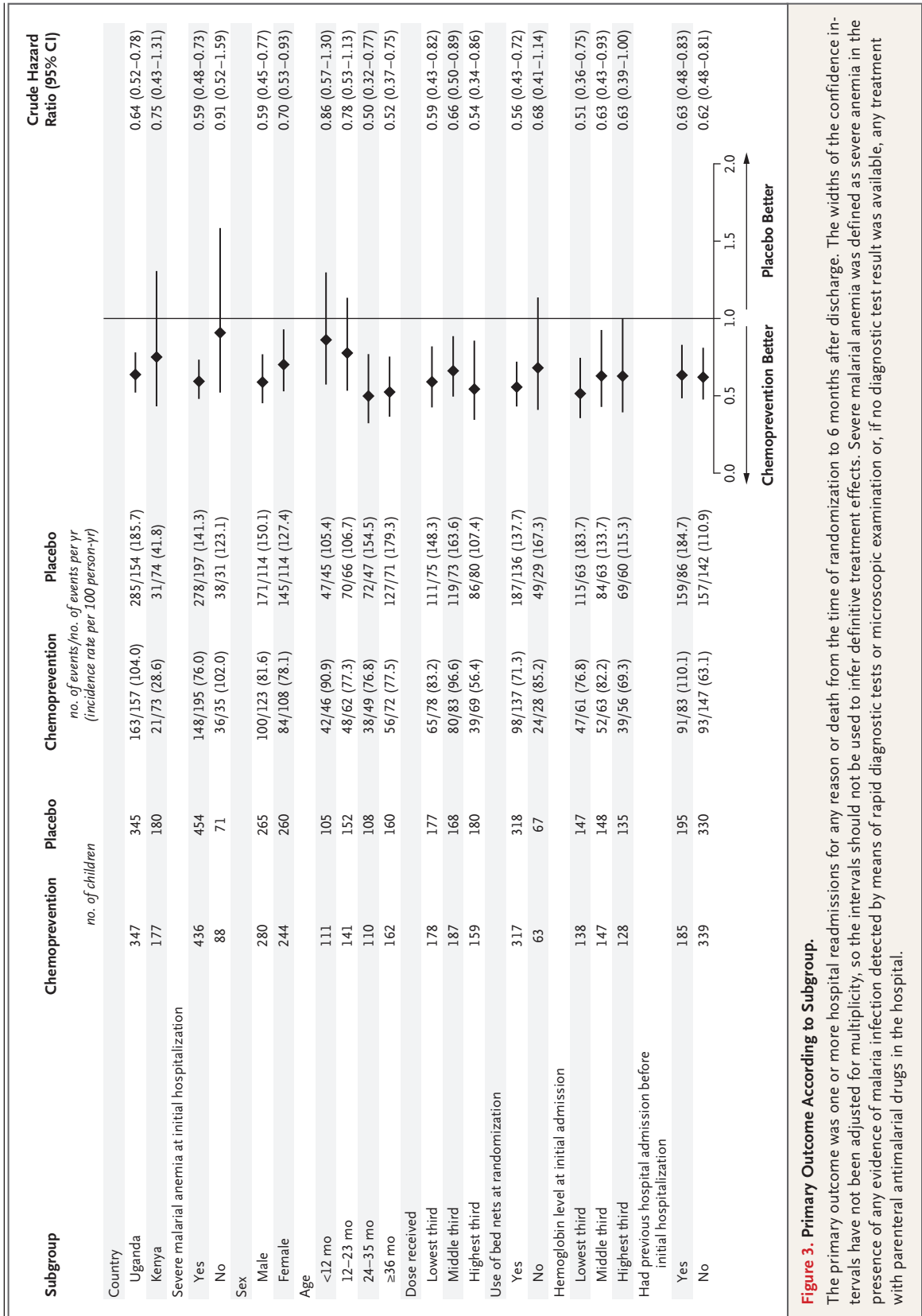


Figure 3. Primary Outcome According to Subgroup.

The primary outcome was one or more hospital readmissions for any reason or death from the time of randomization to 6 months after discharge. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. Severe malarial anemia was defined as severe anemia in the presence of any evidence of malaria infection detected by means of rapid diagnostic tests or microscopic examination or, if no diagnostic test result was available, any treatment with parenteral antimalarial drugs in the hospital.

Table 2. Serious Adverse Events.*

Event	Chemoprevention (N = 524)				Placebo (N = 525)				P Value†
	No. of Children with Event (%)	Total No. of Events	Incidence per 100 Person-Yr	No. of Children with Event (%)	Total No. of Events	Incidence per 100 Person-Yr	No. of Children with Event (%)		
Any event	138 (26.3)	284	123.4	177 (33.7)	534	234.6	0.009		
Blood and lymphatic system disorders	51 (9.7)	62	26.9	89 (17.0)	130	57.1	0.001‡		
Cardiac disorders	1 (0.2)	1	0.4	0	0	0.0	0.50		
Ear and labyrinth disorders	1 (0.2)	1	0.4	1 (0.2)	1	0.4	1.00		
Gastrointestinal disorders	2 (0.4)	2	0.9	4 (0.8)	4	1.8	0.69		
General disorders and administration site conditions	9 (1.7)	9	3.9	14 (2.7)	14	6.1	0.40		
Hepatobiliary disorders	1 (0.2)	1	0.4	0	0	0.0	0.50		
Infections and infestations	117 (22.3)	166	72.1	159 (30.3)	324	142.3	0.003‡		
Metabolism and nutrition disorders	8 (1.5)	8	3.5	3 (0.6)	3	1.3	0.14		
Musculoskeletal and connective-tissue disorders	1 (0.2)	1	0.4	0	0	0.0	0.50		
Nervous system disorders	2 (0.4)	2	0.9	3 (0.6)	3	1.3	1.00		
Renal and urinary disorders	5 (1.0)	5	2.2	17 (3.2)	24	10.5	0.02		
Respiratory, thoracic, and mediastinal disorders	23 (4.4)	25	10.9	30 (5.7)	31	13.6	0.40		
Skin and subcutaneous-tissue disorders	1 (0.2)	1	0.4	0	0	0.0	0.50		

* Serious adverse events were classified according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0, system organ class. Multiple events could be included in one primary-outcome event if more than one MedDRA system organ class was involved, and children could have had more than one event in any category.

† The P values are the unadjusted values calculated with the use of Fisher's exact test, unless otherwise indicated, on the basis of the number of children with at least one event.

‡ The P value was calculated with the use of the chi-square test on the basis of the number of children with at least one event.

enrollment in the trial). Overall, however, the 70% lower incidence of readmission or death in the chemoprevention group than in the placebo group during the intervention period outweighed the 13% higher risk in the chemoprevention group than in the placebo group during the extended follow-up period.

Although the incidence of readmission or death in the placebo group was highest in the first few months after discharge and declined gradually with longer follow-up, the incidence remained high in both groups during the 3-month postintervention period, when about 28% of the children died or were readmitted. It remains to be determined whether more sustained reductions in readmission or death can be achieved by combining postdischarge malaria chemoprevention with other malaria interventions, such as a malaria vaccine and the provision of long-lasting insecticide-treated bed nets, or whether reductions can be achieved with longer periods of postdischarge malaria chemoprevention (e.g., up to 6 months) and iron supplementation, with or without folate. Other interventions, such as anthelmintics or those that address additional nutritional factors or recurrent bacterial infections, could also be considered, but the interventions may need to be tailored according to the prevalence of these local modifiable risk factors.

We chose dihydroartemisinin–piperaquine because the safety of this combination has been shown in children, and there is evidence for its effectiveness as seasonal malaria chemoprevention or as monthly intermittent preventive therapy in children.^{23–26} Daily cotrimoxazole or monthly sulfadoxine–pyrimethamine, alone or combined with amodiaquine, was not considered because of high-grade resistance of the malaria parasite in southern Africa and East Africa.^{26,27} Dihydroartemisinin–piperaquine is known to provide at least 4 weeks of post-treatment prophylaxis,²⁸ as compared with the 3 weeks of prophylaxis achieved with monthly artemether–lumefantrine in the previous postdischarge malaria chemoprevention trial.¹¹ The initiation of dihydroartemisinin–piperaquine, rather than artemether–lumefantrine, around the time of discharge could allow for pragmatic monthly administration starting 1 month after discharge. The longer duration of post-treatment prophylaxis achieved with dihydroartemisinin–piperaquine may explain

the larger effect size during the 3-month intervention period observed in the current trial (the risk of death or readmission was 70% lower in the chemoprevention group than in the placebo group) than in the previous trial, which used artemether–lumefantrine (41% lower risk in the chemoprevention group than in the placebo group).¹¹ These results are also consistent with two other postdischarge intervention trials involving Gambian children who had been hospitalized for severe anemia. These trials showed that near-complete chemoprevention of malaria after hospital discharge for the remainder of the malaria transmission season with either weekly prophylaxis with pyrimethamine–dapsone²⁹ or monthly sulfadoxine–pyrimethamine³⁰ also significantly reduced the incidence of readmission for any reason³⁰ or readmission for severe anemia, both by 78%.²⁹ These latter two studies were conducted before the widespread introduction of monthly seasonal malaria chemoprevention in the Sahel region.³¹

These reductions in postdischarge events with the use of effective malaria chemoprevention are in contrast to the findings from a recent postdischarge prevention trial involving severely anemic children in similar settings in Uganda and Malawi in which malaria is endemic.¹² Three months of daily cotrimoxazole did not improve 6-month survival or reduce hospital readmissions, possibly reflecting parasite resistance to antifolates in these regions,^{26,32} a low burden of nonmalarial febrile illness,¹² or antimicrobial resistance.³³

No serious adverse events attributable to dihydroartemisinin–piperaquine were observed. Asymptomatic QTc prolongation was, as expected, more common with dihydroartemisinin–piperaquine than with placebo. However, no episode of QTc prolongation was associated with arrhythmias or clinical adverse events — a result consistent with other studies that used monthly dihydroartemisinin–piperaquine in pregnant women³⁴ and in other groups.²⁵ Only a few caregivers withdrew their children from the trial because of perceived adverse events associated with the intervention, and these numbers were similar in the two trial groups.

Nevertheless, similar to seasonal malaria chemoprevention,²¹ when postdischarge malaria chemoprevention is implemented, clear health education for providers and the target popula-

tion is required to achieve effective chemoprevention coverage under real-life conditions. Recent health services research has shown that chemoprevention would most likely be acceptable to caregivers and that a delivery system in which all three chemoprevention courses are given to the caregivers at the time of discharge for them to administer to their children would be likely to result in higher coverage than facility-based delivery that would require caregivers to return to the clinic.^{35,36} This method could be combined with text-message reminders sent to mobile telephones or with home visits by village health workers. Weekly prophylaxis with dihydroartemisinin–piperaquine after a loading dose, as compared with monthly dosing, could allow for more skipped doses without compromising effectiveness and should also be explored.³⁷ Modeling studies to determine the epidemiologic and geographical settings in which postdischarge malaria chemoprevention would be a cost-effective intervention are merited.

The strengths of this trial include the high adherence to the chemoprevention regimen (98%) and the high percentage of children who remained available for follow-up (>92%). Limitations include the limited available diagnostic data for the nonmalaria causes of postdischarge readmissions or deaths. Furthermore, like previous postdischarge trials,^{11,12} the mortality in the placebo group was lower than expected, most likely reflecting enhanced access to standard care as the result of participation in a trial and the early diagnosis of events that would result in readmission.

In children living in areas with intense malaria transmission who had undergone transfusion and had been discharged from the hospital

after treatment for severe anemia, 3 months of postdischarge malaria chemoprevention with dihydroartemisinin–piperaquine resulted in substantial benefits with respect to reducing the incidence of death or readmission for any reason after discharge.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

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APPENDIX

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REFERENCES

- Kiguli S, Maitland K, George EC, et al. Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness. *BMC Med* 2015;13:21.
- Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014;123:615-24.
- Calis JCJ, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *N Engl J Med* 2008;358:888-99.
- Maitland K, Olupot-Olupot P, Kiguli S, et al. Transfusion volume for children with severe anemia in Africa. *N Engl J Med* 2019;381:420-31.
- Pedro R, Akech S, Fegan G, Maitland K. Changing trends in blood transfusion in children and neonates admitted in Kilifi District Hospital, Kenya. *Malar J* 2010;9:307.
- Maitland K, Kiguli S, Olupot-Olupot P, et al. Immediate transfusion in African children with uncomplicated severe anemia. *N Engl J Med* 2019;381:407-19.
- Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *Malawi Med J* 2016;28:99-107.
- Opoka RO, Hamre KES, Brand N, Bangirana P, Idro R, John CC. High post-discharge morbidity in Ugandan children with severe malarial anemia or cerebral malaria. *J Pediatric Infect Dis Soc* 2017;6(3):e41-e48.
- Phiri KS, Calis JC, Faragher B, et al. Long term outcome of severe anaemia in Malawian children. *PLoS One* 2008;3(8):e2903.
- Zucker JR, Lackritz EM, Ruebush TK II, et al. Childhood mortality during and after hospitalization in western Kenya: effect of malaria treatment regimens. *Am J Trop Med Hyg* 1996;55:655-60.
- 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, randomised, placebo-controlled trial. *Lancet Infect Dis* 2012;12:191-200.
- Maitland K, Olupot-Olupot P, Kiguli S, et al. Co-trimoxazole or multivitamin multiminer supplement for post-discharge outcomes after severe anaemia in African children: a randomised controlled trial. *Lancet Glob Health* 2019;7(10):e1435-e1447.
- ter Kuile FO, van Eijk AM, Filler SJ. Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: a systematic review. *JAMA* 2007;297:2603-16.
- Kurtzhals JA, Rodrigues O, Addae M, Commye JO, Nkrumah FK, Hviid L. Reversible suppression of bone marrow response to erythropoietin in *Plasmodium falciparum* malaria. *Br J Haematol* 1997;97:169-74.
- Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention with monthly dihydroartemisinin-piperazine 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, randomised, placebo-controlled, superiority trial. *Trials* 2018;19:610.
- Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. *Biometrika* 1981;68:373-9.
- Verbal autopsy standards: 2012 WHO verbal autopsy instrument. Geneva: World Health Organization, 2012.
- van Eijk AM, Adazu K, Ofware P, Vulule J, Hamel M, Slutsker L. Causes of deaths using verbal autopsy among adolescents and adults in rural western Kenya. *Trop Med Int Health* 2008;13:1314-24.
- Wiens MO, Kumbakumba E, Larson CP, et al. Postdischarge mortality in children with acute infectious diseases: derivation of postdischarge mortality prediction models. *BMJ Open* 2015;5(11):e009449.
- Lackritz EM, Hightower AW, Zucker JR, et al. Longitudinal evaluation of severely anemic children in Kenya: the effect of transfusion on mortality and hematologic recovery. *AIDS* 1997;11:1487-94.
- Kweku M, Liu D, Adjui M, et al. Seasonal intermittent preventive treatment for the prevention of anaemia and malaria in Ghanaian children: a randomized, placebo controlled trial. *PLoS One* 2008;3(12):e4000.
- Cissé B, Sokhna C, Boulanger D, et al. Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial. *Lancet* 2006;367:659-67.
- Cisse B, Cairns M, Faye E, et al. Randomized trial of piperazine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. *PLoS One* 2009;4(9):e7164.
- Bojang K, Akor F, Bittaye O, et al. A randomised trial to compare the safety, tolerability and efficacy of three drug combinations for intermittent preventive treatment in children. *PLoS One* 2010;5(6):e11225.
- Gutman J, Kovacs S, Dorsey G, Stergachis A, Ter Kuile FO. Safety, tolerability, and efficacy of repeated doses of dihydroartemisinin-piperazine for prevention and treatment of malaria: a systematic review and meta-analysis. *Lancet Infect Dis* 2017;17:184-93.
- Bigira V, Kapisi J, Clark TD, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. *PLoS Med* 2014;11(8):e1001689.
- Okell LC, Griffin JT, Roper C. Mapping sulphadoxine-pyrimethamine-resistant *Plasmodium falciparum* malaria in infected humans and in parasite populations in Africa. *Sci Rep* 2017;7:7389.
- Akpaloo W, Pursell E. Does the use of dihydroartemisinin-piperazine in treating patients with uncomplicated falciparum malaria reduce the risk for recurrent new falciparum infection more than artemether-lumefantrine? *Malar Res Treat* 2014;2014:263674.
- Bojang KA, Milligan PJM, Conway DJ, et al. Prevention of the recurrence of anaemia in Gambian children following discharge from hospital. *PLoS One* 2010;5(6):e11227.
- Bojang KA, Palmer A, Boele van Hensbroek M, Banya WA, Greenwood BM. Management of severe malarial anaemia in Gambian children. *Trans R Soc Trop Med Hyg* 1997;91:557-61.
- York A. Seasonal malaria chemoprevention in the Sahel. *Lancet Infect Dis* 2017;17:588.
- van Eijk AM, Larsen DA, Kayentao K, et al. Effect of *Plasmodium falciparum* sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19:546-56.
- Prendergast AJ, Walson JL. Seeking interventions to reduce post-discharge mortality among children in sub-Saharan Africa. *Lancet Glob Health* 2019;7(10):e1306-e1307.
- Kajubi R, Ochieng T, Kakuru A, et al. Monthly sulfadoxine-pyrimethamine versus dihydroartemisinin-piperazine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial. *Lancet* 2019;393:1428-39.
- Svege S, Kaunda B, Robberstad B, Nkosi-Gondwe T, Phiri KS, Lange S. Post-discharge malaria chemoprevention (PMC) in Malawi: caregivers' acceptance and preferences with regard to delivery methods. *BMC Health Serv Res* 2018;18:544.
- Nkosi-Gondwe T, Robberstad B, Blomberg B, Phiri KS, Lange S. Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation. *BMC Health Serv Res* 2018;18:984.
- Permala J, Tarning J, Nosten F, White NJ, Karlsson MO, Bergstrand M. Prediction of improved antimalarial chemoprevention with weekly dosing of dihydroartemisinin-piperazine. *Antimicrob Agents Chemother* 2017;61(5):e02491-16.

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