# 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

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## Summary

**Background** Young children with severe malarial anaemia in Africa are at high risk of readmittance to hospital or death within 6 months of discharge. We aimed to assess whether 3 months of chemoprevention with artemether–lumefantrine reduced this risk.

**Methods** We did a randomised, placebo-controlled, multicentre trial in four hospitals in Malawi testing the efficacy and safety of intermittent preventive therapy post-discharge (IPTpd) in children aged 4–59 months admitted for severe malarial anaemia. All convalescent children who had completed a blood transfusion received artemether–lumefantrine at discharge and were randomly assigned by a computer-generated sequence to receive placebo or artemether–lumefantrine at 1 month and 2 months after discharge, providing about 1 month and 3 months of protection, respectively. Patients and study staff were masked throughout the study. The primary endpoint was a composite of all-cause mortality or hospital readmittance because of all-cause severe anaemia or severe malaria between 1 and 6 months after enrolment. This trial is registered, number ISRCTN89727873.

**Results** Of 1414 children enrolled, 708 were assigned to receive placebo and 706 the intervention. By 6 months, 192 children (14%) had died or were readmitted with severe malaria or severe anaemia. 1–6 months after randomisation, 109 primary events occurred in 85 children in the placebo group and 86 in 74 children in the intervention group (adjusted protective efficacy [PE] 31%, 95% CI 5–50; absolute rate reduction 11·7 per 100 children years, 95% CI 1·8–18·9; p=0·024). The protective effect was greatest during the IPTpd period (1–3 months), when 58 primary events occurred in 49 children in the placebo group and 37 in 34 children in the intervention group (PE 41%, 10–62; p=0·01), but was not sustained after the third month (4–6 months, PE 17%, –27 to 45; p=0·395). When episodes in the first month were included—ie, before the first dose of IPTpd, when both groups benefited from the post-treatment prophylactic effect of artemether–lumefantrine provided at discharge—the overall cumulative PE by 6 months was 26% (–2 to 46; p=0·06).

**Interpretation** In areas with intense malaria transmission, chemoprevention with IPTpd given to children with severe malarial anaemia might reduce rates of readmittance to hospital for severe anaemia or malaria. Studies to confirm these findings and to investigate different delivery mechanisms and cost-effectiveness are needed.

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## Introduction

Severe anaemia is a major cause of hospital admissions in sub-Saharan Africa and contributes substantially to paediatric mortality, particularly among young children in areas of high malaria transmission. Previous studies in western Kenya and southern Malawi indicate that not only are young children admitted to hospital for severe anaemia at high risk of in-hospital mortality, but also an additional 10–16% of patients die or are readmitted in the first 3–6 months after discharge.[1–6]

In children who have recovered from severe malarial anaemia, the initial rise in haemoglobin resulting from blood transfusions is likely to be negated by subsequent episodes of new or recrudescent malaria infections after discharge. Recovery from malaria-associated anaemia is slow—full haematological recovery takes at least 6 weeks and takes substantially longer in patients with recrudescence or reinfection,[7,8] with infections with other pathogens, or with prolonged nutritional deficiencies.[9] Although continued destruction of unparasitised erythrocytes after radical clearance of parasitaemia is a contributing factor, persistent dyserythropoiesis and bone-marrow suppression can persist for much longer.[9] We postulated that interventions that result in radical cure and prevention of subsequent malaria episodes could provide a time-window during which the bone marrow of recently transfused children can recover, allowing haemoglobin to be restored and reducing the risk of readmittance to hospital because of severe malaria or recurrence of severe anaemia.

The standard treatment for severe malaria anaemia in Malawi and many other countries in sub-Saharan Africa is a blood transfusion and intravenous quinine, then artemether–lumefantrine when children can switch to oral medication, but no policy exists to address the high risk of morbidity and mortality after discharge. The lumefantrine component in artemether–lumefantrine can provide several weeks of post-treatment prophylaxis.[10]

Intermittent preventive therapy is the administration of full treatment courses of long-acting antimalarial drugs at pre-defined time intervals, irrespective of whether patients are known to have malaria. Such therapy clears existing infections and provides prolonged periods of prophylaxis against new infections after each treatment course.[11] This strategy can prevent clinical malaria and malaria-associated severe anaemia in pregnant women,[12] infants,[13] and children,[14] and could be cost-effective for the management of children with severe malarial anaemia after discharge.[15] We designed a randomised, double-blind, placebo-controlled trial to test the efficacy and safety of intermittent preventive therapy post-discharge (IPTpd) in the management of young children admitted for severe malarial anaemia requiring a blood transfusion.

## Methods

### Participants

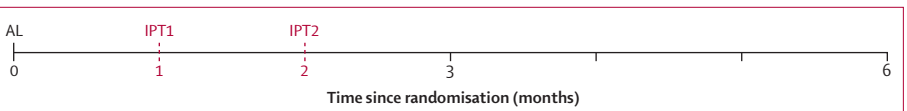
We recruited children aged 4–59 months from four hospitals in southern Malawi, the Queen Elizabeth Central Hospital (Blantyre) and three hospitals within an hour drive of Blantyre: Chikwawa and Thyolo District Hospitals, and Zomba Central Hospital. This area has moderate to intense perennial malaria transmission. All children had been admitted with severe malarial anaemia, had received a blood transfusion, and had completed the in-hospital course of intravenous quinine. Convalescent children surviving this initial in-hospital phase were eligible for inclusion if after transfusion they had haemoglobin concentrations of more than 5 g/dL, weighed more than 5 kg, were able to switch to oral medication, and could sit unaided. Children with blood loss due to trauma, haematological malignancy, a known bleeding disorder, or known sickle-cell disease were excluded. Other exclusion criteria were known hypersensitivity to artemether–lumefantrine, treatment with artemether–lumefantrine within the week before admission, non-residency in the study area, previous participation in the study, participation in another clinical trial, known need for medication prohibited during the intervention period, and surgery scheduled during the study. Written, informed consent was obtained. The study was approved by the research ethics committees of the College of Medicine (Malawi) and the Liverpool School of Tropical Medicine (UK).

### Procedures

Eligible children in both groups received six doses as part of the standard 3 day course of artemether–lumefantrine (Novartis, 20 mg artemether, 120 mg lumefantrine) in hospital. Children weighing less than 15 kg received one tablet and those weighing 15 kg or more received two tablets, about once every 12 h for 3 days. They were then randomly assigned during convalescence to receive either IPTpd with the same 3 day course of artemether–lumefantrine or placebo (Lab-Allied, Nairobi, Kenya) at 1 month and 2 months after discharge (figure 1).

The first daily doses of IPTpd or placebo at 1 month and 2 months after discharge were provided in the community by study team members who visited each home in the morning for 3 days; the second daily dose was left with the parents or guardian to give in the evening. Adherence was assessed the next morning. Children were followed up for 6 months by passive case detection.

The observation time was divided into three periods: the first month after discharge before IPTpd, the IPTpd period starting at 1 month after discharge when children received the first course of IPT or placebo and ended at 3 months (1 month after the second IPTpd dose), and the extended follow-up period (4–6 months) to assess whether any initial beneficial effect of IPTpd was sustained beyond the intervention period. Parents and guardians were asked to take children to a study clinic if they had fever or were unwell. At these visits clinical information was recorded on standardised forms, the axillary temperature and haemoglobin concentrations measured, and a malaria blood smear taken. Children with a positive malaria smear were treated with 5 days of quinine during the first 3 months after discharge or with a standard 3 day course




| Period | Pre-IPTpd | IPTpd | Post-IPTpd (extended follow-up) |
|---|---|---|---|
| Trial intervention | AL for both groups at discharge | Two AL courses as IPTpd or two courses placebo | No intervention |
| Rescue treatment for acute malaria | Oral quinine, 5 days | | AL |
| Treatment for severe malaria | Intravenous quinine and oral quinine, 5 days | | Intravenous quinine and AL |

***Figure 1:*** **Study treatment and follow-up**
A cross-sectional survey was done 6 months after randomisation. AL=artemether–lumefantrine. IPTpd=intermittent preventive therapy post-discharge.

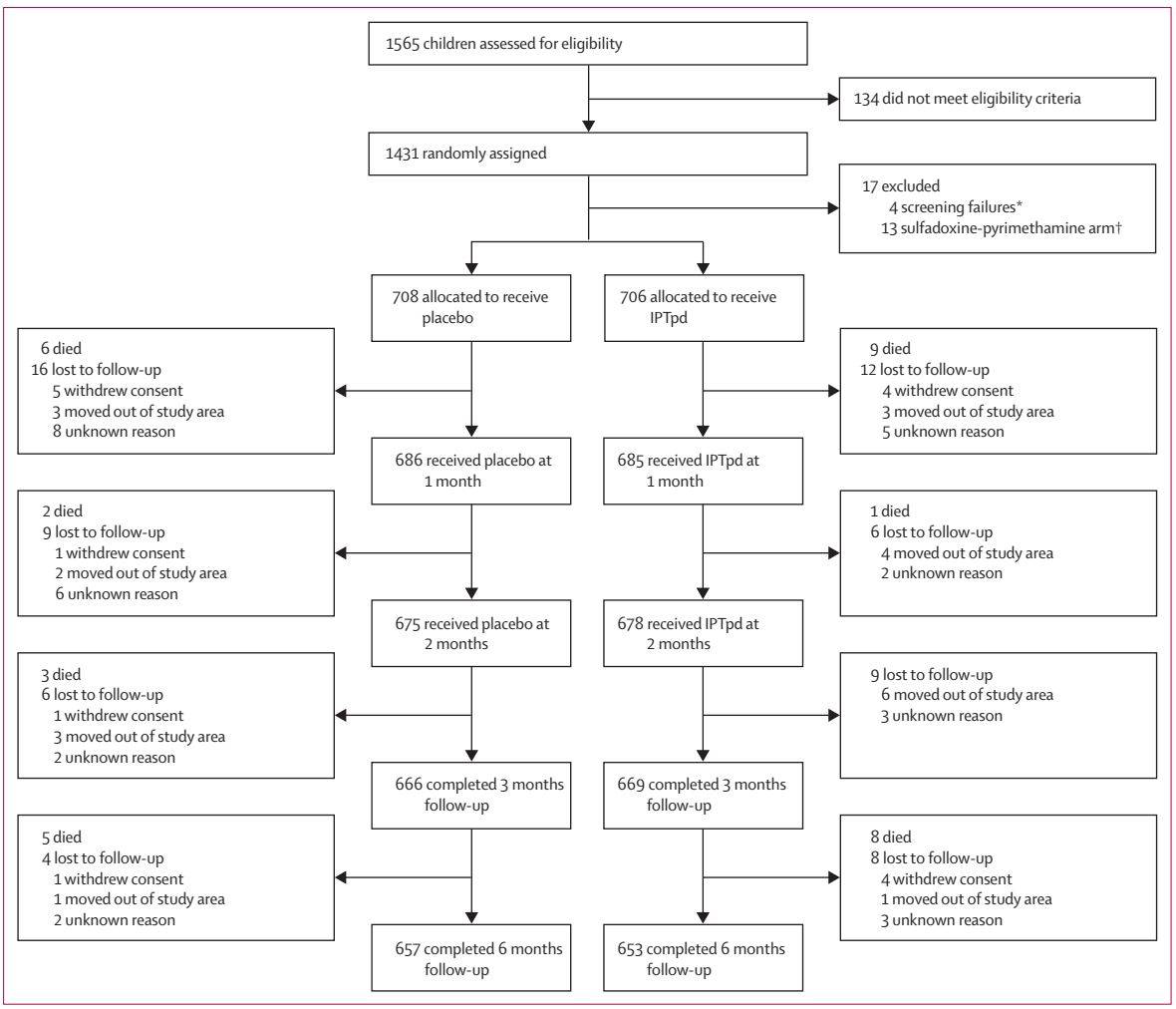



***Figure 2:*** **Trial profile**

IPTpd=intermittent preventive therapy post-discharge. *Four patients diagnosed with sickle cell disease after randomisation. †The original design included a third group (436 patients) of sulfadoxine–pyrimethamine at discharge, then placebo at 1 and 2 months (according to the national policy in Malawi in 2006) and used mean haemoglobin concentrations at 3 months as the primary endpoint. However, shortly after the trial started, the national policy changed to artemether–lumefantrine, so the sulfadoxine–pyrimethamine group was discontinued. By that time 40 patients had been recruited. Recruitment in the other two groups was continued with a new randomisation list. The primary endpoint was changed to the composite endpoint by 6 months. Masking was maintained throughout trial and the 13 patients in the sulfadoxine–pyrimethamine group were identified after closure of all datasets and breaking of the study code.

of artemether–lumefantrine during the extended follow-up period. Children with severe disease were admitted to hospital. Children with recurrent severe anaemia received a blood transfusion. Bacterial and other infections were treated at the discretion of clinicians. All children were seen at 6 months for assessment of haemoglobin concentrations and malaria parasitaemia.

Haemoglobin was measured at point-of-care with the HemoCue B-haemoglobin analyser. Malaria infection was defined as the presence of asexual *Plasmodium falciparum* in a blood smear. HIV testing was done according to WHO guidelines with two rapid tests (Determine and Uni-Gold). Discordant results and reactive results in children younger than 18 months were resolved by PCR.

The primary outcome was a composite of all-cause mortality and hospital readmission because of all-cause severe anaemia or severe malaria between 1 and 6 months. Severe anaemia was defined as a haemoglobin concentration of less than 5 g/dL or a clinical indication for blood transfusion. Severe malaria was defined as readmittance to hospital because of confirmed malaria treated with parenteral quinine. Secondary endpoints were all-cause mortality, hospital readmission because of all-cause severe anaemia or severe malaria, all-cause hospital admission, all-cause sick-child clinic visits, and clinic visit because of microscopically confirmed non-severe malaria.

## Randomisation and masking

The trial statistician in Liverpool generated the random numbers by computer to allocate children to groups. The randomisation sequence was stratified by hospital and

| | Total (n=1414) | Placebo (n=708) | IPTpd (n=706) |
|---|---|---|---|
| **Parental and household characteristics** | | | |
| Study site | | | |
| Blantyre | 512 (36%) | 257 (36%) | 255 (36%) |
| Chikwawa | 472 (33%) | 237 (33%) | 235 (33%) |
| Thyolo | 215 (15%) | 107 (15%) | 108 (15%) |
| Zomba | 215 (15%) | 107 (15%) | 108 (15%) |
| Maternal age (years) | 26·6 (6·0) | 26·6 (6·0) | 26·6 (5·9) |
| Maternal health | | | |
| Healthy | 1369 (97%) | 678 (96%) | 691 (98%) |
| Died | 16 (1%) | 11 (2%) | 5 (1%) |
| Sick | 27 (2%) | 17 (2%) | 10 (1%) |
| Maternal educational level | | | |
| None | 361 (26%) | 176 (25%) | 185 (26%) |
| Primary completed | 920 (65%) | 465 (66%) | 455 (64%) |
| Secondary or tertiary | 119 (8%) | 56 (8%) | 63 (9%) |
| Guardian or father employment status | | | |
| Unemployed | 161 (11%) | 78 (11%) | 83 (12%) |
| Employed | 1245 (88%) | 626 (88%) | 619 (88%) |
| Have electricity in the household | 49 (3%) | 27 (4%) | 22 (3%) |
| Child mosquito net use in the past week | | | |
| Treated net | 497 (35%) | 232 (33%) | 265 (38%) |
| Untreated net | 233 (16%) | 125 (18%) | 108 (15%) |
| No net | 683 (48%) | 350 (49%) | 333 (47%) |
| **Child characteristics** | | | |
| Age at admission (months) | 23·9 (13·4) | 24·2 (13·3) | 23·7 (13·5) |
| Sex (males) | 684 (48%) | 335 (47%) | 349 (49%) |
| Blantyre coma score at admission | | | |
| Deep coma (0–2) | 27 (2%) | 11 (2%) | 16 (2%) |
| Coma (3–4) | 49 (3%) | 20 (3%) | 29 (4%) |
| Fully conscious | 1327 (94%) | 672 (95%) | 655 (93%) |
| General feeding conditions at admission | | | |
| Poor | 52 (4%) | 28 (4%) | 24 (3%) |
| Fair | 642 (45%) | 321 (45%) | 321 (45%) |
| Good | 719 (51%) | 358 (51%) | 361 (51%) |
| Previous blood transfusion | 166 (12%) | 87 (12%) | 79 (11%) |
| Chest recessions at admission | 116 (8%) | 55 (8%) | 61 (9%) |
| Fever at randomisation | 165 (12%) | 75 (11%) | 90 (13%) |
| Positive malaria smear at randomisation | 483 (34%) | 232 (33%) | 251 (36%) |
| Haemoglobin concentration before transfusion (g/dL) | 3·8 (0·8) | 3·7 (0·8) | 3·8 (0·8) |
| Haemoglobin concentration at randomisation (g/dL) | 7·6 (1·6) | 7·5 (1·5) | 7·7 (1·6) |
| HIV status | | | |
| Infected | 113 (8%) | 47 (7%) | 66 (9%) |
| Not infected | 1123 (79%) | 575 (81%) | 548 (78%) |
| Data missing | 178 (13%) | 86 (12%) | 92 (13%) |

Data are n (%) or mean (SD). IPTpd=intermittent preventive therapy post-discharge.

*Table 1:* **Demographic and health baseline characteristics**

weight group (<15 kg and 15 kg or more) in randomly varying block sizes of two, four, or six. An independent statistician in Blantyre assigned the labels A and B to either the active drug or placebo and oversaw the packaging and coding of sequentially numbered drug envelopes by a pharmacist. When children meeting the enrolment criteria were able to switch to oral medication they were allocated to one of the two study groups by the coordinating clinician in each hospital in order of their study identification number by drawing successive envelopes from the box corresponding to each weight stratum.

## Statistical analysis

A composite endpoint, rather than all-cause mortality only, was used to decrease the sample size needed for a given power by increasing the observed event rate. The individual components were judged to have similar pathophysiological pathways with substantial potential for overlap.[16]

The study was designed to detect a 40% reduction in the cumulative incidence of the primary endpoint from 9·75% in the placebo group to 5·85% in the IPTpd group, with 80% power and a two-sided significance threshold of 5%. The 40% reduction in primary endpoint was based on the average protective efficacy (43%) from four completed studies of intermittent preventive therapy in infants.[17] The anticipated risk of 9·75% in the control group was chosen on the basis of preliminary results of observational studies in Malawi, in which the researchers reported a risk of about 16%.[1] During these studies sulfadoxine–pyrimethamine was the treatment of choice to complete intravenous quinine in hospitals. Malawi changed to artemether–lumefantrine in 2006 because of sulfadoxine–pyrimethamine resistance. We anticipated that recrudescent infection had contributed substantially to morbidity after discharge, therefore we assumed that replacing sulfadoxine–pyrimethamine with artemether–lumefantrine would reduce the risk of morbidity after discharge by 40%, from 16% to 9·75%. Assuming 10% loss to follow-up, the study aimed to recruit 1650 participants (825 patients per group) or until 126 primary events had occurred.

Analysis was stratified by time period (figure 1). We anticipated that artemether–lumefantrine would provide prophylaxis for about 1 month after each course and that children in the IPTpd group would therefore be protected from malaria for the first 3 months after discharge, whereas children in the placebo group, who only received artemether–lumefantrine at discharge, would be protected for 1 month. Because both groups received artemether–lumefantrine at discharge, no effect was expected in the period 0–1 month after discharge. The main treatment effect was anticipated at 1–3 months. However, an extended follow-up period between 4 and 6 months was included in the primary time period of interest, because any potential rebound effect resulting from a delayed acquisition of protective immunity to malaria once the direct pharmacological protective effect has waned, would decrease the public health significance of the intervention. 0–6 months after discharge was also analysed because an IPTpd strategy is likely to be considered for policy only if it substantially adds benefit to the effect of artemether–lumefantrine at discharge.

Furthermore, any intervention starting 1 month after discharge is likely to be arranged with carers around the time of discharge.

Analysis was by intention to treat and done with SAS (version 9.2) and STATA (version 11). The predictive analytics software missing values module was used to create five datasets in which any missing values were imputed with the fully conditional specification, which is an iterative Markov chain Monte Carlo method (ten iterations for each of the five imputations; done with PASW version 18). 13% of parents withheld consent to test their child for HIV; therefore, no HIV status was imputed and a separate category for missing HIV status was used.

The primary analyses included all events.[18] Endpoints with overlap (eg, a child with severe malaria who also had severe anaemia) were counted as a single event. We counted events as distinct if the child had been discharged before the next event and a minimum of 3 days had passed since the diagnosis of the earlier event. We calculated protective efficacy adjusted for prognostic factors at baseline, calculated as 100 multiplied by (1–hazard ratio). Hazard ratios were calculated by Cox regression for repeated events with robust standard error estimation methods to account for correlation between episodes within children. All covariates with a p value less than 0·2 in the univariate Cox-regression models and other potential predictors identified in our previous observational studies[1] were entered into the initial multivariate model. These covariates were maternal education, presence of electricity in the household, number of siblings in household, the child's age, sex, HIV status, use of a bednet, history of previous hospital admissions and blood transfusion, disease severity at admission, presence of malaria parasitaemia and haemoglobin concentrations at randomisation (ie, post-transfusion), and study dose (mg/kg). The unadjusted absolute rate reduction was calculated as incidence in the placebo group minus incidence in the IPTpd group. The adjusted absolute rate reduction was calculated as the adjusted hazard ratio multiplied by incidence per person-year in the placebo group. We also calculated unadjusted incidence rates per person-year. Poisson regression was used to assess the effect of the intervention on anaemia and malaria at the survey at the end of the 6 months observation period and results expressed as adjusted prevalence ratios.

Prespecified subgroup analyses were done to test to what extent the magnitude of treatment effects depended on age, HIV status, and use of insecticide-treated nets, and exploratory subgroup analysis by history of previous hospital admissions, baseline haemoglobin concentration, presence of malaria parasites at randomisation, season, and study site. Because the study was not powered to test effect modification, we used the magnitude of the difference in treatment effect between subgroups as well as the corresponding p value of the interaction terms to analyse interactions. The trial is registered with Current Controlled Trials, number ISRCTN89727873.

| | Placebo | | IPTpd | | PE (%; 95% CI) | p value | ARR |
|---|---|---|---|---|---|---|---|
| | Number of events (number of children) | Incidence per 100 person-years | Number of events (number of children) | Incidence per 100 person-years | | | |
| **Primary endpoint** | | | | | | | |
| 1–6 | 109 (85) | 38·1 | 86 (74) | 30·0 | 21% (–10 to 43) | 0·155 | 8·1 |
| 0–1 | 19 (18) | 33·0 | 21 (19) | 36·2 | –10% (–109 to 41) | 0·742 | –3·2 |
| 1–3 | 58 (49) | 52·3 | 37 (34) | 33·5 | 36% (0·2 to 59) | 0·049 | 18·9 |
| 4–6 | 51 (42) | 29·1 | 49 (45) | 27·8 | 4% (–54 to 41) | 0·859 | 1·2 |
| 0–6 | 128 (101) | 37·2 | 107 (91) | 31·0 | 17% (–14 to 39) | 0·253 | 6·2 |
| **Mortality** | | | | | | | |
| 1–6 | 10 (10) | 3·5 | 9 (9) | 3·1 | 10% (–122 to 63) | 0·821 | 0·4 |
| 0–1 | 6 (6) | 10·4 | 9 (9) | 15·5 | –49% (–327 to 47) | 0·436 | –5·1 |
| 1–3 | 5 (5) | 4·5 | 1 (1) | 0·9 | 80% (–71 to 98) | 0·142 | 3·6 |
| 4–6 | 5 (5) | 2·8 | 8 (8) | 4·5 | –60% (–389 to 48) | 0·410 | –1·7 |
| 0–6 | 16 (16) | 4·7 | 18 (18) | 5·2 | –12% (–120 to 43) | 0·734 | –0·6 |
| **All-cause hospital admission** | | | | | | | |
| 1–6 | 146 (112) | 51·0 | 119 (97) | 41·5 | 19% (–8 to 39) | 0·153 | 9·5 |
| 0–1 | 27 (26) | 46·8 | 33 (32) | 56·8 | –21% (–105 to 27) | 0·449 | –10·0 |
| 1–3 | 76 (64) | 68·6 | 53 (48) | 47·9 | 30% (0·9 to 51) | 0·044 | 20·6 |
| 4–6 | 70 (59) | 39·9 | 66 (59) | 37·5 | 6% (–39 to 37) | 0·746 | 2·4 |
| 0–6 | 173 (131) | 50·3 | 152 (126) | 44·1 | 12% (–14 to 33) | 0·321 | 6·2 |
| **Readmittance because of severe malaria or severe anaemia** | | | | | | | |
| 1–6 | 99 (79) | 34·6 | 79 (68) | 27·5 | 20% (–12 to 44) | 0·195 | 7·0 |
| 0–1 | 13 (12) | 22·5 | 13 (13) | 22·4 | 1% (–118 to 54) | 0·997 | 0·2 |
| 1–3 | 53 (46) | 47·8 | 37 (34) | 33·5 | 30% (–10 to 56) | 0·120 | 14·4 |
| 4–6 | 46 (38) | 26·2 | 42 (38) | 23·8 | 9% (–52 to 46) | 0·718 | 2·4 |
| 0–6 | 112 (89) | 32·6 | 92 (79) | 26·7 | 18% (–15 to 41) | 0·244 | 5·9 |
| **All-cause sick-child clinic visits** | | | | | | | |
| 1–6 | 714 (356) | 249·3 | 695 (350) | 242·3 | 3% (–11 to 15) | 0·695 | 6·9 |
| 0–1 | 115 (106) | 199·5 | 128 (120) | 220·4 | –10% (–46 to 15) | 0·435 | –20·9 |
| 1–3 | 338 (257) | 304·9 | 285 (219) | 257·7 | 15% (–0·2 to 29) | 0·052 | 47·2 |
| 4–6 | 375 (253) | 213·6 | 410 (273) | 232·7 | –9% (–29 to 7) | 0·277 | –19·1 |
| 0–6 | 828 (386) | 240·7 | 823 (374) | 238·6 | 1% (–13 to 12) | 0·923 | 2·0 |
| **Clinical malaria clinic visits** | | | | | | | |
| 1–6 | 371 (238) | 129·5 | 298 (207) | 103·9 | 20% (4 to 33) | 0·017 | 12·8 |
| 0–1 | 50 (49) | 86·7 | 44 (43) | 75·8 | 13% (–34 to 42) | 0·554 | 5·5 |
| 1–3 | 186 (155) | 167·8 | 94 (86) | 85·0 | 49% (35 to 61) | 0·000 | 41·4 |
| 4–6 | 185 (155) | 105·4 | 204 (159) | 115·8 | –10% (–37 to 11) | 0·372 | –5·2 |
| 0–6 | 421 (258) | 122·4 | 342 (228) | 99·2 | 19% (4 to 32) | 0·018 | 11·6 |

Follow-up ranges are months since randomisation. PE computed by univariate Cox regression for repeated events with the exception of the effect on mortality, which included time to first event only. Total number of children at the start of each follow-up period and corresponding follow-up time (in person-days) for 0–1, 1–3, and 4–6 months: placebo, 708 (21 057), 687 (40 490), 669 (64 122); IPTpd, 706 (21 213), 685 (40 396), 669 (64 352). PE=unadjusted protective efficacy. ARR=unadjusted absolute rate reduction per 100 person-years. IPTpd=intermittent preventive therapy post-discharge.

*Table 2:* **Crude incidence per person-year and treatment effect by follow-up**

## Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. KP, FOtK, CK, and BF had full access to all the data in the study. All authors reviewed the manuscript and had final responsibility for the decision to submit for publication.

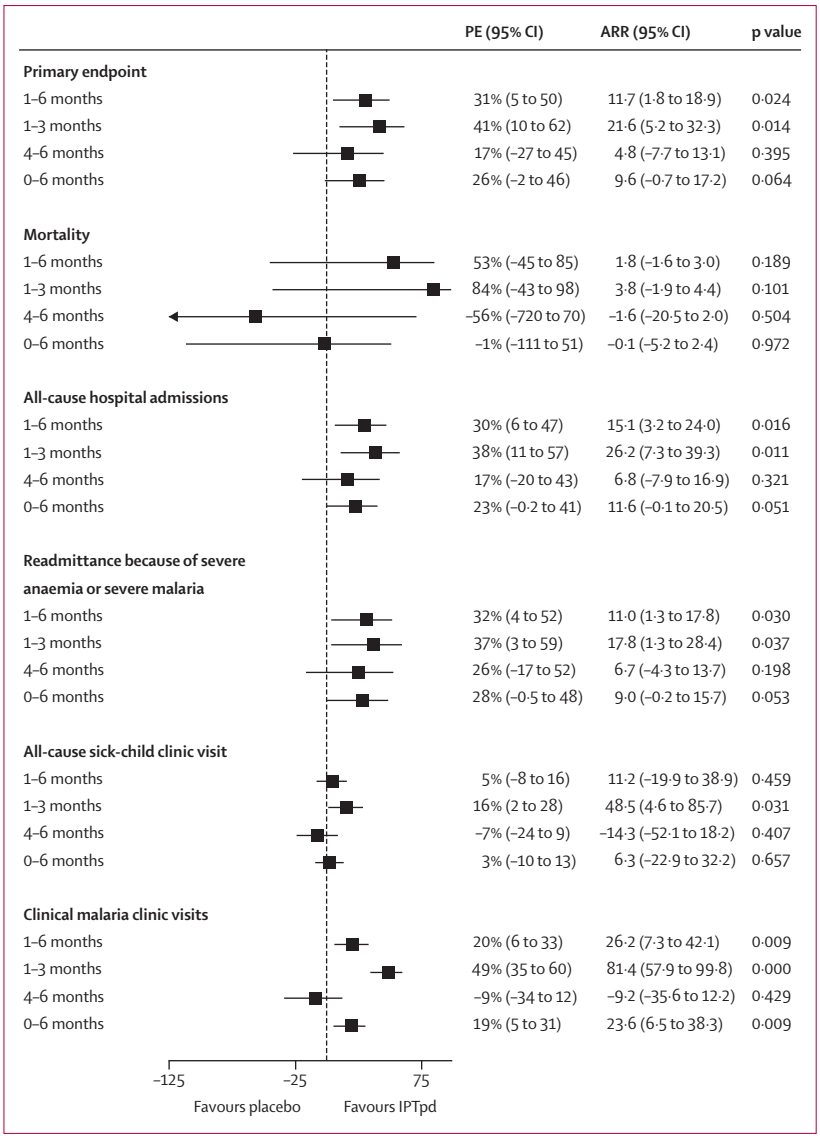



***Figure 3:*** **Adjusted treatment effect by endpoint and time period**
PE=adjusted protective efficacy. ARR=adjusted absolute rate reduction per 100 children years.
*Protective efficacy (1–6 months) for severe anaemia was 25% (95% CI –13 to 50, p 0·165) and for severe malaria 28% (–3 to 50, p=0·072).

## Results

Between June, 2006, and August, 2009 (when the required number of events was reached), 1414 eligible children aged 4–59 months were randomly assigned to receive placebo or intervention (figure 2); 1310 children (93%) completed the 6 months follow-up, and 34 (2%) died during this period. These percentages were much the same in the two groups (figure 2). 15 deaths (44%) occurred within 1 month of discharge. Demographic characteristics were similar between groups, but the occurrence of HIV, cerebral malaria, and some other markers of disease severity were slightly higher in the IPTpd group than in the placebo group (table 1). Only six HIV-infected patients (5%) were receiving co-trimoxazole prophylaxis.

Overall, 192 (14%) of 1414 children had 235 primary events. Between 1 and 6 months after randomisation more primary events had occurred in the placebo group than had in the intervention group (table 2). Adjusted protective efficacy [PE] was 31% (95% CI 5–50); the absolute rate reduction was 11·7 per 100 children years (95% CI 1·8–18·9; p=0·024; figure 3). The protective effect was greatest during the IPTpd period (1–3 months; PE 41%, 95% CI 10–62; p=0·01), but was not sustained after the third month (17%, –27 to 45; p=0–395; figure 3). Inclusion of the pre-IPTpd period showed that IPTpd prevented about one in four primary events up to 6 months (figure 3). The effect did not differ between age groups, by HIV status, bednet use, baseline haemoglobin concentration, or the presence of active malaria infection at enrolment (figure 4).

IPTpd reduced the number of all-cause hospital admissions (figure 3), a result of the reduced admissions because of severe malaria and severe anaemia; mortality was not affected significantly (figure 3). IPTpd also reduced the number of clinic visits resulting from non-severe clinical malaria, which was most evident during the IPTpd period (figure 3). Pooling of artemether–lumefantrine courses showed that episodes of clinical malaria became evident from day 19 after the start of artemether–lumefantrine, with a substantial increase from day 23 onwards. At the final 6 months follow-up visit, treatment groups did not differ for the prevalence of malaria parasitaemia (151 of 653 patients [23%; IPTp] *vs* 162 of 657 patients [25%; placebo]; prevalence ratio [PR] 0·96 [95% CI 0·79–1·16]; p=0·654), moderate anaemia (haemoglobin concentration <8 g/dL; 79 of 653 patients [12%] *vs* 80 of 657 patients [12%]; PR 0·98 [0·73–1·30]; p=0·870), and mean haemoglobin (10·6 g/dL *vs* 10·6 g/dL; adjusted mean difference 0·12 g/dL [95% CI 0·09–0·39]; p=0·291). No drug-related serious adverse events were reported.

## Discussion

Compared with a standard single course of artemether–lumefantrine at discharge, which provides a maximum of 1 month of post-treatment prophylaxis, provision of an additional 2 months of chemoprevention by two full treatment courses of artemether–lumefantrine at 1 month and 2 months after discharge prevented 40% of deaths or hospital admissions because of recurrence of severe anaemia or severe malaria 1–3 months after discharge. IPTpd also halved the number of clinic visits needed because of uncomplicated malaria. The protective effect was not sustained after 3 months, when the direct pharmacodynamic effect of the drugs had waned.[19] No rebound effect occurred in the intervention group in the 4–6 months period, and the overall cumulative protective efficacy up to 6 months, although smaller than that seen at 3 months, was still in favour of IPTpd. Importantly, the beneficial effect of chemoprevention occurred in addition to the effect of untreated or treated nets, consistent with

the effect of seasonal IPT in children[14] and in addition to the initial effect obtained from the first course of artemether–lumefantrine provided at discharge.

The protective effect was much the same irrespective of HIV infection, despite the potentially different aetiology of anaemia, which in HIV-infected children tends to be more related to persistent bone-marrow suppression associated with a chronic state of inflammation.[20,21] HIV-infected and HIV-exposed children were included because antiretroviral therapy and co-trimoxazole prophylaxis in this population were only scaled up to a national level at the end of the recruitment period. Therefore, our data are insufficient to test whether co-trimoxazole prophylaxis had a modifying effect. IPTpd might provide less benefit in children already protected by co-trimoxazole than in those in our study because co-trimoxazole has antimalarial properties and is highly effective for prevention of malaria in HIV-infected adults, children, and pregnant women including in areas with sulfadoxine–pyrimethamine resistance.[22,23]

Intermittent preventive therapy for pregnant women and infants differs from seasonal intermittent preventive therapy in children and IPTpd. The current regimens are two or three courses given over 3–6 months for intermittent preventive therapy in pregnant women and three courses given over 7 months for intermittent preventive therapy in infants, leaving individuals unprotected between doses, which allows reinfection and the acquisition of protective immunity. By contrast, seasonal intermittent preventive therapy for children and IPTpd aim to maintain therapeutic drug concentrations for several months throughout the period of greatest malaria risk. The prophylactic effect is a key component of all these strategies and requires the use of long-acting drugs. Artemether–lumefantrine provided roughly 3 weeks of post-treatment prophylaxis, after which episodes of clinical malaria became apparent. The reduced protection at the end of the month could account for the 50% protective efficacy against clinical malaria during the IPTpd period, which is more modest than the 80–90% reported for a combination of amodiaquine and sulfadoxine–pyrimethamine when used for monthly intermittent preventive therapy in children in the same age group in west Africa,[14] where sulfadoxine–pyrimethamine is still highly effective.[24] The slightly shorter period of post-treatment prophylaxis with artemether–lumefantrine than with sulfadoxine–pyrimethamine is also consistent with the results of comparative trials of amodiaquine–sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine.[10,25,26] We used artemether–lumefantrine because it was the only long-acting drug produced according to good manufacturing standards that was widely available in Malawi and other parts of sub-Saharan Africa, and because high-grade resistance to sulfadoxine–pyrimethamine was widespread in Malawi in 2006. Mefloquine, another long-acting antimalarial, was not used because it is associated with high rates of vomiting in young children.[19,27,28] Dihydroartemisinin–piperaquine had not been assessed for any IPT strategy when the study was designed, but trials of piperaquine have since shown the drug to be very effective for intermittent preventive therapy in children, either as monotherapy or combined with dihydroartemisinin.[29,30]

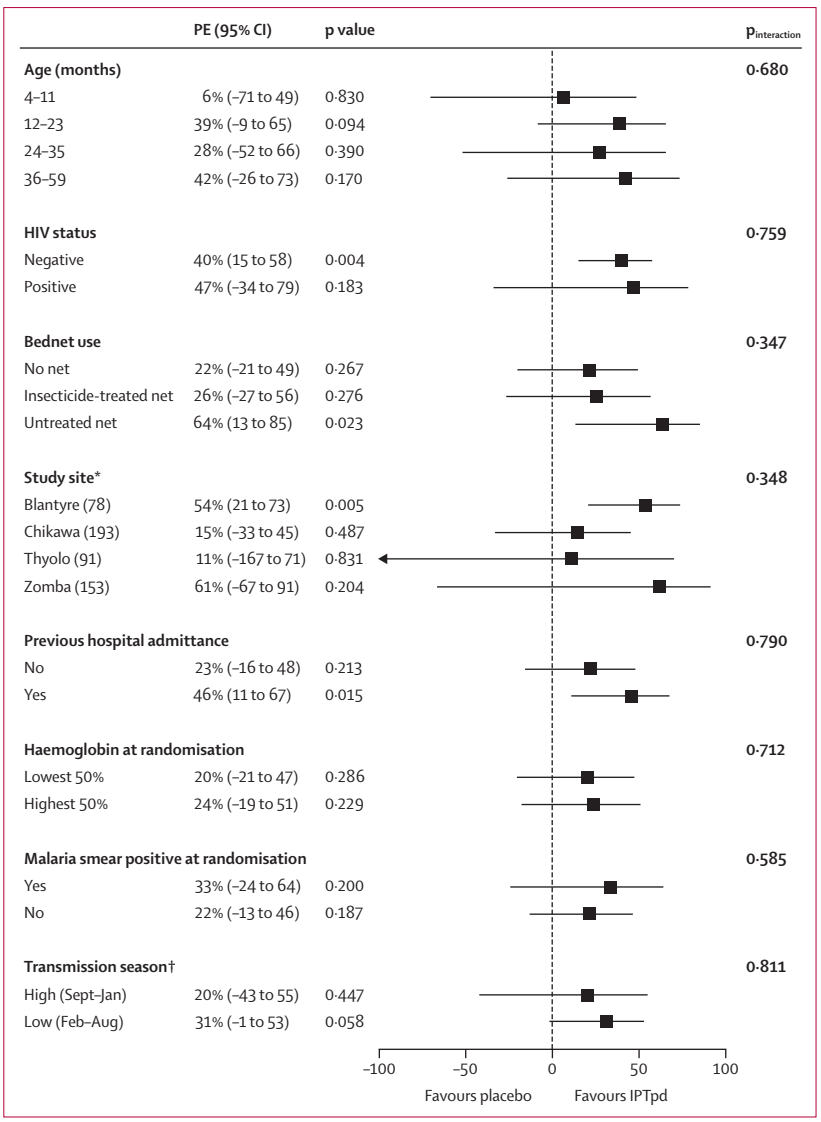



***Figure 4:*** **Subgroup analyses for primary outcome (death or readmittance to hospital for severe malaria or severe anaemia between 1 and 6 months)**

Interaction p values calculated from interaction term Cox regression models. For HIV status, the p value of the interaction term was calculated for the model that excluded children with missing HIV status. *Numbers in parentheses are based on the incidence of clinical malaria recorded in the placebo group in each site, which serves as a proxy indicator of malaria transmission intensity. †Malaria transmission season based on the monthly incidence of clinical malaria in the placebo group.

Five previous trials, two including children with severe anaemia[15,31] and three including children with mild anaemia,[32–34] provide some guidance on the generalisability of our findings (panel). The three trials providing monthly IPT with sulfadoxine–pyrimethamine for mild anaemia each showed that IPT roughly halved the frequency of clinical malaria, as in our trial, but the effect on haematological recovery beyond the effect of a

*Panel:* **Research in context**

**Systematic review**

We searched PubMed up to October 26, 2011 for reports in English (no other restrictions) with the search terms "anaemia" and "malaria", and "children" and "treatment" or "prevention" or "control". This search was supplemented with references obtained from the primary citations. We found no systematic reviews of the control of morbidity or mortality during the management of children with severe malarial anaemia after discharge. Two trials from The Gambia tested the effect of malaria chemoprevention provided during the malaria transmission season on subsequent morbidity in children with severe or moderate to severe anaemia. One was a placebo-controlled trial of children admitted to hospital with severe malarial anaemia (haematocrit <15%) showing that weekly malaria prophylaxis with pyrimethamine–dapsone reduced clinical malaria by 53% and all-cause readmittance by 78% (p=0·02).[31] The second trial assessed monthly sulfadoxine–pyrimethamine during the transmission season, in children with a haemoglobin concentration less than 7 g/dL.[15] Risk of uncomplicated clinical malaria was halved and the incidence of severe anaemia during the rainy season decreased by 78% (p=0·055). Treatment group and bednet use were not related.[6] The rate of readmittance to hospital or deaths in the latter study were lower than those in Malawi and western Kenya, but this could partly be a result of the inclusion of children with moderate anaemia, who constituted about half of the sample.[15] Three other trials provided monthly intermittent preventive therapy with sulfadoxine-pyrimethamine for children with mild anaemia,[32–34] each confirming that intermittent preventive therapy roughly halved the frequency of clinical malaria, but the effect on haematological recovery beyond the effect of a single course of sulfadoxine–pyrimethamine or iron supplementation was small.

**Interpretation**

Children with severe malarial anaemia have a substantially increased risk of subsequent life-threatening morbidity and malaria is an important contributor to morbidity after discharge in this group. Strategies that focus on the adequate treatment and prevention of malaria in the first 3 months after discharge could have a large effect on the risk of readmittance to hospital because of severe malaria or severe anaemia. This effect may be particularly evident in areas with stable perennial malaria transmission, but has also been noted during the rainy season in areas of highly seasonal transmission.

single course of sulfadoxine–pyrimethamine or iron supplementation was small. Thus, IPTpd is likely to be particularly beneficial in severely anaemic children and in settings where malaria is an important contributing factor to severe morbidity after discharge. Although further confirmatory studies are required, our results might also apply beyond areas with moderate to intense perennial malaria transmission and include areas with highly seasonal malaria transmission, such as the Sahel region in west Africa. Two trials in The Gambia (panel) showed that in children with severe malarial anaemia, chemoprevention, as intermittent preventive therapy[15] or prophylaxis,[31] targeted during the malaria transmission season also halved the rate of clinical malaria and in one trial reduced all-cause hospital readmittance by 78%, and in the other trial reduced recurrence of severe anaemia by 78%.

A potential limitation of our study is the focus on children who had severe anaemia and malaria. Although most children admitted to hospital with severe anaemia had malaria, they may have a higher risk of exposure to malaria after discharge than severely anaemic children who do not have concomitant malaria. Thus, whether our findings can be generalised to the latter group is unclear.

Overall, 14% of children had a primary event, confirming the high morbidity and mortality after discharge previously reported.[1] However, in our trial mortality in the placebo group was much lower than that reported for 2002–06 (2% *vs* 8%), likely reflecting the switch from use of sulfadoxine–pyrimethamine to artemether–lumefantrine at discharge and the scale-up of antiretroviral therapies for children with HIV at the end of the study. Another factor is the intensive care provided to children in this study. Therefore, our results might underestimate the true potential effect of IPTpd, because artemether–lumefantrine provided prophylaxis for just less than a month, and because of the high degree of care provided to participants.

The lower than anticipated mortality and the absence of a consistent effect on all-cause mortality also shows the potential limitation of the use of composite endpoints in clinical trials when they include components of unequal clinical importance (eg, mortality *vs* non-fatal hospital admissions) and heterogeneity in treatment effect between these components is observed.[16,35] Analysis of the individual components of our primary endpoint showed that the beneficial effect was largely due to a reduction in hospital admissions because of severe malaria and anaemia. We used the composite endpoints because we anticipated that this would increase the power of the study by increasing the event rates. However, our findings do not show that this occurred, which is consistent with a systematic review[35] of the role of endpoint selection, which reported that trials using composite endpoints are less likely to generate positive results than are those that do not. A possible explanation proposed by the authors is that a disproportionately high percentage (81%) of trials using a composite endpoint include mortality as part of the endpoint, and the mortality endpoints in many trials were associated with negative or neutral results.

Although IPTpd is a relatively simple intervention, its implementation requires appropriate delivery mechanisms. By contrast with intermittent preventive

therapies in infants and pregnant women, which are delivered through the expanded programme on immunisation and antenatal clinics, systems for the delivery of IPTpd would need to be established, as was done for intermittent preventive therapy in children. Studies in rural areas in west Africa have shown that delivery of intermittent preventive therapy to children through community health workers is feasible and well accepted.[36,37] Several countries, including Malawi, have systems of community health workers that could be used to deliver IPTpd or to arrange scheduled visits after discharge to clinics or hospital outpatient departments. One advantage of IPTpd is that it is targeted at a very high-risk group of hospitalised children who have already had contact with the health-care system, providing a potential point of entry. The optimum delivery mechanism could vary with the available health infrastructure and should be explored in future studies, ideally using mobile telephone technology where appropriate.

IPTpd should be assessed in other settings with either regimens of artemether–lumefantrine given every 3 weeks or less frequent regimens of other long-acting artemisinin-based combination therapies. Data are also needed to compare different delivery mechanisms and to test the cost-effectiveness of IPTpd. Although malaria was a major contributor, severe anaemia is often caused by a combination of aetiological factors that result in persistent failure to produce red blood cells. Interventions that target a broader range of aetiologies, including bacterial infections (a major cause of severe anaemia in this group),[11] micronutrient deficiencies, and hookworm,[5] might provide an even greater benefit that can be sustained for longer.[21] Our study clearly shows that a proactive approach to the management of transfused children after discharge could provide important public health benefits. Urgent attention should be given to this neglected issue.

#### Contributors

KP, MBvH, and FOtK conceived the concept of intermittent preventive therapy post-discharge. FOtK, KP, MBvH, and BF designed the study. KP coordinated the field work with support from ME. CK did the analysis with statistical support from BF. KP, MBvH, BF, and FOtK interpreted the data. FOtK and KP wrote the first draft of the manuscript; all authors reviewed and revised the final version.

#### Conflicts of interest

The authors declare that they have no conflicts of interest.

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