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The clinical impact of combining intermittent preventive treatment with home management of malaria in children aged below 5 years: cluster randomised trial

Harry Tagbor[1], Matthew Cairns[2], Emmanuel Nakwa[1], Edmund Browne[1], Badu Sarkodie[3], Helen Counihan[4], Sylvia Meek[4] and Daniel Chandramohan[2]

1 *Department of Community Health, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana*
2 *Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK*
3 *District Health Administration Ejisu-Juaben, Ashanti, Ghana*
4 *Malaria Consortium, London, UK*

Summary

OBJECTIVE To investigate the impact of seasonal intermittent preventive treatment (IPTc) on malaria-related morbidity in children <5 years of age who already had access to home-based management of malaria (HMM) for presumptive treatment of fevers.

METHOD Thirty community-based drug distributors (CDDs) from all 13 communities of a rural sub-district in Ghana were trained to provide prompt treatment for presumptive malaria using artesunate-amodiaquine (AS+AQ) to all children under 5 years of age. Six communities were randomised to also receive bimonthly courses of seasonal IPTc with AS+AQ in May, July and September of 2007. The primary outcome was the incidence rate of febrile episodes diagnosed presumptively as malaria by the CDDs in the communities in each intervention group. Cross-sectional surveys were conducted to determine the prevalence of parasitaemia and anaemia among the study children.

RESULTS During the 6 months in which IPTc was delivered, incidence of fevers in communities given HMM+IPTc was lower than in communities given HMM alone, but this difference was not statistically significant (protective efficacy: 37.0%(95% CI: −9.7 to 63.8; $P = 0.14$). However, incidence of presumptive malaria was significantly lower in IPTc communities when only children who received all three courses of IPTc were included in the analysis: protective efficacy 61.5% (95% CI:31.2–78.5; $P = 0.018$). Protection with IPTc was not followed by rebound morbidity in the following year. At the end of the intervention period, prevalence of asymptomatic parasitaemia was lower in communities that had received IPTc, but there were no differences in anaemia or haemoglobin concentration.

CONCLUSION In this study area, incidence of fevers was lower in communities given three courses of IPTc during the time of peak transmission than in communities that received only HMM. However, high levels of coverage for IPTc will be necessary for maximum impact.

keywords home, management, malaria, intermittent, preventive, treatment

Introduction

WHO (2009) estimates that the global incidence of malaria is between 190 and 311 million cases annually, resulting in approximately 850 000 deaths. Morbidity and mortality from malaria is greatest in sub-Saharan Africa, with children under 5 years of age the most vulnerable group (WHO 2005). A number of strategies are available to help reduce this burden, but there is limited evidence of how effective different interventions are when deployed together.

Home-based management of malaria (HMM) has been recommended by WHO as a means to improve access to prompt and effective antimalarial treatment (Pagnoni 2009). In this strategy, antimalarials are given presumptively by trained members of the community in the case of symptoms suggestive of malaria. HMM reduces the incidence of severe malaria and mortality among children under 5 years (Sirima *et al.* 2003), is acceptable to caregivers and can be implemented widely (Salako *et al.* 2001; Browne 2002). Artemisinin combination therapies (ACTs) can be used for HMM, but there is no current recommendation on which is most suitable (Ajayi *et al.* 2008a,b). However, presumptive diagnosis may lead to over-use of antimalarials, and preventive approaches that can reduce the number of fevers that require treatment may be advantageous.

One preventive strategy that may be of value is intermittent preventive treatment of children (IPTc), which consists of delivery of full therapeutic courses of long-acting antimalarials at intervals to prevent malaria morbidity. IPTc given at the time of seasonal peaks in malaria transmission substantially reduces the incidence of clinical malaria (Cisse *et al.* 2006; Dicko *et al.* 2008; Kweku *et al.* 2008; Sokhna *et al.* 2008; Cisse *et al.* 2009). Most studies have used sulfadoxine-pyrimethamine (SP) as monotherapy either with amodiaquine (AQ) or with artesunate (AS), but AQ+AS has also been used successfully. In Burkina Faso and Mali, seasonal IPTc with SP-AQ was shown to add substantially to the protection from long-lasting insecticide-treated nets (LLINs) (Konaté *et al.*, in press Dicko *et al.*, in press), and to reduce the incidence of severe malaria. However, it is not known if IPTc is of similar value in children who have access to prompt diagnosis and treatment provided via HMM.

In this study, we therefore investigated the potential of seasonal IPTc to reduce the incidence of fevers presumptively diagnosed as malaria when implemented in communities with an existing HMM programme. To attribute effectiveness to the strategy rather than the drug combination used, the same drug combination, AQ-AS, was used for both IPTc and HMM.

Subjects and methods

Study population

The study was conducted among children aged 3–59 months in the Kwaso subdistrict of the Ejisu-Juaben district of the Ashanti Region of Ghana from April 2007 to November 2008. The subdistrict has 13 communities with a total population of 29 362. As in the rest of the district, malaria is hyper-endemic and is the leading cause of outpatient visits, accounting for 44.3% of out patient department visits in the district (Browne *et al.* 2000). It has one health centre but inhabitants can access the services of a nearby district hospital.

Implementation of home management of malaria and IPTc programmes

In March 2007, thirty community members identified by opinion leaders from all 13 communities of the study area were trained and designated as community-based drug distributors (CDDs) to provide HMM. CDDs provided AS+AQ treatment for febrile episodes of under-fives, defined as an illness characterised by a temperature of ≥37.5 °C, or a history of fever within the past 48 h, if there was no other obvious cause for the fever. The CDDs were trained to use a checklist of signs and symptoms of uncomplicated and complicated malaria to make a judgement to treat or to refer the child. They were also trained to correctly measure and interpret axillary temperatures using digital thermometers, to keep records of children consulting using forms designed for that purpose and to properly administer AS+AQ based on age. The research team from the Department of Community Health, KNUST, supplied and supervised use of AS+AQ by CDDs throughout the study period.

After the implementation of HMM in the subdistrict, six communities were randomly selected for administration of IPTc during the malaria transmission season of 2007. The community was the unit of randomisation as effective randomisation of individuals to receive or not receive IPTc would not have been practical in this setting.

Thus, children in seven communities had only HMM for malaria control while those in the remaining six had HMM plus IPTc. CDDs administered only the home management of malaria intervention and played no further role in the study. The IPTc dosing was taken by an independent study team from the Department of Community Health, KNUST, who visited the IPTc communities at scheduled time points to administer IPT.

Follow-up of cohort

A cohort of 1490 children aged 3–59 months randomly selected from community registers was admitted into the study if their parents or guardians gave consent. All children were eligible for enrolment unless they were known to suffer from chronic diseases such as sickle cell disease that might adversely affect the interpretation of study results. All children received AS+AQ treatment for febrile episodes as described earlier; children with signs and symptoms of severe malaria were referred by CDDs to the hospital.

Children living in communities randomised to the HMM + IPTc arm (n = 741) also received up to three courses of AS+AQ for IPTc; the first in May, the second in July and the third in September 2007. Children in the HMM+IPTc communities were not eligible to receive a course of IPTc if they had a temperature of 37.5 °C or above or history of fever in the last 48 h; if they had a clinical condition classified as severe according to IMCI guidelines or if the mother/caregiver did not give or withdrew consent. However, fever was only a temporary exclusion criterion. If a child had fever when he/she was due for an IPTc course, treatment was given for the fever and the IPTc course given 1 month after the fever had subsided.

The same drugs and dosage were used for IPTc as for HMM. Children aged 1–5 years received half a tablet of AS (25 mg) and AQ (75 mg) twice a day for 3 days. Infants received a quarter of a tablet twice a day for 3 days.

Surveillance for malaria and cross-sectional morbidity surveys

Community-based drug distributors kept records of the children who had been presumptively treated for malaria based on clinical symptoms; these were reviewed weekly by a team of field supervisors. The prevalence of parasitaemia, parasite density and anaemia was measured by cross-sectional survey at baseline in April 2007 and at the end of the intervention period in November 2007 in all children regardless of symptoms.

Endpoints

The primary endpoint was incidence rate of febrile episodes presumptively diagnosed as malaria in the study communities. The primary hypothesis under investigation was therefore that presumptively treated fevers would be lower in communities that received IPTc in addition to HMM, assessed at the cluster level.

Secondary outcome measures included the risk of a febrile episode in the study communities (the proportion of children experiencing a febrile episode in each community), the prevalence of peripheral parasitaemia and anaemia at the end of the intervention period in November 2007 in the study communities and the incidence of adverse drug effects within 7 days of treatment.

The aim of this study was to assess the effectiveness of IPTc in communities where HMM was already deployed. Because treatment for febrile episodes was delivered presumptively by members of the community without reference to formal health services or study staff, it was not possible to maintain comprehensive surveillance of adverse events and compliance. AQ-AS is well tolerated when used for treatment of malaria (Brasseur *et al.* 2007); this study therefore focused on assessment of individuals after they received IPTc. A subset of children, approximately 100 in each intervention group, was also assessed for adverse events after treatment for febrile episodes.

Sampling and sample size

Prior to the study, registration of children aged 3–59 months was conducted to obtain a sampling frame from which participants were randomly selected. In the smallest community, 114 children under five were registered.

At the time of designing the study, there was no evidence to inform neither the expected reduction in fevers because of bimonthly AS+AQ for IPTc nor the coefficient of variation in fever incidence. A range of sample size calculations were thus performed. For the final sample size, it was assumed that the incidence rate of febrile episodes in the HMM alone arm would be 0.4 per child per year and the coefficient of variation between communities (k) would be 0.25, i.e. the true incidence rate in the HMM communities would vary between 0.2 and 0.6 episodes per person-year. On the basis of practical and logistical constraints, including the available 13 communities with 114 children per community, and allowing for a loss to follow-up of up to 30%, the study would have 80% power to detect a 45% decrease in the incidence of clinical episodes of malaria per person-year because of IPTc at the 5% two-sided significance level.

Statistical analysis

All analyses were performed in Stata version 10 (StataCorp, College Station, TX, USA). For the primary endpoint of the incidence rate of febrile episodes in study communities, both intention-to-treat (ITT) and according-to-protocol (ATP) analyses were performed. All children enrolled by time of the first survey who were known to remain in the study area were included in the ITT population, regardless of whether they received any courses of IPTc or HMM.

The ATP analyses were based on the number of bimonthly IPTc courses received by children in HMM+IPTc communities. The first dose of each IPTc course was given under the supervision of the study team from KNUST, with the remaining 2 days to be taken at home, delivered by the caregiver. Receipt of the first dose of the bimonthly IPTc course was documented by the study team and was therefore known for all children. ATP analyses were performed for children who received at least one, at least two and all three courses of IPTc from the study team. The effect of IPTc on the primary outcome was assessed over different time periods: the intervention period (April 2007–November 2007), the intervention year (April 2007–April 2008) and the entire study period (April 2007–November 2008). The incidence of febrile episodes in the potential rebound period (the transmission season of the following year, i.e. from April 2008 until November 2008) was also examined.

To take account of the cluster-randomised design, analysis was based on the (unweighted) mean (for continuous variables) or proportion (for binary variables) for each community. Comparison of malaria incidence between the treatment groups was based on a t-test of the

cluster level rates; two-sided 95% confidence intervals were constructed for the rate ratio as described in Bennett *et al.* (2002). Adjustment for covariates pre-specified in the analytical plan (age of the child and sex) was performed by the two-stage method using aggregated residuals from a Poisson regression model fitted to the data for individuals (Bennett *et al.* 2002). Secondary endpoints (risk of a febrile episode over the course of the study, and prevalence of parasitaemia and anaemia, geometric mean parasite density (GMPD) and mean haemoglobin at the survey in November 2007) were also analysed at the cluster level using the *t*-test, with adjustment for age and sex was performed using aggregated residuals from either a logistic (for risk of febrile episode, prevalence of parasitaemia and anaemia) or linear regression model (for GMPD and haemoglobin) fitted to the data for individuals.

Ethics

The study protocol was approved by the Committee on Human Research and Publications Ethics of the School of Medical Sciences, Kwame Nkrumah University of Science & Technology, Kumasi, Ghana. A data safety and monitoring board (DSMB) approved the protocol, standard operating procedures and analysis plan. The purpose of the study and procedures to be undertaken were verbally explained to all caregivers and any questions were answered. Caregivers agreeing for their children to participate signed a written consent form. For caregivers who were not literate, a witness signed on their behalf and they assented.

Results

Participant flow

Thirteen communities were enrolled and randomised to the intervention group (HMM or HMM+IPTc); all remained in the study until its completion. In total, 1490 children were enrolled in April 2007, of whom 1480 attended the baseline survey; 1163 children (554 in the HMM group and 609 in the HMM+IPTc group) formed the ITT population, and 818 children (55%) attended the cross-sectional survey in November 2007, although 1129 children (76%) remained in follow-up at this time. Additional surveys were attended by 780 and 774 children in April and November 2008. Attrition rates were slightly higher in the HMM only group (Fig. 1). Of the 741 children in the IPTc group, 222 (30%) received all three IPTc courses, 268 (36.2%) received two courses, 179 (24.2%) received one course and 72 individuals (9.7%) received no IPT.

Baseline characteristics

The two study groups were similar in terms of the number, age and gender of the children (Table 1). Prevalence of asymptomatic parasitaemia was similar in both groups, 32.3% overall had parasitaemia of any density and 17.8% of children had parasitaemia >1000/μl. *Plasmodium falciparum* was the most prevalent malaria species. Mean haemoglobin level was 10.6 g/dl among the children, similar in both groups. Adjustment for the covariates pre-specified in the analytical plan (age and sex) made only small differences to the treatment effects, and in no case would alter the interpretation. Results in this section show the adjusted estimates.

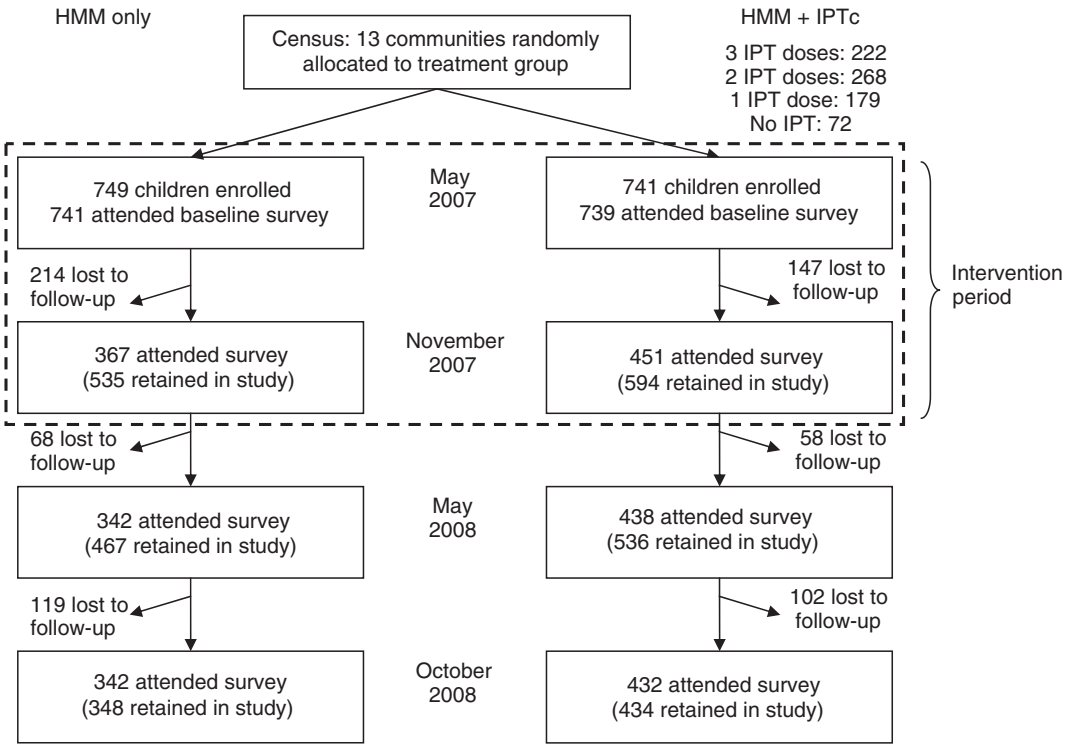
Incidence of febrile episodes

Of the 649 fevers treated during the study period, 190 (29.3%) were based on a measured temperature of 37.5 °C and 459 (70.7%) were based on history of fever within the last 48 h.

During the intervention period, incidence of febrile episodes was lower in the communities that received IPTc than in communities given only HMM, but this was not statistically significant in the ITT analysis: protective efficacy (PE) 36.6% (95% CI: −10.7 to 63.6), $P = 0.14$. However, in the ATP analysis including only children who received all three bimonthly courses of AS+AQ, the incidence of febrile episodes was significantly lower in communities given HMM+IPTc: PE 61.5% (31.2–78.5), $P = 0.018$. Trends indicated a smaller benefit for children who received fewer courses of IPTc (Table 2).

A similar benefit of the intervention in communities given IPTc was seen over the entire year when children who received three courses of IPTc were included; this was of borderline statistical significance: PE 59.7% (−0.5 to 83.8), $P = 0.057$. Findings over the whole study period (April 2007 until November 2008) and the potential rebound period (April 2008 until November 2008) did not indicate higher incidence in children who had received IPT in the year after the intervention (Table 2).

The risk of experiencing at least one febrile episode in the different study periods was similar to those for the analysis of incidence rates (Table 3). In the ITT analysis, there was a non-significant reduction in communities given IPTc; in the per-protocol analyses, there was lower risk of febrile episodes during the intervention period in communities given IPTc when the analysis was restricted to children who received all three IPTc courses: PE 54.6% (95% CI: 22.9–73.2; $P = 0.02$).



Abbreviations: HMM, home management of malaria; IPTc, intermittent preventive treatment in children.

Figure 1 Trial profile. HMM, home management of malaria; IPTc, intermittent preventive treatment in children.

Table 1 Baseline characteristics of study children

Characteristics	HMM	IPTc
Number of children	741	739
Number of clusters	7	6
Mean cluster size (range)	105.9 (52, 148)	123.2 (70, 204)
Mean age in months (SD)	27.5 (15.9)	23.9 (15.3)
Gender, (% male)	47.1 (336/713)	49.6 (357/720
Mean haemoglobin (g/dl)	10.7 (1.33)	10.5 (1.47)
Prevalence of parasitaemia (%)		
>1000/μl	17.1 (125/733)	18.6 (134/721)
Any density	31.4 (230/733)	33.3 (240/721)

IPTc, intermittent preventive treatment of children.

Parasitaemia and anaemia

At the end of the intervention period in November 2007, GMPD was similar in both HMM and HMM+IPTc communities. Prevalence of parasitaemia of any density was lower in the communities that had received IPTc ($P = 0.045$); prevalence of parasitaemia >1000/μl was also lower in IPTc communities but this was not statistically significant (Table 4).

Haemoglobin was similar in both study groups at the end of the intervention period, and prevalence of moderate anaemia was similar. The prevalence of severe anaemia was lower in the IPTc communities (0.4% *vs.* 1.8%), but this was based on a small number of cases and could be because of chance.

Adverse events and compliance

Amodiaquine-artesunate appeared to be well tolerated when used for IPTc (Table 5). The most commonly reported adverse event was dark urine (5.4% of individuals), weakness (3.0%), headache, sleeplessness and itching (all 2.6%). Only three individuals vomited, and only five individuals sought medical attention as a result of their symptoms. The number of assessments of adverse events made after presumptive treatment of febrile episodes was low, but does not indicate any major problems with tolerability (Table 5). Children in the HMM only group reported more adverse events than children in the HMM+IPTc group, notably sleeplessness, weakness and skin rash, and a higher proportion sought medical attention. Given the small numbers, these differences may be attributed to chance.

Table 2 Incidence of febrile episodes

	Febrile episodes	Incidence rate*	Protective efficacy† (%)	*P*-value
Intervention period (k = 0.46)				
HMM only	204	0.763	–	–
IPTc (ITT)	145	0.481	37.0 (−9.7, 63.8)	0.14
IPTc (ATP: ≥1 course)	135	0.483	36.6 (−10.7, 63.6)	0.14
IPTc (ATP: ≥2 courses)	102	0.460	39.9 (−5.5, 65.8)	0.11
IPTc (ATP: 3 courses)	33	0.294	61.5 (31.2, 78.5)	0.018
First year (k = 0.60)				
HMM only	269	0.545	–	–
IPTc (ITT)	198	0.349	35.8 (−38.1, 70.2)	0.25
IPTc (ATP: ≥1 course)	187	0.351	35.3 (−38.9, 69.9)	0.26
IPTc (ATP: ≥2 courses)	148	0.340	37.9 (−37.7, 72)	0.23
IPTc (ATP: 3 courses)	50	0.220	59.7 (−0.5, 83.8)	0.057
Whole study (k = 0.70)				
HMM	380	0.593	–	–
IPTc (ITT)	269	0.374	36.7 (−47, 72.8)	0.29
IPTc (ATP: ≥1 course)	256	0.379	35.7 (−48.8, 72.2)	0.31
IPTc (ATP: ≥2 courses)	206	0.365	38.6 (−46.3, 74.3)	0.27
IPTc (ATP: 3 courses)	72	0.256	57.0 (−0.8, 81.7)	0.094
Rebound Period (k = 1.03)				
HMM only	112	0.752	–	–
IPTc (ITT)	71	0.460	37.6 (−118.8, 82.2)	0.46
IPTc (ATP: ≥1 course)	69	0.473	35.6 (−125.4, 81.6)	0.48
IPTc (ATP: ≥2 courses)	58	0.439	40.4 (−107.9, 82.9)	0.42
IPTc (ATP: 3 courses)	22	0.361	51.3 (−68.6, 85.9)	0.29

HMM, home management of malaria; IPTc, intermittent preventive treatment in children; k, coefficient of variation; ITT, Intention-to-treat analysis; ATP, according-to-protocol analysis. For the ATP analysis, the number of courses of IPTc received are indicated (one or more courses, two or more courses, all three courses).
*Mean incidence rate across cluster summaries, per person year at risk.
†Adjusted for age and sex.

Self-reported compliance among the children who received AS-AQ for IPTc was very high: 99% reported that the prescribed 3-day treatment course had been completed without any problems and had no remaining tablets. Compliance with AS-AQ given as HMM in the IPTc group was 93%. For both IPTc and HMM in the IPTc group, the most common reason given for not completing the course of AS-AQ was that the child vomited (0.7% and 5.6%, respectively). Children in the HMM only group reported lower compliance after treatment of febrile episodes (67%), with refusal being the main reason for non-compliance (26/117, 22%). However, the number of children assessed after treatment was low.

Discussion

This study evaluated the impact of delivering seasonal IPTc in communities already using home management of malaria. The incidence of febrile episodes was lower in the communities where seasonal IPT was delivered during the peak in transmission in addition to HMM, but the difference was not statistically significant in the analysis by ITT. However, when the analysis was restricted to children who received all three bimonthly IPTc courses from the study team, incidence of febrile episodes was substantially lower in the IPTc communities than in those given only HMM. These benefits are still apparent over the course of a calendar year. The remaining ATP analyses indicate a smaller benefit for those who received fewer IPTc courses. Similar findings were seen for the proportion of children experiencing at least one febrile episode during the different study periods. It therefore appears that IPTc is of value in reducing the number of fevers that must be managed in the community, but that high coverage will be necessary for maximum impact.

At the end of the intervention period, overall prevalence of parasitaemia was lower in communities that had received IPTc. Seasonal IPT was not associated with higher levels of haemoglobin or lower prevalence of moderate anaemia. The point estimate for severe anaemia was lower

Table 3 Risk of a febrile episode

	Risk (%)	Protective efficacy	*P*-value
Intervention period			
HMM only	30.4		–
IPTc (ITT)	21.0	31.6 (−12.6, 58.4)	0.162
IPTc (ATP: ≥1 course)	20.7	32.3 (−10.9, 58.7)	0.148
IPTc (ATP: ≥2 courses)	20.2	34.3 (−8.3, 60.1)	0.132
IPTc (ATP: 3 courses)	13.9	54.6 (22.9, 73.2)	0.020
First year			X
HMM only	35.5		–
IPTc (ITT)	25.6	28.6 (−35.2, 62.3)	0.278
IPTc (ATP: ≥1 course)	25.4	29.1 (−33.3, 62.3)	0.260
IPTc (ATP: ≥2 courses)	25.1	30.6 (−33.6, 63.9)	0.260
IPTc (ATP: 3 courses)	18.6	48.2 (−12.2, 76.1)	0.078
Whole study			X
HMM only	42.5		–
IPTc (ITT)	31.7	26.1 (−41.4, 61.4)	0.352
IPTc (ATP: ≥1 course)	31.6	26 (−40.3, 60.9)	0.346
IPTc (ATP: ≥2 courses)	30.6	28.9 (−36.3, 62.9)	0.308
IPTc (ATP: 3 courses)	25.6	40.3 (−16.1, 69.3)	0.148
Rebound period			X
HMM only	23.1		–
IPTc (ITT)	14.1	38.3 (−117.3, 82.5)	0.447
IPTc (ATP: ≥1 course)	14.4	36.8 (−121.6, 81.9)	0.464
IPTc (ATP: ≥2 courses)	13.3	41.7 (−99.7, 83)	0.399
IPTc (ATP: 3 courses)	11.7	49.6 (−71.1, 85.1)	0.319

HMM, home management of malaria; IPTc, intermittent preventive treatment in children; *k*, coefficient of variation; ITT, Intention-to-treat analysis; ATP, according-to-protocol analysis. For the ATP analysis, the number of courses of IPTc received are indicated (one or more courses, two or more courses, all three courses). Coefficient of variation (*k*): intervention period, 0.39; first year, 0.47; whole study, 0.51; rebound period, 1.04.

in the communities that had received IPTc, which could be important; however, the number of cases in this study is too small to draw robust conclusions about this endpoint.

Among the children who were assessed, AS+AQ appeared to be well tolerated when used for IPTc. There were no serious adverse events considered to be linked to the treatment. This agrees with previous use of AS+AQ for IPTc (Kweku *et al.* 2008; Sokhna *et al.* 2008). Although the number of assessments were low, AS-AQ was well tolerated when used for case management, which is compatible with previous studies that have shown it to be safe and efficacious (Brasseur *et al.* 2007). Relatively few individuals received all three bimonthly courses of IPTc from the study team, but compliance with the prescribed 3-day course of AS+AQ was generally good. There were apparent differences in compliance between treatment groups when AS+AQ was used for case management, but these results are based on a low number of assessments and could therefore be because of chance.

Limitations

Incidence of febrile episodes was highly variable between study communities and loss to follow-up in the study cohort was greater than anticipated. Consequently, this study is underpowered to detect an effect of the magnitude used in the sample size calculations. Using standard methods for cluster randomised trials (Hayes & Bennett 1999), the actual power of the study is estimated as approximately 32% to detect a reduction of 45% in incidence of fevers during the intervention period (when $k = 0.46$) and only 20% to detect a reduction in this size during the entire first year of the study (when $k = 0.6$). Additionally, the impact of the intervention was slightly smaller than expected (35.8% reduction in fevers over the first year compared to 45%). Results of other studies using AS-AQ for IPTc that could have informed the estimate of the treatment effect were not available at the time this study was planned (Kweku *et al.* 2008). Furthermore, by

Table 4 Prevalence of peripheral parasitaemia and anaemia at end of intervention period

	HMM	IPTc	*P*-value*
Mean haemoglobin (g/dl), (SD)	10.92 (0.39)	11.02 (0.42)	0.49
Prevalence of anaemia (%)			
Moderate (hb < 11 g/dl)	47.2	46.4	0.67
Severe (hb < 7 g/dl)	1.75	0.44	0.067
Geometric mean parasite density (per μl)	8703.9	6661.3	0.93
Prevalence of parasitaemia (%)			
>1000/ul	20.4	14.9	0.15
Any density	41.2	29.2	0.045

HMM, home management of malaria; IPTc, intermittent preventive treatment in children. *Adjusted for age and sex. Intra-class correlation coefficient (ratio of between-cluster variance to total variance) for haemoglobin, 0.05; parasite density, 0.04. Coefficient of variation (*k*): moderate anaemia, 0.23; parasitaemia > 1000/μl, 0.23; any parasitaemia, 0.19.

Table 5 Adverse events reported after intermittent preventive treatment of children (IPTc) and home-based management of malaria (HMM)

	Prevention	Treatment	
	IPTc	HMM	IPTc
Adverse event	(*N* = 429)	(*N* = 86)	(*N* = 64)
Dark urine	5.4 (23)	4.7 (4)	0 (0)
Dizziness	0.9 (4)	1.2 (1)	3.1 (2)
Dysphagia	0 (0)	0 (0)	0 (0)
Headache	2.6 (11)	1.2 (1)	6.3 (4)
Itching	2.6 (11)	1.2 (1)	1.6 (1)
Jaundice	0 (0)	2.3 (2)	0 (0)
Nausea	0.5 (2)	1.2 (1)	0 (0)
Palpitation	0 (0)	0 (0)	0 (0)
Skin rash	1.4 (6)	7.0 (6)	0 (0)
Sought medical attention	1.2 (5)	4.7 (4)	3.1 (2)
Sleeplessness	2.6 (11)	15.1 (13)	3.1 (2)
Sore mouth	0 (0)	0 (0)	4.7 (3)
Vomiting	0.7 (3)	2.3 (2)	0 (0)
Weakness	3.0 (13)	7.0 (6)	3.1 (2)
Other	2.1 (9)	1.2 (1)	1.6 (1)

randomising a small number of clusters to the two intervention groups, the impact of individual clusters on the estimate of the intervention effect is larger than would be the case with a large number of smaller clusters. In this study, a single community in the HMM only group recorded a very low incidence of fevers (during the intervention period, the incidence rate was 0.17 episodes per child year; fewer than 8% of individuals experienced fever). In a subanalysis with this cluster removed, PE in the ITT population during the intervention period was 44.2% (8.5–66); $P = 0.03$.

Although it is possible that one outlying community affected the ITT analysis, this subgroup analysis cannot be given the same emphasis as those pre-specified in the analytical plan. In the ITT analysis, the point estimate was consistent with a benefit of IPTc, which given the issues of study power may reflect a true and potentially important impact of IPTc. A statistically significant reduction in febrile episodes was seen among children who received all three courses of IPTc from the study team, which is biologically plausible because these individuals would have the highest level of protection from IPTc. However, this association may be partially because of confounding if the particular individuals who received all three courses are at lower overall malaria risk. This would be plausible if individuals living in outlying rural areas, who are likely to have been at higher risk of malaria than those living in the villages, were more difficult for the study team to contact to deliver IPTc. This possibility may be supported by the finding that during the potential rebound period (April 2008–November 2008), incidence of febrile episodes in the group of children who had taken three bimonthly courses of IPTc remained lower than among other children, despite there being no possibility of residual protection from the drugs given for IPTc in the previous year.

A further limitation is that the use of presumptively treated fevers as the primary endpoint in this study is unlikely to be specific. Misclassification of non-malaria fevers as presumptive malaria could have diluted the treatment effect because IPTc will be less effective at reducing overall incidence of fevers than at reducing true cases of malaria. However, if receipt of IPTc prevented individuals seeking HMM from the CDD, this may have exaggerated the benefit of IPTc. Repeating this study with a more specific endpoint (e.g. providing rapid diagnostic tests (RDTs) for diagnosis of malaria in addition to febrile symptoms) might help to answer these questions without dramatically altering the conditions from those that would occur if IPTc was implemented alongside HMM in this setting. Incorporation of RDTs may be a sensible future step for HMM programmes in any case for other reasons, discussed later.

Interpretation

The finding that seasonal IPTc adds to the benefit of HMM is plausible because although post-treatment prophylaxis after HMM will prevent malaria episodes, it can only do so once children have received presumptive treatment for fever. Conversely, IPTc can prevent first malaria episodes by providing prophylaxis before children become unwell. This result agrees with a growing evidence base that seasonal IPT is a safe and effective means to reduce the burden of malaria in areas with high and seasonal transmission (Cisse *et al.* 2006, 2009; Dicko *et al.* 2008; Kweku *et al.* 2008; Sokhna *et al.* 2008). In this study, significant protection was only seen in children who had received all three IPT courses, underscoring the importance of achieving high IPTc coverage for maximum impact. Coverage of three IPTc courses in this setting was not high, around 30%, despite having been delivered over a short period by a well-trained study team. This suggests that centralised delivery of IPTc may not be a particularly successful means to achieve high coverage. Better coverage of seasonal IPT has been achieved elsewhere using community-based delivery (Cisse *et al.* 2009; Kweku *et al.* 2009), which may be preferable because if a child is absent at the time scheduled to receive IPTc, they can more easily be retreated when they return to the community, something that was not possible with the approach used in this study. Whatever delivery system is ultimately chosen for

IPTc will need to achieve high and equitable coverage, particularly for highly exposed individuals without good access to treatment.

IPTc reduced fevers by 37% during the intervention period and 35% over the first year. As discussed previously, the trial was underpowered to detect effects of this magnitude. Assuming that a larger study would have detected these as true differences, these reductions are not trivial, particularly given that this study took place under conditions that may provide a realistic estimate of the impact of implementing IPTc in practice. A PE of 35% would have important benefits because of the high incidence rate of fevers in the study area (0.76 per child year in the HMM only group): a substantial number of presumptive treatments would be averted by the use of IPTc. The prevention of a large number of infections through combined chemoprevention strategies may also affect transmission at the population level, though this requires further investigation.

The drugs for IPTc and HMM need to be separate, to avoid both accelerated development of drug resistance and toxicity issues with children receiving multiple courses of the same drug combination (Alexander *et al.* 2007). For this reason alone, further studies of tolerability of HMM+IPTc will be necessary. To inform policy decisions, surveillance of adverse events and compliance may need to be more rigorous than the approach used here. Long-acting drugs are essential for maximum efficacy in IPTc, because prophylaxis is an important component of the protection provided by IPT (Cairns *et al.* 2008; May *et al.* 2008). Two possible options that could be used for HMM and IPTc if implemented together are (i) SP+AQ for IPTc and dihydroartemisinin-piperaquine (DHA+PQ) for HMM or (ii) SP-piperaquine (SP+PQ) for IPTc and AS+AQ for HMM. Artemether-lumefantrine could also be used for HMM as the cost has now decreased substantially, although it is not as long-acting as AS+AQ or DHA-PQ (Tarning *et al.* 2008; Mwesigwa *et al.* 2010). SP-PQ may be more suited to IPTc as both drugs are longer acting and better tolerated than AQ (Sokhna *et al.* 2008; Cisse *et al.* 2009); however, there is understandable concern about using piperaquine outside the currently formulated ACT; option (i) may therefore be most likely to be implemented. In either case, using a non-ACT combination for prevention would reduce the number of individuals that require an ACT for management of fever, reducing drug pressure on the ACT. Both HMM and IPTc strategies would be aided by development of a 1 day rather than a 3 days course.

Regardless of the drug combination chosen for HMM and IPTc, WHO now recommends that diagnosis by RDT or blood smear is undertaken before prescribing an antimalarial in all situations where this is possible to avoid accelerating the development of resistance to the ACTs currently in use for case management (WHO 2009). If RDTs can be incorporated successfully into the HMM package, and if drug distributors can be trained to trust their results, this could minimise over diagnosis and increase the proportion of non-malaria fevers that are appropriately treated with other medications. Preventing malaria using IPTc with a non-ACT combination and improving diagnosis with RDTs could be two approaches to reduce drug pressure on ACTs. Additionally, introduction of RDTs could allow HMM to continue to play a major role in ensuring access to prompt and effective treatment in areas where transmission is low and where presumptive treatment is not appropriate.

Conclusion

This study indicates that there may be an important additional benefit in including seasonal IPT in communities where home management of malaria programmes are in place. However, further studies are needed to confirm the usefulness of chemoprevention in children who already have access to prompt and effective treatment for fevers presumed to be malaria.

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Corresponding Author **Harry Tagbor,** Department of Community Health, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, P.O. Box UP 861, Kumasi, Ghana. E-mail: Harry.Tagbor@lshtm.ac.uk