Delivery effectiveness of and adherence to intermittent preventive treatment for malaria in pregnancy with dihydroartemisinin–piperaquine with or without targeted information transfer or sulfadoxine–pyrimethamine in western Kenya: a three-armed, pragmatic, open-label, cluster-randomised trial

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Summary

Background High-level resistance to sulfadoxine–pyrimethamine threatens the efficacy of WHO-recommended intermittent preventive treatment in pregnancy (IPTp) with single-dose sulfadoxine–pyrimethamine to prevent malaria. Monthly IPTp with dihydroartemisinin–piperaquine, a 3-day regimen, is an emerging alternative, but this regimen poses potential implementation and adherence challenges. We aimed to assess adherence to a multiday IPTp with dihydroartemisinin–piperaquine regimen and its delivery effectiveness in routine antenatal care settings in western Kenya.

Methods We conducted a pragmatic, three-armed, open-label, cluster-randomised trial in antenatal clinics in 18 health-care facilities (six facilities per group) in Kisumu County and Homa Bay County in western Kenya. Clusters were facilities offering routine antenatal care services provided by trained Ministry of Health staff with 100 or more antenatal clinic attendances per month between July, 2018, and June, 2019. Private or mission hospitals, dispensaries, referral hospitals, and trial sites were excluded. Individuals in their first trimester, living with HIV, or who were not attending a scheduled antenatal clinic visit were excluded. The 18 antenatal clinics were grouped into matched triplets stratified by location and clinics in each matched triplet were randomly assigned to one of the three study groups (1:1:1). Masking was not possible. Two groups were given IPTp with dihydroartemisinin–piperaquine (one group with a targeted information transfer intervention and one group without any additional interventions) and one group was given the standard of care (ie, IPTp with sulfadoxine–pyrimethamine). The primary endpoint, adherence, was defined as the proportion of participants completing their most recent 3-day IPTp with dihydroartemisinin–piperaquine regimen. This completion was verified by pill counts during home visits no more than 2 days after participants' 3-day regimens ended. The secondary endpoint, delivery effectiveness, was defined as the proportion of participants who received the correct number of IPTp tablets and correctly repeated dosing instructions (ie, correctly recalled the instructions they received about self-administered dihydroartemisinin–piperaquine doses and the number of sulfadoxine–pyrimethamine tablets they had received) at their exit from the antenatal clinic. Individuals receiving treatment for malaria, visiting a clinic for registration only, or interviewed during IPTp drug stock-outs were excluded from analyses. We used generalised linear mixed models to compare endpoints among the IPTp with dihydroartemisinin–piperaquine groups. This trial was registered with ClinicalTrials.gov, NCT04160026, and is complete.

Findings 15 facilities (five per group) completed the trial, with 1189 participants having exit interviews (377 in the IPTp with sulfadoxine–pyrimethamine group, 408 in the IPTp with dihydroartemisinin–piperaquine only group, and 404 in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group) and 586 participants having home visits (267 in the IPTp with dihydroartemisinin–piperaquine only group and 319 in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group) from Sept 8 to Dec 10, 2020. Relative to the IPTp with dihydroartemisinin–piperaquine only group, adherence was 16% higher in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (266 [83%] of 319 participants *vs* 196 [73%] of 267 participants; adjusted relative risk [RR] 1·16, 95% CI 1·03–1·31; p=0·0140). Delivery effectiveness in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group was not significantly different from that in the IPTp with sulfadoxine–pyrimethamine group (352 [87%] of 403 participants *vs* 335 [89%] of 375 participants; adjusted RR 0·97, 95% CI 0·90–1·05; p=0·4810). However, delivery effectiveness in the IPTp with dihydroartemisinin–piperaquine only group was significantly lower than in the IPTp with sulfadoxine–pyrimethamine group (300 [74%] of 404 participants *vs* 335 [89%] of 375 participants; 0·84, 0·75–0·95; p=0·0030).

Lancet Glob Health 2024; 12: e1660–72

See **Comment** page e1569

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Interpretation Targeted information transfer interventions to health-care providers and pregnant individuals boost antenatal care delivery adherence to a multiday regimen with dihydroartemisinin–piperaquine.

Funding European and Developing Countries Clinical Trials Partnership 2, UK Joint Global Health Trials Scheme of the Foreign, Commonwealth and Development Office, Medical Research Council, National Institute for Health and Care Research, and Wellcome Trust; and Swedish International Development Cooperation Agency.

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Research in context

Evidence before this study

Highly resistant malaria parasites emerging in east and southern Africa threaten the efficacy of monthly intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine. Dihydroartemisinin–piperaquine, an artemisinin-based combination therapy antimalarial, is the most promising candidate to replace sulfadoxine–pyrimethamine for IPTp. Unlike the single-dose, single-day, monthly regimen for IPTp with sulfadoxine–pyrimethamine that can be delivered via directly observed therapy (DOT) to ensure complete adherence, IPTp with dihydroartemisinin–piperaquine comprises one dose per day over 3 days as a monthly regimen. Only the first dose is given via DOT, and the subsequent two doses are self-administered at home. However, even delivery of a simple regimen such as that for IPTp with sulfadoxine–pyrimethamine has faced health system challenges, with low coverage of three or more doses across sub-Saharan Africa. A shift to a monthly 3-day regimen for IPTp with dihydroartemisinin–piperaquine will be more complicated for the health system to deliver. Furthermore, women's adherence to these multiday IPTp regimens in routine antenatal care settings is unknown. We searched electronic literature with the following search terms: "Intermittent" AND "prevent*" AND "treat*" AND "dihydroartemisinin piperaquine" AND "pregnan*" AND "adherence". We searched PubMed, Web of Science, ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform, and the Malaria in Pregnancy Library (containing references from Web of Knowledge, SCOPUS, CINAHL, Bioline, the Cochrane Library databases, WHO Global Health Library, grey literature, and conference abstracts) from the inception of the databases to April 14, 2024, but did not find similar studies. No language restrictions were used. However, a feasibility study of intermittent screening and IPTp with dihydroartemisinin–piperaquine in antenatal clinics in government health facilities providing routine antenatal care in western Kenya, in which women only received dihydroartemisinin–piperaquine when testing positive for malaria, showed that 71% of women who tested positive received the correct treatment and only 6% received counselling on how to take the subsequent doses at home. In addition, an acceptability study in the context of an adjacent parallel clinical trial of intermittent screening and IPTp with dihydroartemisinin–piperaquine (NCT01669941) showed that health providers were unconvinced women would adhere to multiday regimens in non-trial settings. The authors concluded that targeted interventions would be needed to optimise health provider practices and support adherence. A meta-analysis of 31 studies in sub-Saharan Africa and southeast Asia showed that good provider practices in public hospitals, such as clear dosing instructions and prescribing the exact number of tablets, were associated with 71% adherence to 3-day artemisinin-based combination therapies.

Added value of this study

This trial is the first study to assess adherence to a complex multiday IPTp with dihydroartemisinin–piperaquine regimen and the delivery effectiveness of this regimen in routine care settings. In anticipation of poor adherence and informed by previous studies, we included two IPTp with dihydroartemisinin–piperaquine groups, one with the addition of a targeted information transfer intervention. We hypothesised that a targeted information transfer intervention (ie, a package of training and information, education, and communication tools to support providers and users) would improve both women's adherence to and the effectiveness of antenatal clinics in delivering IPTp with dihydroartemisinin–piperaquine. Overall, adherence and delivery effectiveness were high enough to support a regimen change should IPTp with dihydroartemisinin–piperaquine prove more efficacious in preventing malaria than IPTp with sulfadoxine–pyrimethamine. The targeted information transfer intervention further boosted adherence to the IPTp with dihydroartemisinin–piperaquine regimen and enhanced antenatal clinics' delivery effectiveness for IPTp with dihydroartemisinin–piperaquine, achieving similar levels of delivery effectiveness as for IPTp with sulfadoxine–pyrimethamine (the standard of care).

Implications of all the available evidence

Areas with high-grade parasite resistance to sulfadoxine–pyrimethamine will probably need to consider alternative drugs or drug combinations with more complex, multiday regimens. This study shows that implementing a complex multiday IPTp with dihydroartemisinin–piperaquine regimen with both high adherence and high delivery effectiveness is feasible. Additional support with targeted information transfer interventions to providers and users further boosts adherence and the delivery effectiveness of antenatal clinics for multiday IPTp with dihydroartemisinin–piperaquine.

Introduction

Malaria in pregnancy is associated with adverse pregnancy outcomes, including low birthweight, preterm delivery, intrauterine growth restriction, and increased risk of fetal, neonatal, and childhood mortality.[1,2] Annually, without pregnancy-specific malaria interventions, an estimated 961 000 infants with low birthweight could result from 13·3 million malaria-exposed pregnancies in the WHO African region.[3] WHO recommends monthly chemoprevention in the second and third trimesters through intermittent preventive treatment in pregnancy (IPTp) with monthly sulfadoxine–pyrimethamine in HIV-negative women.[3] The efficacy of sulfadoxine–pyrimethamine in east and southern Africa is threatened by increasing parasite resistance.[4] IPTp with dihydroartemisinin–piperaquine, an artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria,[5] has emerged as an alternative to IPTp with sulfadoxine–pyrimethamine.[6–10] Other alternatives, including mefloquine, chloroquine–azithromycin, and amodiaquine, were either poorly tolerated or not superior to IPTp with sulfadoxine–pyrimethamine in preventing malaria.[11]

A policy switch from IPTp with sulfadoxine–pyrimethamine to IPTp with dihydroartemisinin–piperaquine poses health system and adherence challenges. The health system has been geared towards IPTp with sulfadoxine–pyrimethamine in malaria-endemic regions of Kenya since 1998, yet coverage has remained suboptimal.[3,12,13] Despite its recommended administration as a single-dose, single-day regimen via directly observed therapy (DOT) at an antenatal clinic to ensure complete adherence, only 40–57% of women received sulfadoxine–pyrimethamine through DOT in western Kenya between 2010 and 2015.[13,14] Replacement of sulfadoxine–pyrimethamine with dihydroartemisinin–piperaquine could further undermine IPTp coverage. First, dihydroartemisinin–piperaquine is currently used for treatment, meaning its prescription for prevention would be a new indication in routine antenatal care settings. Second, although IPTp with sulfadoxine–pyrimethamine is given as a regimen of three tablets taken once a day via DOT, IPTp with dihydroartemisinin–piperaquine has a 3-day, weight-based regimen with only the first dose given via DOT and subsequent doses self-administered at home.[5] In a study in western Kenya, published in 2016, in which women received 3-day treatment with dihydroartemisinin–piperaquine after a positive malaria test,[15] providers were unconvinced that otherwise healthy women in non-trial settings would adhere to a 3-day regimen for prevention; pregnant individuals, including those who reported full adherence, also found adherence challenging. When the feasibility of the same intervention was assessed in routine antenatal care settings, 71% of women with positive malaria tests received the correct treatment, and only 6% received adequate counselling for subsequent self-administered doses of dihydroartemisinin–piperaquine.[14] Targeted interventions aimed at providers and pregnant individuals (such as training, supervision, and group problem-solving)[16] could improve provider practices and adherence.[14]

This study was conducted in western Kenya, an area with high-grade resistance to sulfadoxine–pyrimethamine and in which 27% of women are infected with malaria at their first visit to an antenatal clinic. 97·3% of *Plasmodium falciparum* parasites in western Kenya carry quintuple *dhfr* and *dhps* mutations (resulting in high resistance to sulfadoxine–pyrimethamine) and 10·8% of parasites carry sextuple *dhfr* and *dhps* mutations (resulting in very high resistance to sulfadoxine–pyrimethamine).[17] We aimed to assess the delivery effectiveness of IPTp with dihydroartemisinin–piperaquine in routine antenatal care settings and women's adherence to a weight-based, multiday IPTp with dihydroartemisinin–piperaquine regimen in western Kenya, both with and without a targeted information transfer intervention. The targeted information transfer intervention consisted of a package of enhanced training and information, education, and communication tools (ie, job aids) for health providers and pregnant women to improve IPTp with dihydroartemisinin–piperaquine uptake and adherence. Although IPTp involves the delivery of monthly IPTp courses in the second and third trimesters, we assessed delivery effectiveness and adherence to a single IPTp course in this study.

Methods

Study design and participants

From Nov 11, 2019, to Dec 10, 2020, we conducted a three-armed, pragmatic, open-label, cluster-randomised trial in antenatal clinics in 18 health facilities (four level 3 facilities [ie, health centres] and 14 level 4 facilities [ie, subcounty hospitals, formerly known as district hospitals]) in Kisumu County (n=9) and Homa Bay County (n=9) in western Kenya (appendix 1 p 9). The trial had a 10-month implementation phase and an endline evaluation that included antenatal clinic exit interviews and home visit follow-ups in the final 4 months (ie, from Sept 8 to Dec 10, 2020). This trial was conducted parallel to an individually randomised clinical trial to compare IPTp with dihydroartemisinin–piperaquine (with or without azithromycin) with IPTp with sulfadoxine–pyrimethamine (ie, the standard of care).[17] The clusters were health facilities that had more than 100 antenatal clinic attendances per month between July, 2018, and June, 2019;[18] offered routine antenatal services (including IPTp with sulfadoxine–pyrimethamine) provided by trained Ministry of Health (MoH) staff; and received sulfadoxine–pyrimethamine through MoH central medical stores. Private or mission hospitals, level 2 health facilities (ie, dispensaries) and level 5 health facilities (ie, referral hospitals), and facilities enrolled in

See Online for appendix 1

the IMPROVE trial[17] were excluded to ensure a similar standard of antenatal clinic across clusters. Pregnant individuals in their first trimester, living with HIV, or who were not attending a scheduled antenatal clinic visit were excluded. Recruitment stopped once the minimum number of study participants (ie, 1000 exit interviews [n=333 per group] and 500 home visits [n=250 per group]) had been exceeded and all efforts to achieve the maximum sample size (1400 exit interviews [n=467 per group] and 700 home visits [n=350 per group]) had been made based on feasibility (budget and time). Participants' gestational ages, dates of last clinic visits, and HIV test results were recorded by antenatal clinic staff in mother–child health handbooks and were accessed by research staff to confirm participants' eligibility criteria. Endpoints were assessed during exit interviews with pregnant individuals attending a scheduled antenatal clinic visit at a study facility in their second or third trimester and during subsequent home visits.

This trial received ethical approval from the Kenya Medical Research Institute's Scientific and Ethics Review Unit, Kenya (KEMRI/SERU/CGHR/005/3751); the research ethics committees of the Liverpool School of Tropical Medicine, UK (18–073); the London School of Hygiene & Tropical Medicine, UK (17179); and the University of Bergen, Norway (2018/2112/REK vest). The study team obtained written informed consent from all participants before data collection. The protocol is available in appendix 1 (pp 25–62). This trial is registered on ClinicalTrials.gov, NCT04160026, and is complete.

Randomisation and masking

To ensure balanced baselines across the study groups, antenatal clinics in facilities that met the inclusion criteria were grouped into matched triplets (ie, units of three clinics) stratified by location (ie, county) on the basis of three criteria: the ratio of total clinic attendance to clinic staff; the ratio of first IPTp doses provided by the clinic to second IPTp doses; and the health facility level (ie, level 3 or level 4). Clinics in each matched triplet were randomly assigned to one of the three study groups (1:1:1) with the Microsoft Excel RANDBETWEEN function. Masking was not possible in this real-life setting. Individuals attending routine antenatal clinic visits at a study clinic received care according to the clinic's assigned study group for the duration of the study and were not masked.

Procedures

Antenatal clinic staff administered IPTp to pregnant participants attending their scheduled antenatal clinic visits in all three study groups. The three study groups were: IPTp with sulfadoxine–pyrimethamine (standard of care; given via DOT as an oral, single-day course of three tablets of quality-assured sulfadoxine [500 mg per tablet]–pyrimethamine [25 mg per tablet]); IPTp with dihydroartemisinin–piperaquine alone (given as an oral, 3-day course of three to five tablets of dihydroartemisinin [40 mg per tablet]–piperaquine [320 mg per tablet] per day depending on the individual's bodyweight; and IPTp with dihydroartemisinin–piperaquine combined with a targeted information transfer intervention (appendix 1 p 2). The delivery steps for dihydroartemisinin–piperaquine involved weighing pregnant participants at their first antenatal clinic visit to establish their weight band, recording their weight-based dose in mother–child health handbooks for reference at subsequent monthly visits, giving participants the first dose of IPTp via DOT, and counselling participants on how to take the day 2 and day 3 doses at home for the dihydroartemisinin–piperaquine groups. At 5 months after the study start date, providers switched from DOT to self-administered dosing for IPTp with sulfadoxine–pyrimethamine and the first doses of IPTp with dihydroartemisinin–piperaquine due to SARS-CoV-2 infection, prevention, and control measures.

The study team trained MoH staff (including county and subcounty malaria coordinators, reproductive health coordinators, heads of facilities, and some antenatal clinic staff) in all three study groups on malaria in pregnancy, correct IPTp dosing, and managing and reporting side-effects and serious adverse events. Trained MoH staff then trained antenatal clinic staff at their respective health facilities and supervised IPTp delivery. Each facility received standard operating procedures appropriate to their intervention group. Intervention sites were supplied with dihydroartemisinin–piperaquine, and stocks were monitored by MoH staff and replenished by study staff to avoid stock-outs. Control sites (ie, for the IPTp with sulfadoxine–pyrimethamine group) received drugs via MoH channels, but the study team supplemented sulfadoxine–pyrimethamine if clinics reported stock-outs. The targeted information transfer intervention was deployed to sites in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group 4 months into the implementation phase. To ensure standardised delivery of targeted information across clusters in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group, study staff trained antenatal clinic staff and their supervisors at the relevant sites to use job aids. The antenatal clinic supervisors provided continuous supportive supervision and trained new clinic staff.

Patient information and education offered by antenatal clinic staff in routine care settings were not standardised in the groups with sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine only and involved either group antenatal clinic talks about care during pregnancy in general or individual patient-level education on drugs and other interventions given during pregnancy; individual-level education would occur during scheduled antenatal clinic visits. However, for the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group, the targeted information intervention

included training and the provision of information, education, and communication tools (ie, job aids; appendix 1 pp 10–11) aimed to enhance support to both providers and participants to increase IPTp with dihydroartemisinin–piperaquine uptake and adherence. The targeted information intervention is described following the Template for Intervention Description and Replication checklist (appendix 1 p 4)[19] for replicability. Briefly, job aids (appendix 1 pp 10–11) targeting providers, including flip charts for group antenatal clinic talks and wall charts inside antenatal clinics for individual-level education, addressed correct weight-based dosing and patient counselling on known barriers to adherence identified in previous studies[15] and the ongoing IMPROVE trial.[17] They also included instructions on multiday dosing. Stickers (appendix 1 pp 11) attached by providers on mother–child health handbooks contained the participant's weight-based dose and served as reminders to providers and participants of the correct dosing by weight at home and at each subsequent clinic visit. Detailed descriptions of the interventions are in appendix 1 (p 2).

Study staff conducted health facility audits during the first month of the evaluation phase to identify cluster-level characteristics such as facility level, number and type of antenatal clinic staff available per cluster, presence of clinicians who provided malaria treatment, and IPTp drug stock-outs. Data were collected sequentially to assess delivery effectiveness and adherence. First, antenatal exit interviews with eligible participants (ie, pregnant individuals attending a scheduled antenatal care visit in the second or third trimester who received one of the three study interventions) were conducted in all three study groups to assess antenatal clinic IPTp delivery effectiveness. Individuals who received the correct number of tablets at antenatal clinic exit were followed up with a home visit in the two dihydroartemisinin–piperaquine groups no more than 2 days after their 3-day regimen ended to assess adherence. Interviewers stationed at the antenatal clinic approached all individuals arriving at antenatal clinic registration and provided them with the study information; individuals who consented were interviewed at the end of their clinic visit (appendix 1 p 7). Each facility had at least one interviewer assisted by a field supervisor. Participants were eligible for home visits in the dihydroartemisinin–piperaquine groups if they received the correct number of dihydroartemisinin–piperaquine tablets at the antenatal clinic exit (ie, a 3-day weight-based course); home visit participants were called a day before each visit to schedule the visits.

Exit interview questions included questions about participants' socioeconomic and demographic information, obstetric history, antenatal clinic services and tests, and knowledge, use, preference, perceptions, IPTp drug acceptability opinions, and experiences of IPTp. Other information included details of IPTp drugs, such as the number of tablets given, health worker instructions, and instruction methods, such as flip charts or posters. Interviewers also recorded data from mother–child health handbooks, including any previous IPTp that had been administered, the participant's weight at their first antenatal clinic visit, and mother–child health handbook stickers indicating their weight-based dosing in the IPTp with dihydroartemisinin–piperaquine plus targeted information intervention group. Home visit interview questions included self-reported adherence, dosing frequency, problems recalling and completing doses, sharing tablets with family members, side-effects, and any episodes of illness between antenatal clinic visits. Interviewers verified self-reported adherence with pill counts.[20] Field workers collected data on tablets with CommCare. Field supervisors conducted daily quality control and data cleaning on CommCare electronic data.

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Outcomes

The primary endpoint was full adherence, defined as the proportion of pregnant individuals visited at home who reported completing their 3-day dihydroartemisinin–piperaquine treatment for their most recent course as prescribed, verified by pill count. The secondary endpoint (delivery effectiveness) was defined as the proportion of pregnant individuals in their second and third trimesters receiving the correct number of IPTp tablets and correctly repeating health provider dosing instructions at antenatal clinic exit. In the sulfadoxine–pyrimethamine group, participants needed to report the number of doses they had received via DOT. In the two dihydroartemisinin–piperaquine groups, participants needed to recall the number of doses they received at their antenatal care visit and indicate what tablets they were expected to take in the two following days. This endpoint was measured by interviewing participants, verifying their number of tablets at antenatal clinic exit, and verifying that they understood provider instructions for the doses they were expected to take at home. Participants' post-hoc assessment of the IPTp they received was measured by asking how they felt about the drugs prescribed, with responses categorised as "Good/very good", "Don't mind", and "Not good" (appendix 1 p 13).

Statistical analysis

The study used a pragmatic design. Within budgetary constraints, we estimated that 18 clusters (six per group) could be enrolled, with a mean cluster size of 82·5 women seen over 3 months. A sample size of six clusters with 62 participants contributing to the primary endpoint adherence (assuming 75% would receive the correct IPTp tablets and dosing instructions at antenatal clinic exit) would allow the estimation of 65% adherence with 6·5% precision and two-sided 95% CIs in the IPTp with dihydroartemisinin–piperaquine only group (design effect 1·80). The same

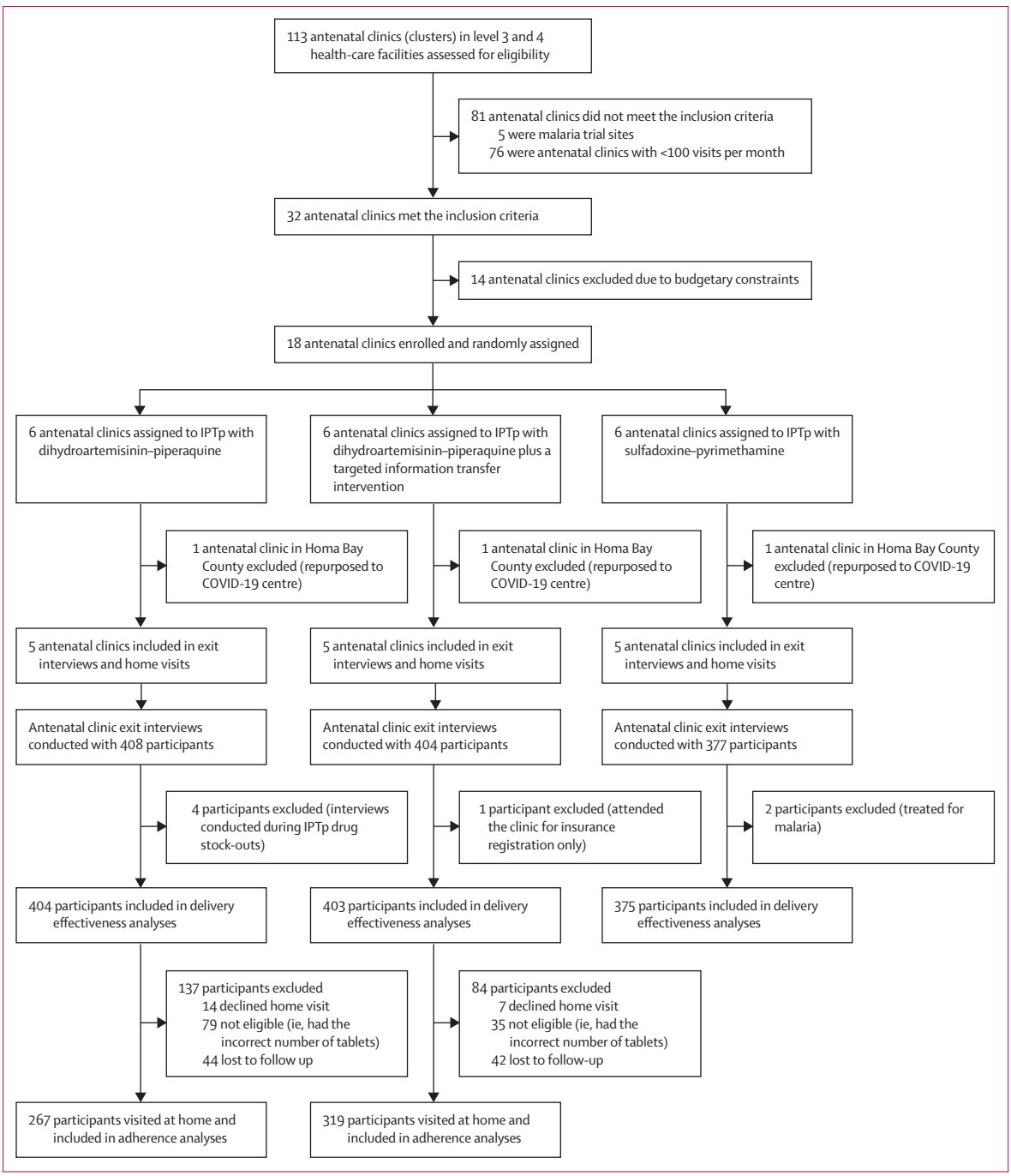

Figure: **Trial profile**
IPTp=intermittent preventive treatment in pregnancy.

sample size would allow the detection of a 20% relative increase in adherence from 65% in the IPTp with dihydroartemisinin–piperaquine only group to 78% in the IPTp with dihydroartemisinin–piperaquine plus targeted information intervention group (relative risk [RR] 1·20) with 84% power (intracluster correlation [ICC] 0·013, two-sided α=0·05). The 65% baseline adherence in the dihydroartemisinin–piperaquine only group,[12] and a 75% treatment rate and an ICC of 0·013[13] were informed by similar studies in sub-Saharan Africa and western Kenya, respectively. We used the same sample size in the IPTp with sulfadoxine–pyrimethamine group (the control group) for the secondary endpoint, delivery effectiveness.

Due to the repurposing of facilities to COVID-19 centres, we estimated that a smaller number of 15 clusters

(five clusters per group) could enrol between 67 (with 50 participants contributing to the adherence endpoint) and 93 (70 participants contributing to the adherence endpoint) participants per cluster within the same 3-month period. This enrolment would allow the estimation of a 65% adherence rate with either a 7·6% precision (50 participants per cluster; design effect 1·65), or a 6·9% precision (70 participants per cluster; design effect 1·91). These revised sample sizes of 50 participants and 70 participants per cluster would have 80% power to detect an increase in adherence from 65% with IPTp with dihydroartemisinin–piperaquine only to 79·2% with IPTp with dihydroartemisinin–piperaquine plus targeted information intervention (RR 1·22) for the cluster size of 50 participants or to 78·0% (RR 1·20) for the cluster size of 70 participants (ICC 0·013, two-sided α=0·05).

Generalised linear mixed models were used with cluster as a random intercept term for the primary and secondary endpoint analyses under Poisson regression with a log-link function and robust SEs to estimate relative risk and corresponding 95% CIs. The primary analysis was the adjusted analysis. We assessed adherence in the intervention groups (IPTp with dihydroartemisinin–piperaquine only and IPTp with dihydroartemisinin–piperaquine plus targeted information intervention) and delivery effectiveness in all three groups. The modelling used an iterative stepwise selection method that adds or removes covariates from the model on the basis of their statistical significance, their effect size, whether they affect the intervention effect or its precision, and model fit following the Akaike Information Criteria, as suggested by Kleinbaum and Klein.[21] Variables considered for the initial full model included those associated with the endpoint with p values of 0·2 or less or effect sizes greater than 1·10 or less than 0·90 at univariable analyses. The final model retained variables with p values less than 0·05 and variables whose retention improved the model according to their Akaike Information Criteria value. All analyses were done with Stata 17. We excluded pregnant individuals who received treatment for malaria on the same day as the day of the exit interview, women visiting an antenatal clinic for registration only, or individuals interviewed during IPTp drug stock-outs.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 113 antenatal clinics in health-care facilities from the Kenya Master Health Facility List[22] that were assessed for eligibility, 32 met our inclusion criteria. 14 antenatal clinics were excluded due to feasibility and budgetary constraints. Antenatal clinics in 18 health-care facilities were enrolled in the trial and randomly assigned to the three treatment groups: six clinics in the IPTp with dihydroartemisinin–piperaquine only group; six clinics in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group; and six clinics in the IPTp with sulfadoxine–pyrimethamine. The COVID-19 pandemic in Kenya occurred 4 months into the implementation phase of the trial, resulting in three of the 18 study health facilities (one facility per group) in Homa Bay County being dropped from the trial after randomisation when the Kenyan Government converted them into COVID-19-only treatment centres and they stopped offering antenatal clinic services, including IPTp (figure). Selected facilities were sparsely distributed reducing the risk of contamination (appendix 1 p 9). The remaining 15 health-care facilities were audited. Core antenatal clinic staff capacity (comprising nurses, doctors,

	IPTp with dihydroartemisinin–piperaquine only (N=404)	IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention (N=403)	IPTp with sulfadoxine–pyrimethamine (N=375)
Age, years	24 (5); n=404	25 (6); n=403	25 (6); n=375
Maternal weight, kg	64 (10); n=403	65 (11); n=402	65 (12); n=374
Married	309/404 (77%)	309/403 (77%)	286/375 (76%)
Completed education level			
None	70/404 (17%)	75/403 (19%)	62/375 (17%)
Primary	159/404 (39%)	170/403 (42%)	146/375 (39%)
Secondary or higher	175/404 (43%)	158/403 (39%)	167/375 (45%)
County of residence			
Kisumu	196/404 (49%)	263/403 (65%)	225/375 (60%)
Homa Bay	208/404 (52%)	140/403 (35%)	150/375 (40%)
Dholuo ethnic group	357/404 (88%)	349/403 (87%)	330/375 (88%)
Socioeconomic status			
1 (lowest)	107/404 (27%)	110/403 (27%)	81/375 (22%)
2	106/404 (26%)	118/403 (29%)	70/375 (19%)
3	92/404 (23%)	96/403 (24%)	106/375 (28%)
4 (highest)	99/404 (25%)	79/403 (20%)	118/375 (32%)
Covered by basic health insurance	296/404 (73·3%)	288/402 (72%)	269/371 (72·5%)
Gravidity			
Primigravidae	143/404 (36%)	135/403 (34%)	116/375 (31%)
Secundigravidae	96/404 (24%)	92/403 (23%)	112/375 (30%)
Multigravidae	165/404 (41%)	176/403 (44%)	147/375 (39%)
Trimester			
Second trimester	93/403 (23%)	57/401 (14%)	68/375 (18%)
Third trimester	310/403 (77%)	344/401 (86%)	307/375 (82%)
First antenatal clinic visit	59/404 (15%)	51/403 (13%)	25/375 (7%)
Previous use of IPTp with sulfadoxine–pyrimethamine during the current pregnancy	8/404 (2%)	17/402 (4%)	..
Unwell at any antenatal clinic visit	73/404 (18%)	43/403 (11%)	86/375 (23%)
Previous malaria infection	89/404 (22%)	63/403 (16%)	99/374 (27%)

Data are mean (SD) or n/N (%). IPTp=intermittent preventive treatment in pregnancy.

Table 1: **Characteristics of participants included in delivery effectiveness analyses, by study group**

	Primary endpoint (adherence; dihydroartemisinin–piperaquine groups only)*					Secondary endpoint (delivery effectiveness; all groups)†				
	n/N (%)	Univariable analysis		Multivariable analysis		n/N (%)	Univariable analysis		Multivariable analysis	
		Crude RR (95% CI)	p value	Adjusted RR (95% CI)‡	p value		Crude RR (95% CI)	p value	Adjusted RR (95% CI)§	p value
IPTp with sulfadoxine–pyrimethamine	..	..	..	..	..	335/375 (89%)	1	..	1	..
IPTp with dihydroartemisinin–piperaquine only	196/267 (73%)	1	..	1	..	300/404 (74%)	0·83 (0·71–0·97)	0·0230	0·84 (0·75–0·95)	0·0030
IPTp with dihydroartemisinin–piperaquine and targeted information transfer	266/319 (83%)	1·10 (0·87–1·40)	0·4220	1·16 (1·03–1·31)	0·0140	352/403 (87%)	0·98 (0·88–1·08)	0·6610	0·97 (0·90–1·05)	0·4810

RR=relative risk. IPTp=intermittent preventive treatment in pregnancy. *IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention versus IPTp with dihydroartemisinin–piperaquine only. †IPTp with dihydroartemisinin–piperaquine (both groups) versus IPTp with sulfadoxine–pyrimethamine. ‡Adjusted RR covariates retained in the final adherence model were: residence; insurance; trimester; previous use of IPTp with sulfadoxine–pyrimethamine; and antenatal clinic core staff. §Adjusted RR covariates retained in the final deliverance effectiveness model (all groups) were: residence and insurance.

Table 2: **Study outcomes**

and clinical officers) was reasonably matched across the study groups. All facilities offered HIV and malaria tests. A total of 75 antenatal clinic staff (three to eight people per facility) were interviewed to describe baseline health worker characteristics (ie, for the health workers delivering the intervention; appendix 1 p 14). Most of the antenatal clinic staff were nurses (39 [52%] of 75), female (43 [57%] of 75), residents of the catchment area (47 [63%] of 75), and most (68 [91%] of 75) had received training on malaria in pregnancy in the past 3 years, either through workshops or on-the-job training (appendix 1 p 14).

In total, 1189 antenatal clinic exit interviews were conducted (377 in the IPTp with sulfadoxine–pyrimethamine group, 408 in the IPTp with dihydroartemisinin–piperaquine only group, and 404 in the dihydroartemisinin–piperaquine plus targeted information transfer intervention group) and 586 individuals in the two IPTp with dihydroartemisinin–piperaquine groups were visited at home (267 in the dihydroartemisinin–piperaquine only group and 319 in the dihydroartemisinin–piperaquine plus targeted information transfer intervention group; figure) from Sept 8 to Dec 10, 2020. The mean cluster size was 84 participants (SD 23) overall, 77 (10) participants in the IPTp with sulfadoxine–pyrimethamine group, 86 (19) participants in the IPTp with dihydroartemisinin–piperaquine only group, and 90 (33) participants in the dihydroartemisinin–piperaquine plus targeted information transfer intervention group.

Participant characteristics were similar across the groups (table 1). A third of participants in each group were primigravidae, with a mean age of 24 years, and a mean weight of 65 kg (table 1). The proportion of first antenatal clinic visit attendees was 15% or lower in all groups and a small proportion of participants in the two IPTp with dihydroartemisinin–piperaquine groups reported use of IPTp with sulfadoxine–pyrimethamine during their current pregnancy (table 1).

The proportions of participants eligible for adherence monitoring who were lost to follow-up and for whom no home visit could be arranged were 58 (18%) of 325 in the IPTp with dihydroartemisinin–piperaquine only group and 49 (13%) of 368 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (RR 1·02, 95% CI 0·97–1·08; p=0·3970; appendix 1 p 17). However, the baseline characteristics were similar for the participants who were lost to follow-up and those who were seen successfully at home, with the exception of the proportion who were married (RR 1·03, 1·00–1·06; p=0·0420) and those who reported having had malaria during the current pregnancy (RR 0·93, 0·86–0·99; p=0·0150; appendix 1 pp 18–20). Relative to the IPTp with dihydroartemisinin–piperaquine only group, adherence for IPTp with dihydroartemisinin–piperaquine was 16% higher in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (adjusted RR 1·16, 95% CI 1·03–1·31, p=0·0140; table 2). Previous use of IPTp with sulfadoxine–pyrimethamine in the current pregnancy was associated with a 16% higher adherence to IPTp with dihydroartemisinin–piperaquine than non-use (table 3). Predictors of lower adherence included residing in Homa Bay County rather than Kisumu County and attending antenatal clinics staffed with ten or more health workers (table 3). Adherence was similar between participants who received their first dose via DOT and those who did not (174 [79%] of 221 participants *vs* 288 [79%] of 365; RR 0·99, 95% CI 0·82–1·20; p=0·9020; appendix 1 p 20).

Delivery effectiveness was highest in the control group, IPTp with sulfadoxine–pyrimethamine, compared with the IPTp with dihydroartemisinin–piperaquine only group and IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (table 2; appendix 1 p 24). Relative to the IPTp with sulfadoxine–pyrimethamine group, delivery effectiveness

was 16% lower in the IPTp with dihydroartemisinin–piperaquine only group but similar to the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (table 2). Residing in Homa Bay County rather than Kisumu County and having basic health insurance were associated with 12% and 4% lower delivery effectiveness, respectively (table 4).

When comparing the two IPTp with dihydroartemisinin–piperaquine groups, delivery effectiveness was 14% higher in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group than in the IPTp with dihydroartemisinin–piperaquine only group (table 5; appendix 1 p 26). Predictors of lower delivery effectiveness were residing in Homa Bay County rather than Kisumu County, Dholuo ethnicity rather than non-Dholuo ethnicity, and attending antenatal clinics staffed with clinicians rather than antenatal clinics without clinicians (tables 4, 5; appendix 1 p 26).

In general, IPTp was liked, with 349 (93%) of 374 participants in the IPTp with dihydroartemisinin–piperaquine only group and 362 (95%) of 381 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group describing IPTp as good or very good compared with 305 (87%) of 351 participants in the IPTp with sulfadoxine–pyrimethamine group (appendix 1 p 16). Perceived protective effects on the unborn baby and mother (229 [75%] of 304 participants in the IPTp with sulfadoxine–pyrimethamine group, 324 [93%] of 347 participants in the IPTp with dihydroartemisinin–piperaquine only group, and 298 [82%] of 362 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group) and clear provider instructions, especially in the dihydroartemisinin–piperaquine plus targeted information transfer intervention group (37 [12%] of 304 participants in the IPTp with sulfadoxine–pyrimethamine group, 16 [5%] of 347 participants in the IPTp with dihydroartemisinin–piperaquine only group, and 140 [39%] of 362 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group), were some reasons listed for positive perceptions of IPTp (appendix 1 p 16). During home visits, participants also reported clear provider instructions as having aided their adherence to IPTp with dihydroartemisinin–piperaquine (167 [72%] of participants in the IPTp with dihydroartemisinin–piperaquine only group and 257 [86%] of 300 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group; appendix 1 p 17). Few participants disliked IPTp, with a higher proportion in the IPTp with sulfadoxine–pyrimethamine group (30 [9%] of 351 participants in the IPTp with sulfadoxine–pyrimethamine group, 10 [3%] of 374 participants in the IPTp with dihydroartemisinin–piperaquine only group, and 8 [2%] of 381 participants in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group; appendix 1 p 16). Fewer participants reported side-effects in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group (44 [12%] of 381 participants) than in the IPTp with

	Mean (SD) or n/N (%)	Univariable analysis*		Multivariable analysis	
		Crude RR (95% CI)	p value	Adjusted RR (95% CI)†	p value
Sociodemographic variables					
Age, years	25·0 (6); n=462	1·01 (1·00–1·02)	0·0750*	..	..
Residence county					
Kisumu	306/357 (86%)	1	..	1	..
Homa Bay	156/229 (68%)	0·81 (0·66–0·99)	0·0360*	0·74 (0·66–0·83)	<0·0001
Socioeconomic status (quartiles)					
1 (lowest)	133/157 (85%)	1	0·0820‡	..	..
2	134/174 (77%)	0·91 (0·82–1·01)	..	..	..
3	93/128 (73%)	0·87 (0·77–0·97)	..	..	..
4 (highest)	102/127 (80%)	0·96 (0·88–1·06)	..	..	..
Basic health insurance					
No	142/198 (85%)	1	..	1	..
Yes	319/417 (77%)	0·93 (0·84–1·04)	0·2040‡	0·98 (0·87–1·10)	0·7580
Trimester					
Second trimester	71/104 (68%)	1	..	1	..
Third trimester	389/480 (81%)	1·15 (1·00–1·32)	0·0530‡	1·14 (1·00–1·31)	0·0550
First antenatal clinic visit					
No	403/500 (81%)	1	..	..	..
Yes	59/86 (67%)	0·86 (0·67–1·10)‡	0·2510	..	..
Unwell at any antenatal clinic visits					
No	408/508 (80%)	1	..	..	..
Yes	54/78 (69%)	0·90 (0·90–1·17)‡	0·4270	..	..
Previous infection with malaria					
No	386/493 (78%)	1	..	..	..
Yes	76/93 (82%)	1·10 (0·95–1·26)	0·2100‡	..	..
Previous use of IPTp with sulfadoxine–pyrimethamine§					
No	446/570 (78%)	1	..	1	..
Yes	16/16 (100%)	1·18 (1·02–1·36)	0·0250‡	1·16 (1·04–1·30)	0·0090
Health facility factors					
Antenatal clinic core staff ≥10 people					
No	212/263 (81%)	1	..	1	..
Yes	250/323 (77%)	0·90 (0·70–1·17)‡	0·4300	0·80 (0·71–0·89)	<0·0001
Antenatal clinic with curative services¶					
No	91/108 (84%)	1	..	..	..
Yes	371/478 (78%)	0·90 (0·67–1·21)‡	0·4790	..	..

RR=relative risk. IPTp=intermittent preventive treatment in pregnancy. *Group included in the model. †Adjusted RR output shows the covariates retained in the final model: residence; insured; trimester; previous use of IPTp with sulfadoxine–pyrimethamine; and antenatal clinic core staff. ‡Covariates included in the multivariable model if p<0·2 or the effect size ≥10%: age; residence; socioeconomic status group 4; insured; trimester; first antenatal clinic visit; unwell at any visit; previous malaria infection; previous use of IPTp with sulfadoxine–pyrimethamine; antenatal clinic core staff; and antenatal clinic has curative services. §During the current pregnancy. ¶Antenatal clinic staffed with clinicians providing malaria treatment.

Table 3: **Predictors of participants' adherence to IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention *vs* IPTp with dihydroartemisinin–piperaquine only**

	n/N (%)	Univariable analysis*		Multivariable analysis	
		Crude RR (95% CI)	p value	Adjusted RR (95%CI)†	p value
Completed education level					
None	166/207 (80%)	1	..	..	..
Primary	408/475 (86%)	1·07 (0·98–1·17)	0·1410‡	..	..
Secondary or higher	413/500 (83%)	1·03 (0·93–1·14)	0·5640	..	..
County of residence					
Kisumu	610/684 (89%)	1	..	1	..
Homa Bay	377/498 (76%)	0·86 (0·80–0·94)	<0·0001‡	0·88 (0·81–0·96)	0·0040
Dholuo ethnic group					
No	130/146 (89%)	1	..	..	..
Yes	857/1036 (83%)	0·93 (0·86–1·01)	0·0820‡	..	..
Basic health insurance					
No	291/324 (90%)	1	..	1	..
Yes	691/853 (81%)	0·90 (0·86–0·95)	<0·0001*	0·96 (0·92–1·00)	0·0330

RR=relative risk. IPTp=intermittent preventive treatment in pregnancy. *Group included in the model. †Adjusted RR output shows the covariates retained in the final model (ie, residence and insured). ‡Covariates included in the multivariable model if p<0·2 or the effect size ≥10%: education level; residence; ethnic group; and insured.

Table 4: **Predictors of IPTp delivery effectiveness (all groups), IPTp with dihydroartemisinin–piperaquine, and IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention *vs* IPTp with sulfadoxine–pyrimethamine**

sulfadoxine–pyrimethamine group (66 [19%] of 351 participants) and IPTp with dihydroartemisinin–piperaquine only group (68 [18%] of 374 participants; appendix 1 p 16).

Discussion

This is the first study to evaluate the delivery of IPTp with dihydroartemisinin–piperaquine in routine antenatal care settings and participants' adherence to a weight-based multiday IPTp with dihydroartemisinin–piperaquine. The study showed that participants' adherence to and the delivery effectiveness of antenatal clinics for multiday IPTp with dihydroartemisinin–piperaquine in routine care settings were sufficiently high to provide reassurance on the uptake of multiday regimens should a policy change including IPTp with dihydroartemisinin–piperaquine be made. Targeted information transfer further improved uptake of multiday IPTp with dihydroartemisinin–piperaquine regimens, making the uptake similar to that for the current standard of care (IPTp with sulfadoxine–pyrimethamine).

There are no similar studies on IPTp with dihydroartemisinin–piperaquine adherence. We noted high adherence to IPTp with dihydroartemisinin–piperaquine in both the IPTp with

	Mean (SD) or n/N (%)	Univariable analysis*		Multivariable analysis	
		Crude RR (95% CI)	p value	Adjusted RR (95% CI)†	p value
Group					
IPTp with dihydroartemisinin–piperaquine only	300/404 (74%)	1	..	1	..
IPTp with dihydroartemisinin–piperaquine and IPTp with dihydroartemisinin–piperaquine plus a targeted information transfer intervention	352/403 (87%)	1·18 (1·00–1·39)	0·0520‡	1·14 (1·04–1·26)	0·0050
Sociodemographic variables					
Age, years	24·6 (5); n=652	1·01 (1·00–1·01)	0·0450‡	..	..
County of residence					
Kisumu	400/459 (87%)	1	..	1	..
Homa Bay	252/348 (72%)	0·85 (0·76–0·95)	0·0050‡	0·88 (0·81–0·96)	0·0040
Dholuo ethnic group					
No	91/101 (90%)	1	..	1	..
Yes	561/706 (80%)	0·89 (0·81–0·97)	0·0110‡	0·90 (0·82–0·98)	0·0210
Basic health insurance					
No	192/222 (87%)	1	..	1	..
Yes	459/584 (79%)	0·91 (0·86–0·97)	0·0030‡	0·96 (0·92–1·00)	0·0330
Maternal weight, kg	64·9 (11); n=652	1·00 (1·00–1·00)	0·1410‡	..	..
Previous use of IPTp with sulfadoxine–pyrimethamine§					
No	635/782 (81%)	1	..	..	..
Yes	17/25 (68·0%)	0·81 (0·57–1·17)‡	0·2610	..	..
Health facility factors					
Antenatal clinic has curative services¶	534/676 (79%)	0·88 (0·70–1·11)‡	0·2870	0·85 (0·77–0·93)	0·0010

RR=relative risk. IPTp=intermittent preventive treatment in pregnancy. *Group included in the model. †Adjusted RR output shows the covariates retained in the final model (ie, residence and insured). ‡Covariates included in the multivariable model if p<0·2 or effect size ≥10%: education level; residence; ethnic group; and insured. §During the current pregnancy. ¶Antenatal clinic staffed with clinicians providing malaria treatment.

Table 5: **Predictors of IPTp delivery effectiveness in the IPTp with dihydroartemisinin–piperaquine groups, IPTp with dihydroartemisinin–piperaquine, and IPTp with dihydroartemisinin–piperaquine plus a targeted information transfer intervention *vs* IPTp with dihydroartemisinin–piperaquine only**

dihydroartemisinin–piperaquine only group and the IPTp with dihydroartemisinin–piperaquine plus targeted information intervention group. Health providers and pregnant individuals were familiar with dihydroartemisinin–piperaquine due to its routine use for second-line treatment of uncomplicated malaria and might therefore have perceived it as a so-called good or effective drug. A higher proportion of participants in the two dihydroartemisinin–piperaquine groups listed the protective effects of IPTp on their current pregnancy as their main reason for liking IPTp than in the sulfadoxine–pyrimethamine group. Notably, delivering the first dose of dihydroartemisinin–piperaquine with or without DOT had no effect on adherence. In a previous acceptability study conducted alongside a trial comparing intermittent screening and IPTp with dihydroartemisinin–piperaquine or IPTp only with dihydroartemisinin–piperaquine versus IPTp with sulfadoxine–pyrimethamine,[15] dihydroartemisinin–piperaquine was perceived by providers and participants as more effective in preventing malaria compared with sulfadoxine–pyrimethamine, which was seen as an unsuccessful drug. Although women reported experiencing side-effects from both dihydroartemisinin–piperaquine and sulfadoxine–pyrimethamine in that study (including nausea and vomiting), sulfadoxine–pyrimethamine was associated with a "bad taste in the mouth".[15] In this study, fewer participants reported side-effects in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer group compared with the IPTp with dihydroartemisinin–piperaquine only group and the IPTp with sulfadoxine–pyrimethamine group, probably due to the targeted information, which addressed expected side-effects and their management at home. Participants' improved awareness might have resulted in less misclassification of side-effects and better mitigation practices (eg, participants taking their tablets at night and not noticing the side-effects). Targeted information also boosted adherence in the IPTp with dihydroartemisinin–piperaquine plus targeted information transfer intervention group that was similar to the boost from clear health worker instructions reported by a systematic review of 37 studies measuring ACT adherence.[23] Similarly, a trial in India showed improved patient adherence to ACTs by up to 81% when participants received information, education, and communication tool materials on correct dosing and managing side-effects in addition to verbal instructions in the clinic.[24]

The high IPTp delivery effectiveness noted across all our study groups could be attributed to an overall health systems improvement in IPTp delivery with or without DOT. For instance, the delivery effectiveness of IPTp with sulfadoxine–pyrimethamine of 89% reported in our study was higher than that observed in our survey in the same area from February to May, 2010, when it stood at 62% in level 4 hospitals and 72% in health centres (with or without DOT).[13] The 15% lower delivery effectiveness in the IPTp with dihydroartemisinin–piperaquine only group compared with the IPTp with sulfadoxine–pyrimethamine group is unsurprising given the complexity of delivering a multiday weight-based regimen and introducing dihydroartemisinin–piperaquine for a new indication. Targeted information transfer substantially improved the delivery effectiveness of IPTp with dihydroartemisinin–piperaquine as it supported provider practices, including correct weight-based prescriptions, patient education, and counselling on multiday dosing through job aids and reminder stickers on mother–child health handbooks. The effect of the targeted information transfer intervention was similar to those reported in a study in Kenya,[25] which showed that sending reminders to health workers on correct ACT prescriptions improved provider adherence to ACT treatment guidelines by 23·7%.

A qualitative study conducted alongside this feasibility study that explored providers' and participants' perspectives on how targeted information transfers improved adherence to and the implementation feasibility of multiday regimens found that although side-effects hampered adherence, information on potential side-effects and how to manage them were valued by participants. Providers reported feeling more confident in advising people on how to manage side-effects. Providers in the IPTp with sulfadoxine–pyrimethamine group saw IPT with dihydroartemisinin–piperaquine as too complex to deliver in routine care settings (J Hoyt, Liverpool School of Tropical Medicine, personal communication).

Although our results showed overall improvement in adherence and delivery effectiveness, the context of subnational and regional health systems needs to be considered. For instance, we noted lower adherence and delivery effectiveness in Homa Bay County than in Kisumu County. One explanation could be devolution of health services from national to county levels resulting in notable county-level differences in governance cultures, the management of human resources for health and essential commodities, and health financing.[26,27] However, this effect would need to be examined in a large-scale health system study. Facilities prioritised curative services over preventive services after devolution.[28] In a previous survey in western Kenya,[13] delivery of sulfadoxine–pyrimethamine via DOT was 13% lower and the overall delivery effectiveness of IPTp with sulfadoxine–pyrimethamine was 10% lower in large level 4 (district) hospitals focused on curative services than in primary care facilities (ie, dispensaries and health centres) that prioritise preventive services.[13]

The results in this study for the feasibility of delivery of and adherence to multiday regimens remain highly relevant for future alternatives to IPTp with sulfadoxine–pyrimethamine. Several trials in areas with high resistance to sulfadoxine–pyrimethamine have confirmed the superior antimalarial activity of IPTp with dihydroartemisinin–piperaquine over IPTp with

sulfadoxine–pyrimethamine.[6–9,17] However, a policy switch from IPTp with sulfadoxine–pyrimethamine to IPTp with dihydroartemisinin–piperaquine is unlikely due to the superiority of IPTp with sulfadoxine–pyrimethamine in preventing adverse birth outcomes. In a randomised, partly placebo-controlled trial,[17] compared with IPTp with dihydroartemisinin–piperaquine, IPTp with sulfadoxine–pyrimethamine improved both maternal weight gain during pregnancy and fetal growth, resulting in fewer small-for-gestational age births and births with low birthweight, probably due to non-malaria-related effects of sulfadoxine–pyrimethamine. However, trials of the combination of sulfadoxine–pyrimethamine and dihydroartemisinin–piperaquine for IPTp versus IPTp with sulfadoxine–pyrimethamine only are ongoing in Uganda (NCT04336189) and Papua New Guinea (NCT05426434) to assess improvements in birth outcomes and malaria infections in pregnancy. If the MoH provides orientation, offering the training and information, education, and communication tools developed in this study to antenatal clinic providers for use in routine care settings would be possible. However, this intervention would not circumvent general health system weaknesses such as staff turnover (as with any health intervention).

See Online for appendix 2

This study has some limitations. Self-reported adherence might be an overestimate due to recall and social desirability bias.[20] We mitigated these biases with pill counts.[29] Obtaining consent to visit participants at home to conduct home visit interviews and scheduling telephone calls the day before home visits might have resulted in higher adherence. We cannot conclude if adherence and delivery effectiveness are sustained over multiple courses during a single pregnancy because these endpoints were assessed for a single course, and reasons for medication non-adherence are often complex and could change over time. We implemented the study in real-life conditions (ie, MoH staff implemented the intervention and IPTp was delivered with typical resource constraints related to human resource capacity, skills, training needs, staff rotation, transfer and attrition, staff absence, financing, and leadership and governance challenges). Study staff involvement in stock-monitoring visits or the training of new facility staff might have affected IPTp delivery, resulting in higher-than-expected delivery effectiveness; however, this factor would not be expected to have differential effects across the study groups. The costs and cost-effectiveness of the different strategies were not assessed in this trial but will be assessed in the parallel clinical trial.[17] Finally, three health facilities, one in each group, were dropped after the MoH repurposed them as COVID-19-only treatment centres. Due to this unplanned change, the number of clusters in this study decreased from 18 to 15. However, the re-estimated sample size to verify our primary and secondary endpoints retained at least 80% power.

In conclusion, delivery of IPTp with dihydroartemisinin–piperaquine in this routine health-care setting was feasible with notably high adherence and delivery effectiveness. The addition of a targeted information transfer intervention increased both adherence and delivery effectiveness of the multiday IPTp with dihydroartemisinin–piperaquine regimen. Our findings suggest that including multiday regimens for IPTp is feasible if introduced alongside a targeted information transfer intervention to optimise adherence and delivery effectiveness. Our findings are encouraging for policy makers who might need to consider alternatives to sulfadoxine–pyrimethamine for IPTp in areas of high resistance to the combination drug.

Contributors

JH and JW conceived this study. JH, JW, HCB, and SK were responsible for the final study design. IAO contributed to the intervention design. HCB, FO, AK'O, MAO, EO, DO, BO, IAO, JH, and JW contributed to data acquisition. HCB, JH, FOtK, and ML contributed to the statistical analysis. HCB, JH, ML, and JD directly accessed and verified the underlying data reported in this Article. HCB and JH wrote the first draft of the manuscript. MT supported HCB with manuscript revisions and data interpretation. All authors contributed to critical revisions of the manuscript. All authors had access to all the data in the study and accept responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol is available in appendix 1 (pp 25–62). Data dictionaries and de-identified participant data can be shared by HCB on request. However, such requests must be reviewed by the Kenya Medical Research Institute Scientific Ethics and Review Unit and must conform to the Kenya Data Protection Act of 2019. Further details are provided in appendix 1 (p 7).

Acknowledgments

We would like to thank the funders of this study: the European and Developing Countries Clinical Trials Partnership EDCTP2 programme (TRIA-2015–1076-IMPROVE) supported by the EU; the UK Department of Health and Social Care, the UK Foreign, Commonwealth and Development Office, the UK Medical Research Council, and the Wellcome Trust through the Joint Global Health Trials scheme (MR/P006922/1); and the Swedish International Development Cooperation Agency. Eurartesim was provided free of charge by AlfaSigma (Bologna, Italy). We would like to thank all the health facilities and study participants who participated in the study and all the research assistants who conducted the study. We are grateful to the county directors of Homa Bay County and Kisumu County, Gordon Okomo and Fredrick Oluoch, for their support in enabling the trial to be conducted in these sites. We are very thankful to Tracy Seddon in Liverpool, UK, and Benta Kamire, Sheila Nyarinda, and Josephine Owade in Kisumu, Kenya, for their excellent managerial and administrative support. We would like to thank Alice Kamau from the Global Health Trials Unit at the Liverpool School of Tropical Medicine for assisting with the study sites map. We are grateful to Lilyana Dayo, the Kisumu County Malaria Coordinator, who supported the training of trainers, and Evelyne Delylah Ondieki for trial coordination in Kenya. We would also like to thank Tony Sang, the lead pharmacist for this study, for his support with the preparations of the study drugs. This study is published with the permission of the Director of the Kenya

Medical Research Institute. The Liverpool School of Tropical Medicine was the sponsor.

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