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Acceptability of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine plus dihydroartemisinin-piperaquine in Papua New Guinea: a qualitative study

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Abstract

Background In moderate-to-high malaria transmission regions, the World Health Organization recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) alongside insecticide-treated bed nets to reduce the adverse consequences of pregnancy-associated malaria. Due to high-grade *Plasmodium falciparum* resistance to SP, novel treatment regimens need to be evaluated for IPTp, but these increase pill burden and treatment days. The present qualitative study assessed the acceptability of IPTp-SP plus dihydroartemisinin-piperaquine (DP) in Papua New Guinea, where IPTp-SP was implemented in 2009.

Methods Individual in-depth interviews (IDIs) and focus group discussions were conducted at health facilities where a clinical trial evaluated IPTp-SP plus DP (three-day regimen) versus IPTp-SP plus DP-placebo. IDIs were conducted with: (1) trial participants at different stages of engagement with ANC and IPTp, e.g. first antenatal clinic visit, subsequent antenatal clinic visits and postpartum; (2) local health workers (nurses, community health workers, midwives, health extension officers, doctors); and (3) representatives of district, provincial and national health authorities involved in programming ANC and IPTp. Focus group discussions comprised pregnant women only, including those engaged in the clinical trial and those receiving routine ANC outside of the trial. All interviews were audio recorded and transcribed. Transcripts were analysed using inductive and deductive thematic analysis applying a framework assessing: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy.

Results Women expressed positive feelings and attitudes towards SP plus DP/DP-placebo; reported limited side effects; and found the size, number, colour, and taste of study medicines acceptable. Health workers and policy-makers were concerned that, compared to SP alone, additional tablets, frequency (three-day regimen), and tablet size might be barriers to acceptability for users outside a non-trial setting. There was a high perceived effectiveness of SP plus DP; most women reported that they did not get malaria or felt sick during pregnancy. Broader healthcare

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benefits received through trial participation and the involvement of health workers, relatives and community members in the clinical trial enabled antenatal clinic attendance and perceived acceptability of this IPTp regimen.

Conclusions In the trial context, IPTp-SP plus DP was acceptable to both users and providers. Healthcare providers were concerned about the realities of acceptability and adherence to SP plus DP outside a clinical trial setting.

Keywords Acceptability, Dihydroartemisinin-piperaquine, Intermittent preventive treatment in pregnancy, Malaria, Papua New Guinea, Pregnancy, Qualitative

Background

Millions of pregnant women are at risk of *Plasmodium falciparum* and *Plasmodium vivax* infection worldwide [1]. Malarial infection during pregnancy is associated with maternal morbidity and mortality and causes adverse pregnancy outcomes such as low birth weight (<2500 g), preterm birth (<37 gestational weeks), fetal growth restriction, pregnancy loss (miscarriage and stillbirth), and neonatal death [2]. *Plasmodium falciparum*-infected erythrocytes sequester in the placental intervillous space, causing placental malaria [3]. In areas of moderate-to-high transmission, most women with placental malaria are asymptomatic [4], and paucigravid women are at the highest risk [5, 6]. The absence of detectable peripheral parasitaemia does not preclude placental infection, making detection and treatment of malaria in pregnancy challenging [4, 7, 8].

The World Health Organization (WHO) recommends the use of intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), together with insecticide-treated bed nets (ITNs), to prevent malaria and reduce the risk of adverse birth outcomes in sub-Saharan Africa, where *P. falciparum* predominates [9]. IPTp is designed to provide intermittent chemoprophylaxis and presumptive treatment of malaria and clears asymptomatic infections. In most settings, pregnant women are offered IPTp-SP at antenatal clinics, given a month apart, from the second trimester until delivery [10]. The implementation of IPTp-SP throughout sub-Saharan Africa has favourably improved maternal and neonatal outcomes [11, 12]. However, antimalarial efficacy of IPTp-SP is threatened by the rising prevalence of *P. falciparum* isolates exhibiting high-grade resistance to SP in Africa [13–16] as well as in parts of Asia and South America [17]. Parasites with five mutations in the *P. falciparum* dihydrofolate reductase and dihydropteroate synthase genes, and increasingly with a sixth additional mutation, dihydrofolate reductase A581G, are now commonly found in Africa, and these mutations are associated with decreased anti-malarial efficacy and treatment failure of SP [13, 14, 18]. Papua New Guinea (PNG) has been the only country outside of sub-Saharan Africa to adopt SP for IPTp, in 2009 [19]. SP has shown poor antimalarial efficacy against *P. vivax* in this setting,

while *P. falciparum* mutations associated with reduced SP efficacy were observed [20, 21], potentially limiting its use for IPTp. Novel anti-malarial candidates for IPTp are needed to ensure adequate protection from malaria.

Several multi-centre clinical trials of alternative drugs for IPTp have been conducted in sub-Saharan Africa [22, 23]. One potentially suitable alternative for IPTp is dihydroartemisinin-piperaquine (DP), which has been shown to have a good safety profile and superior anti-malarial efficacy compared to SP [24–27]. However, despite failing as an anti-malarial, SP was associated with a higher mean birth weight compared to DP in these studies [28]. The mechanisms by which SP improves birth weight are mediated through non-malarial pathways, such as controlling genitourinary infections and enhancing maternal gestational weight gain [28–30]. Combining the anti-malarial benefits of DP with the non-malarial benefits of SP may, therefore, translate into significant improvements in pregnancy outcomes in malaria-endemic settings with a high burden of multicausal low birth weight. The combination of SP plus DP for IPTp is now being evaluated in clinical trials in Uganda (ClinicalTrials.gov NCT04336189) and PNG (ClinicalTrials.gov NCT05426434). DP is provided as a fixed-dose 3-day regimen [31, 32].

Combining a fixed-dose regimen of DP with SP for IPTp increases the number of pills taken by women from a single-dose regimen to a multiple-dose regimen over three days and from three tablets on day one to six tablets on day one. Tolerability and practical aspects (size and number of pills, three-day course) of combining SP plus DP may be challenging to IPTp provision, which could affect user and provider acceptability. Pregnant women and healthcare providers in PNG are familiar with multi-dose anti-malarial regimens, given that the first-line treatment for uncomplicated malaria is a weight-based 3-day (6 doses) treatment regimen of artemether-lumefantrine tablets [33]. However, acceptability may differ when multi-dose regimens are used for prevention. It is important to understand the factors influencing acceptability as these may determine effectiveness and successful implementation of SP plus DP for IPTp. The WHO recognizes that acceptability is an important factor to support implementation of IPTp interventions [10].

The current standard dose of SP for IPTp is widely acceptable and well tolerated, although some women have reported mild and temporary side effects, which are most pronounced with the first treatment course of IPTp-SP [34, 35]. In Kenya, where IPTp-SP is implemented, a qualitative study assessed the acceptability of monthly IPTp-DP alone, administered as a weight-based treatment course consisting of three daily doses ranging from two to four 40 mg/320 mg tablets in the setting of an open-label clinical trial [36]. In this study, IPTp-DP was viewed as an acceptable replacement of IPTp-SP by pregnant women and healthcare providers, based on perceived benefits and side effects and adherence to IPTp-DP [36]. The combination of SP plus fixed-dose DP for IPTp increases the number of treatment days and the pill burden compared to IPTp-DP or IPTp-SP, reducing the transferability of the above-mentioned findings. Furthermore, little is known about the acceptability of IPTp-SP in PNG.

The clinical trial in PNG provides an opportunity for the present qualitative study to evaluate user and provider acceptability of IPTp-SP plus fixed-dose DP regimen. Drawing on the theoretical framework proposed by Sekhon et al. [37], acceptability was defined as a multifaceted construct that reflects the extent to which healthcare providers delivering, or pregnant women receiving, IPTp-SP plus DP consider it to be appropriate, based on anticipated or experienced cognitive and emotional response to the healthcare intervention. In addition to assessing the IPTp regimen's acceptability, this study contributes conceptually and theoretically by contextualizing the Sekhon et al. framework and expanding it to the local setting.

Methods

Study design and setting

The qualitative study conducted in PNG involved pregnant and postpartum women, and healthcare providers which included health workers at the health facilities and policymakers working across district, provincial, and national health authority levels, who were invited to participate following written informed consent. Women attending antenatal clinics who had or had not taken IPTp were eligible, along with healthcare providers involved in administering antenatal care (ANC) and/or IPTp.

The study area located along the north coast of mainland PNG has year-round moderate-to-intense transmission of *P. falciparum* and *P. vivax* malaria, reaching hyperendemic levels rarely found outside of sub-Saharan Africa [38]. PNG currently accounts for 86% of the malaria burden in the Western Pacific region [39]. In this setting, *P. falciparum* and *P. vivax* are significant causes

of maternal anemia and adverse pregnancy outcomes [19, 40, 41].

Clinical trial context

The present study was nested into activities of a double-blind randomized controlled clinical trial (NCT05426434, referred as parent trial) conducted at health facilities in Madang Province, PNG. The parent trial recruitment sites included Mugil Health Centre, Alexishafen Health Centre, Town Urban Clinic, Madang Provincial Hospital (Modilon Hospital), and Yagaum Rural Hospital (Fig. 1). These health facilities cater for urban, peri-urban and rural populations; provided basic ANC at e.g., Mugil Health Center; as well as ANC for higher risk pregnancies, e.g., at Madang Provincial Hospital. Sampling at these sites allowed recruitment of both women who participated in the trial and women who attended routine antenatal clinics.

Pregnant women of all gravidities who were HIV-negative attending antenatal clinic between 12 and 26 weeks' gestation were potentially eligible to participate in the parent trial. Volunteers who had provided written informed consent were randomized to IPTp-SP plus DP (intervention arm) or IPTp-SP plus DP-placebo (control arm). Pregnant women were given treatment courses consisting of three tablets of SP plus three tablets of DP or DP-placebo on day 0, followed by 3 tablets of DP or DP-placebo on days 1 and 2 (Table 1). DP-placebo was manufactured to mimic the appearance and taste of DP (Guilin Pharma, Guilin, PR China). The first dose of study drugs was taken under direct observation at participating clinics, and participants were asked to complete the second and third DP/DP-placebo doses at home. IPTp was scheduled every four weeks, and participants were followed up until six weeks after the end of the postpartum period.

Study participants, procedures, and positionality

Data for this qualitative study was collected between 17 April and 6 September 2023, eight months after the parent trial had commenced. Participants included pregnant and postpartum women, some of which were or had been enrolled in the parent trial and some who had experience of pregnancy and IPTp but were not enrolled in the parent trial (Fig. 2). Furthermore, clinical trial staff as well as health facility staff who were not involved in the clinical trial were included in the study, as were policymakers working at district, provincial and national health authority levels (Fig. 3). Data were collected through in-depth interviews (IDIs) and focus group discussions (FGDs) at the parent trial recruitment sites in Mugil Health Centre, Yagaum Rural Hospital, Town Urban Clinic, and Madang Provincial Hospital. Recruitment sites included

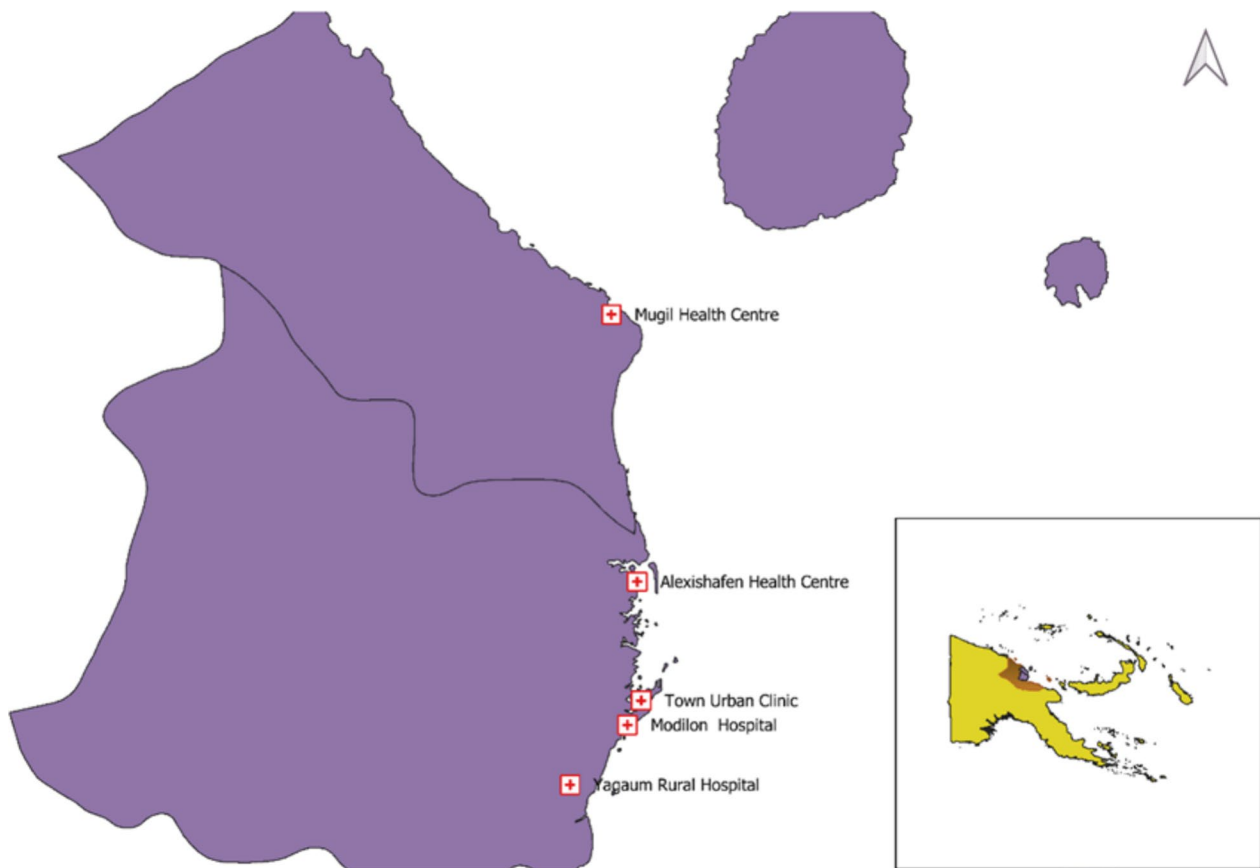


Fig. 1 Health facilities at which the present qualitative study was conducted as part of the parent trial. Alexishafen Health Centre was not included in data collection. Modilon Hospital refers to Madang Provincial Hospital in this study

Table 1 Characteristics of monthly treatments in the Papua New Guinea clinical trial

Time points	Intervention arm		Control arm		Drug formulations per tablet	
	IPTp	Tablets	IPTp	Tablets	SP	DP
Day 0	SP + DP	6	SP + Placebo	6	500 mg/25 mg	40 mg/320 mg
Day 1	DP	3	Placebo	3	–	40 mg/320 mg
Day 2	DP	3	Placebo	3	–	40 mg/320 mg

IPTp: intermittent preventive treatment in pregnancy, SP: sulfadoxine-pyrimethamine, DP: dihydroartemisinin-piperaquine

provincial and rural hospitals, a remote rural health centre and an urban clinic, covering a range of locations (rural, peri-urban or urban). Alexishafen Health Centre was temporarily closed when this qualitative data was collected. Socio-demographic information was collected at the end of each IDI or FGD session. Participants were provided with light refreshments.

A female research assistant with experience in qualitative research assisted a male research officer from the PNG Institute of Medical Research (PNG IMR) to conduct IDIs and FGDs with pregnant and postpartum

women, in respect of local cultural gender norms [42]. A male research officer conducted IDIs for clinical trial staff, health workers and policymakers. Both researchers are PNG nationals with ample experience in malaria research in Madang Province, and are familiar with the study area, local language, and customs.

IDIs and FGDs: pregnant and postpartum women

IDIs were conducted with women who participated in the parent trial, and who were interviewed at selected recruitment sites at different timepoints in relation to

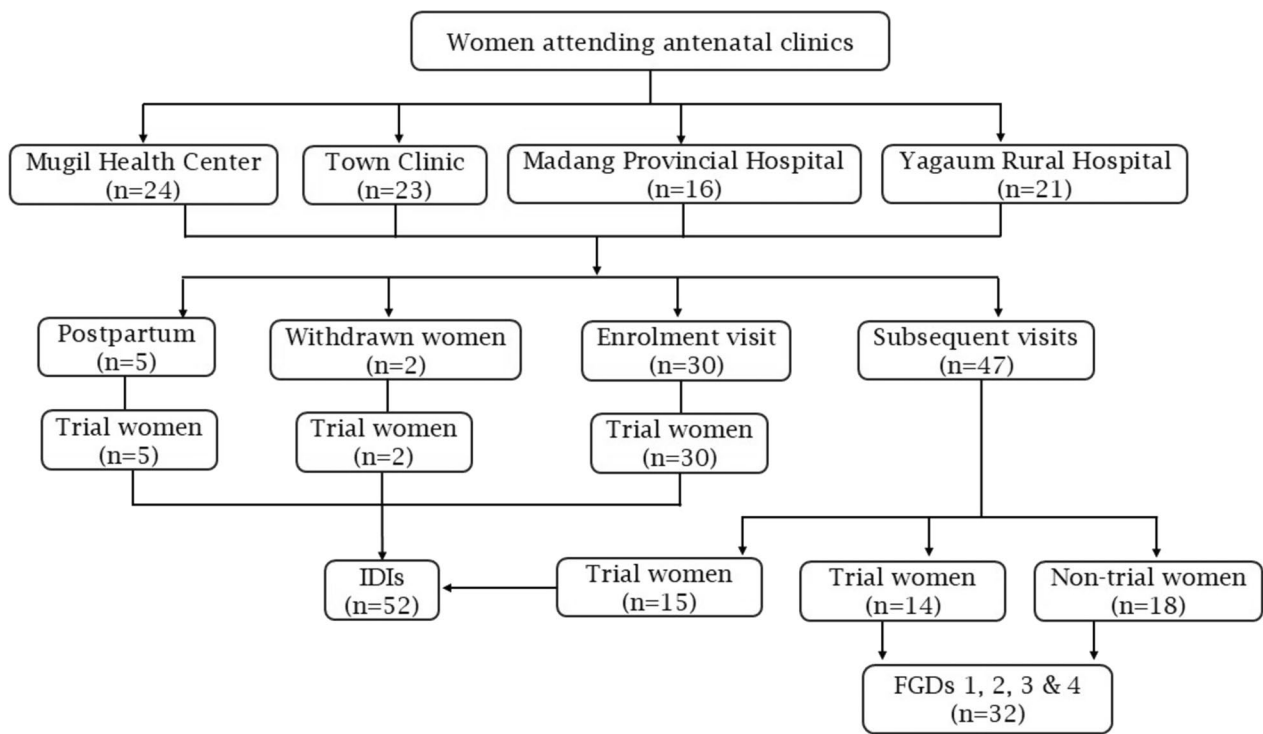


Fig. 2 Flowchart for women involved in in-depth interviews and focus group discussions

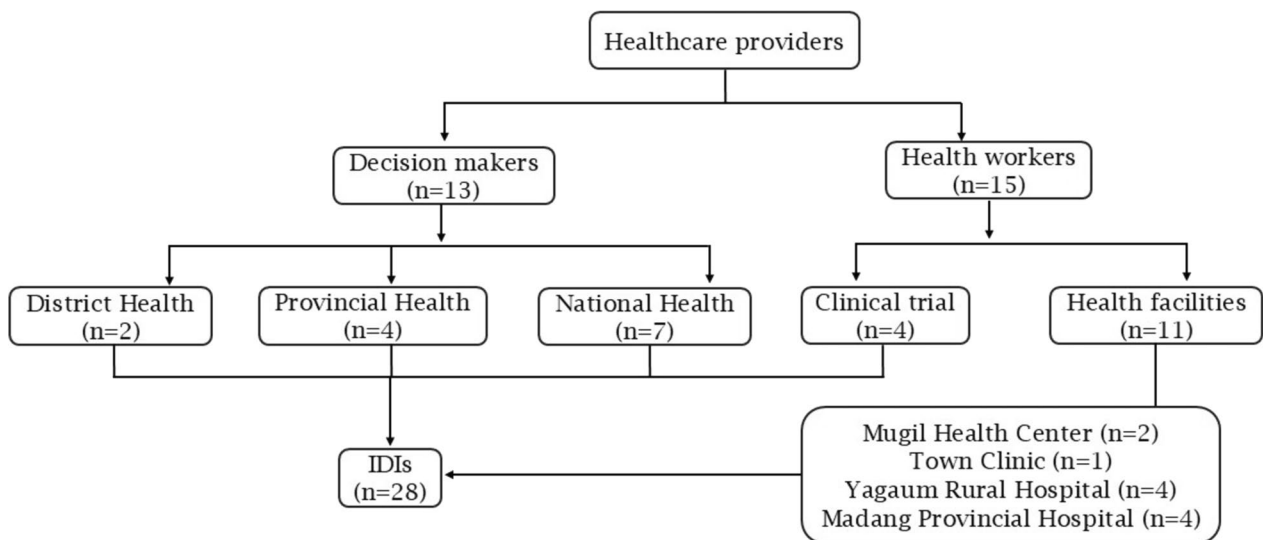


Fig. 3 Flowchart for healthcare providers involved in in-depth interviews

trial proceedings, i.e., prior to commencing IPTp-SP plus DP/DP-placebo course, whilst taking IPTp, or following birth after having taken IPTp. Trial participants who had taken study medications but subsequently withdrew from the parent trial were also invited to take part in IDIs. FGDs were conducted with pregnant women enrolled in the parent trial and pregnant women attending antenatal

clinics but not enrolled in the trial. Semi-structured topic guides for IDIs and FGDs were designed according to the framework of acceptability of healthcare interventions proposed by Sekhon et al. [37]. These guides were tested through mock interviews to refine questions and develop probes that allowed this study to address the framework and other aspects of care. The topic guides

allowed evaluation of acceptability of IPTp-SP plus DP; factors affecting adherence to IPTp; and perception and experiences of preventive care, medical interventions, and the clinical trial (Supplementary file 1). Trial participants were identified by clinical trial staff at either study enrolment (first antenatal clinic visit), subsequent antenatal clinic visits, or postpartum, to reflect different time points in relation to IPTp administration, and to ensure representation across all randomization codes (IPTp-SP plus DP or IPTp-SP plus DP-placebo), without unblinding the trial. For FGDs, pregnant women who were not enrolled in trial but presented to antenatal clinics at the same health facility were selected through purposive (by clinical trial or health facility staff) and/or snowball sampling—all these women had experience with IPTp-SP based on their clinic book. Participation in the present study was voluntary and did not affect women's ANC or parent trial participation. Clinical trial staff worked alongside local health facility staff at the mentioned clinics.

IDIs for trial participants were held in separate rooms at each health facility. The responses obtained from each participant varied, and IDIs lasted 13 to 44 min, as guided by study participants. One FGD per health facility was conducted to engage women exposed to different IPTp regimens (SP plus DP/DP-placebo or SP alone) and residing at various localities (rural, peri-urban or urban), as well as to triangulate and validate views gathered from IDIs. FGDs were held in a conference room or outdoors near the antenatal clinic. FGD participants included pregnant women only, including those engaged in the parent trial and those receiving routine ANC outside of the clinical trial. Each FGD comprised 6–10 participants, with similar proportions of trial and non-trial participants; this group size allowed for active participation and interactive in-depth discussions. Participatory methods were utilized in FGDs to enable engagement and ensure that data collection was culturally appropriate (Supplementary file 2).

The participatory methods of brainstorming, storytelling, fishbowls, and target evaluation were designed to effectively engage women in the group discussions [43, 44]. Each participatory method used different topic guides including interview guides to explore women's experience on pregnancy, ANC, malaria (preconception and during pregnancy) and IPTp (SP plus DP/DP-placebo or SP alone) to draw wide range of opinions relevant to the framework. These methods of data collection obtained a free flow of responses, allowing a quick and easy means of collecting data from all participants. The responses obtained among participants within each group discussion varied, and FGDs lasted from 54 to 67 min, as guided by participants. The IDIs and FGDs for

women were aligned with antenatal clinic visits and were held in a local lingua franca ('Tok Pisin') based on participant availability. All IDIs and FGDs for women were coded as ASTP and ASTP-FGD, respectively.

IDIs: health workers and policymakers

IDIs were conducted with health workers, including clinical trial and health facility staff, and policymakers involved with the provision of ANC and IPTp. Data collection followed semi-structured topic guides that included: perceptions of IPTp; adaptations to working practices that would be required to implement IPTp-SP plus DP; recommendations on factors to be considered to ensure effective implementation; perception of the feasibility of implementing IPTp-SP plus DP into routine practice; and enablers and barriers to the translation of findings into practice in PNG (Supplementary file 3). Health workers were sampled purposively and through snowballing at the health facilities where the parent trial was conducted and included trial and non-trial staff. They included administrators, doctors, health extension officers, midwives, nurses, and community health workers. Stakeholders purposively selected at national, provincial and district levels included academics, programme managers of the relevant Divisions at the National Department of Health in Port Moresby and managers of health authorities in Madang Province. The different cadres of health workers and policymakers identified at each health facilities and across district, provincial and national health authority levels were invited to take part in this study. Participants were interviewed based on their availability. All IDIs for health workers and policymakers were held in 'Tok Pisin' or English, based on the interviewee's preference, and at a location of their choice. The responses obtained from each participants varied, and interviews lasted from 8 to 53 min, as guided by study participants. Data saturation was reached when no new information was generated from interviews or FGDs [45]. Data were triangulated from IDIs and FGDs to corroborate findings. All IDIs for health workers and policymakers were coded as ASHW and ASPM, respectively.

Data management and analysis

All IDIs and FGDs were recorded using a digital audio recorder. Recordings were transcribed verbatim in the originally spoken language and coded to maintain the anonymity and confidentiality of participants. IDIs and FGDs held in 'Tok Pisin' were translated into English. Back-translation was conducted by a co-investigator (NN) and the qualitative research team at the PNG IMR for a selection of interview translations to ensure the translations were accurate. IDIs conducted in English were transcribed using Otter.ai (Otter.ai, Inc.,

California, USA) and edited for accuracy. Transcriptions and translations were verified by the principal investigator (EL) for quality assurance and detection of unintended diversion in meanings of the context.

Finalized transcripts of IDIs and FGDs were manually coded (EL, SP) using both deductive and inductive approaches. Pre-defined themes were identified through the review of existing literature and deductive application of the theoretical framework proposed by Sekhon et al. on acceptability of healthcare interventions [37]. Emerging themes were inductively identified in the data through a content analysis [46]. Any differences in coding between coders and approaches were discussed until a consensus was reached. Concomitant use of deductive and inductive approaches allowed research to build on existing literature while remaining open to new findings from this specific study and context. Building on the theoretical framework of acceptability of healthcare interventions developed by Sekhon et al., the analysis centred on assessments of affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity cost and self-efficacy (Fig. 4a) in relation to IPTp [37]. Quotes in the results are indicated in *italics*. Context and additional information provided in the quotes are indicated with [square brackets] whereas omitted non-relevant section of the texts are indicated with [...].

Results

Characteristics of participants

A total of 112 participants were involved in IDIs and FGDs. 84 women from all health facilities participated in the qualitative study, including 52 in IDIs and 32 in FGDs (Fig. 2 and Table 2). The mean (standard deviation) age of women involved in the study was 26 ± 6 years and the majority were aged 20 to 29 years ($n=50$; 59%). Three-quarters of women were paucigravid ($n=55$, 66%). Most women resided in rural areas ($n=59$, 70%) and were from PNG's Momase region ($n=67$; 80%), predominantly from Madang Province ($n=57$, 85%). Most women were recruited at Mugil Health Centre ($n=26$; 31%), followed by Yagaum Rural Hospital ($n=21$; 25%), Town Urban Clinic ($n=21$; 25%) and Madang Provincial Hospital ($n=16$; 19%) (Table 2).

Of the 80 IDIs conducted, 28 were undertaken with different cadres of healthcare providers including 15 health workers involved in the provision of ANC and IPTp (4 of them were clinical trial staff) and 13 policymakers from the district, provincial and national health authorities (Fig. 3). Most of the healthcare providers ($n=25$; 89%) interviewed had clinical expertise in ANC and IPTp provision.

Affective attitude

The measure of affective attitude focuses on the individual feelings of participants about the intervention. Most women enrolled in the clinical trial expressed positive feelings and attitudes towards the SP plus DP intervention. Women stated that they felt: happy, great, all right, just fine, and satisfied in terms of taking IPTp and participating in the clinical trial. An interviewed pregnant woman involved in the trial stated, "*The SAPOT study (parent trial) is satisfactory, from my observation. Regarding the medicine they provide, it is satisfactory from my observation, so I am happy to have enrolled with them.*" [ASTP001]. Positive feelings were largely associated with how participants were treated during the trial; for example, they felt that they were treated nicely by trial staff and cared for during their antenatal clinic visits. Positive attitudes were also attributed to perceived benefits within the trial context, including thorough examinations, ultrasounds, advice, free health record books and IPTp itself.

An interviewed pregnant woman enrolled in the trial stated, "*I am interested to be in the study because of the treatments that I am going to get.*" [ASTP026]. Some multigravid mothers felt the treatment and care they received in this pregnancy were better, compared to the care received in their previous pregnancies. An interviewed pregnant woman involved in the trial stated, "*For the first [pregnancy], I came, and they only checked the baby, checked my tummy and they only gave the blood medicine. Okay for the current [pregnancy] they are checking thoroughly. They checked the blood, checked the baby [on ultrasound] and they are giving the medicine well.*" [ASTP007].

Aligning with sentiments of trial participants, most healthcare providers had positive perceptions of the SP plus DP/DP-placebo. They felt that the new medication would better protect against malaria and associated complications in pregnancy, identified as enlarged spleen (splenomegaly), anemia, or miscarriage. They recognized limited impacts of SP, reporting more mothers infected with malaria during pregnancy and at delivery despite having taken IPTp-SP. A health worker not involved in the trial stated, "*I think this is a good initiative to find ways to improve malaria treatment in Madang because we were seeing that Fansidar [SP] is not really helping for the last couple of years*" [ASHW006]. In addition, most healthcare providers emphasized the importance of research to achieve positive health outcomes for PNG, particularly for maternal and child health. They felt that research provided the evidence required to change treatment and improve health outcomes.

A health worker not involved in the trial stated, "*I think all our health and treatment and knowledge keeps changing. So, I think by all means, we should do all the*

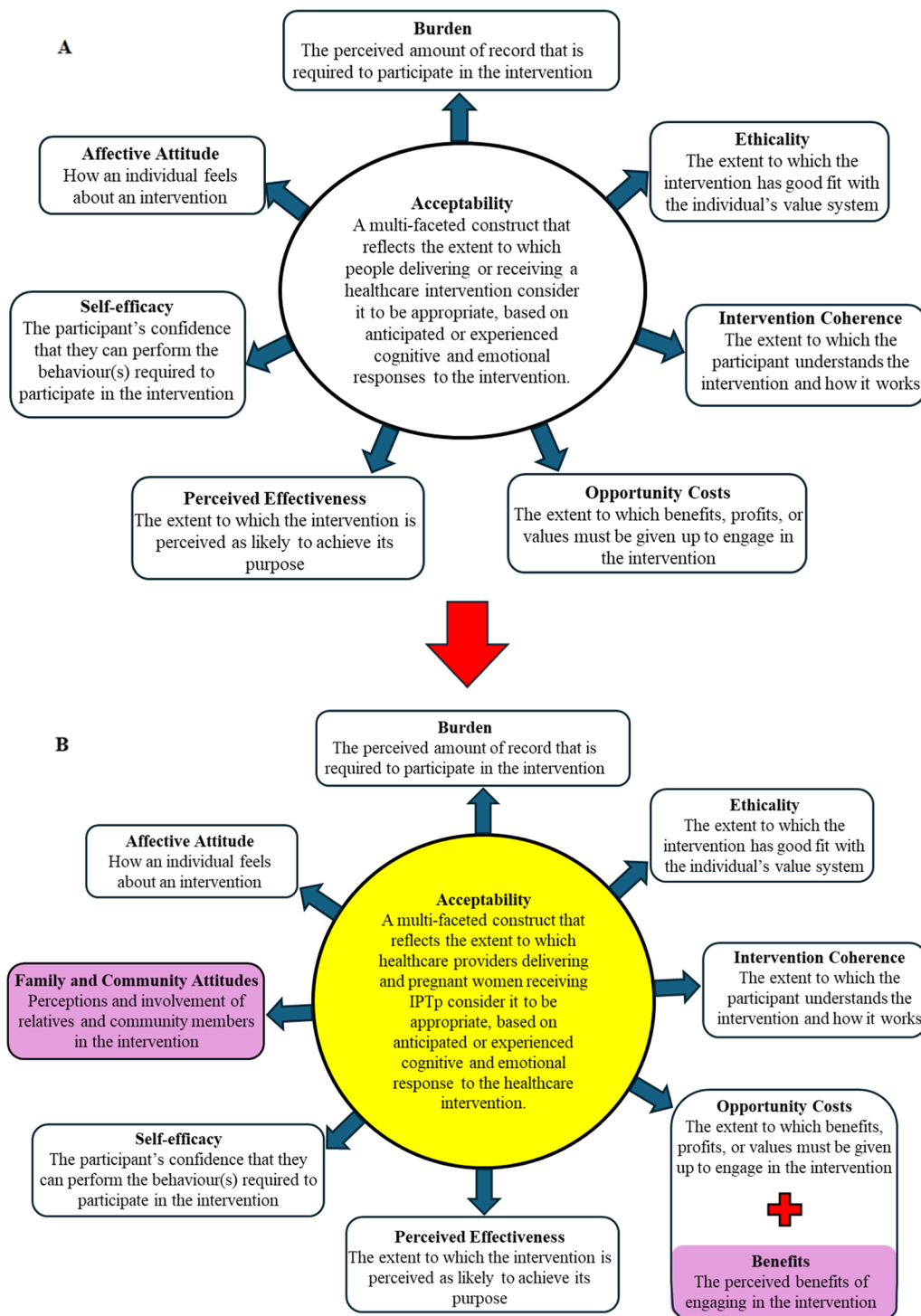


Fig. 4 **a** Analysis framework of acceptability according to Sekhon et al. [37]. **b** Expansion of framework based on emerging additional dimensions are highlighted in purple

studies that we can do. This will just improve our health and outcomes of our health in the future for our people.” [ASHW004].

Burden

Within the conceptual framework, the measure of burden refers to the perceived amount of effort required

Table 2 Characteristics of women involved in in-depth interviews and focus group discussions

Characteristics	Participants		
	IDI	FGD	Total
Number	52	32	84
Age range (years)			
15–19	5 (10)	5 (16)	10 (12)
20–24	17 (33)	5 (16)	22 (26)
25–29	17 (33)	11 (34)	28 (33)
30–34	8 (14)	6 (18)	14 (17)
35 and above	5 (10)	5 (16)	10 (12)
Marital status			
Single	4 (8)	3 (9)	7 (8)
Married	48 (92)	29 (91)	77 (92)
Gravidity			
Gravida 1	20 (38)	10 (31)	30 (36)
Gravida 2	17 (33)	8 (25)	25 (30)
Gravida 3 or more	15 (29)	14 (44)	29 (34)
Place of residence			
Rural	37 (71)	22 (69)	59 (70)
Urban	15 (29)	10 (31)	25 (30)
Education status			
Tertiary	7 (14)	–	7 (8)
Secondary	21 (40)	21 (66)	42 (50)
Primary	23 (44)	10 (31)	33 (40)
No schooling	1 (2)	1 (3)	2 (2)
Region of origin			
Momase	39 (75)	28 (87)	67 (80)
Others	13 (25)	4 (13)	17 (20)
Health facility			
Mugil Health Centre	18 (35)	8 (25)	26 (31)
Town Clinic	14 (27)	7 (22)	21 (25)
Madang Provincial Hospital	9 (17)	7 (22)	16 (19)
Yagaum Rural Hospital	11 (21)	10 (31)	21 (25)

Data are number (percent)

IDI: in-depth interview, FGD: focus group discussion

to participate in the intervention. In the context of this trial, there was a low perceived burden for women taking IPTp (SP plus DP or DP-placebo). Most trial participants included in IDIs reported no side effects and expressed no concerns over the size, number, colour, and taste of the tablets provided. An interviewed pregnant woman enrolled in the trial stated, “When I took it [study medications], it was just normal as I’m drinking medicine. [...] I did not feel anything [side effects].” [ASTP002].

Some trial participants who were questioned in IDIs reported being initially ‘scared’ of the blue-coloured pill (DP/DP-placebo) but persevered with taking study medications. Other women expressed that they had not

previously taken six tablets at once, but they also mentioned that taking this medication was like Panadol, so they were not unfamiliar with the size or taking such tablets. An interviewed postpartum trial participant stated, “Well, six [tablets] are a lot, but I thought of myself and the baby, so I have drunk it.” [ASTP032]. More common side effects reported in IDIs were nausea and vomiting, while dizziness was the least reported side effect and occurred in only a small number of women interviewed. Notably, those IDI participants who reportedly vomited after taking IPTp (SP plus DP/DP-placebo) associated this with taking the medication on an empty stomach. Most of the IDI participants who had reported nausea or vomiting, stated that they experienced these side effects only with the first dose of the first IPTp treatment course and not with the subsequent doses that they took at home, or subsequent IPTp treatment courses. Only two mothers, who withdrew from the clinical trial at the time this qualitative evaluation was conducted, reported repeated episodes of vomiting experienced with their subsequent monthly IPTp doses. Overall, the side effects were outweighed by the perceived benefits of the medication and the benefits of participating in a clinical trial. An interviewed pregnant woman engaged in the trial stated, “The first time I took it, I felt like vomiting. But now I’ve been taking [the medication], it’s normal.” [ASTP015].

From the healthcare provider perspective, interviewed participants indicated that the additional tablets on day one, and the increased number of days to complete a treatment course, may be barriers to acceptability for patients outside the clinical trial setting. Women and health workers are well accustomed to IPTp-SP doses but increasing the treatment course to three days was flagged as a concern. Healthcare providers felt that the SP plus DP medication would be more effective to prevent malaria but were concerned about the pill burden and size of tablets and whether women would be compliant in completing their doses and/or attending their subsequent monthly antenatal clinic visits to receive further IPTp treatment courses. As a policymaker stated, “I think probably that would be the main thing, the number of tablets and I know a lot of our women nowadays will be asking like, is it good for the baby? Like, is it going to have side effects for the baby? I think it’s all just about educating our mothers about the importance of taking many tablets, but for good reason.” [ASPM001].

To improve acceptability of the intervention, healthcare providers highlighted that ANC education is important to raise awareness about malaria in pregnancy and the need for preventive treatment. Furthermore, they emphasized that this education should be provided to both expectant women and health workers to ensure broad community understanding and acceptance. As a

health worker involved in the trial explained, “It [SP plus DP] is good for you and the baby. We know that it will not affect the baby and you. It will help you and the placenta where parasites of malaria are, it will help with that so you can drink. We will say that, and they will drink.” [ASHW011].

Some healthcare providers suggested reducing the size of tablets and/or combining the tablets to reduce the number of pills to increase acceptability. A health worker not involved in the trial stated, “The medicine, I would say it’s plenty. It will be plenty, and some mothers will refuse to take the medicine. They can find a combination for them to take that is valid for three days or just one medicine [combination tablet] only for three days, is okay.” [ASHW009].

Another health worker not involved in the trial stated, “If we reduce the size of the drug or we reduce the number of tablets being given, and we observe, directly observe and they drink, then we are 100% sure that they will drink and also the size of the medicine will make the patient be happy to drink.” [ASHW012].

Ethicality

This measure of acceptability centres on the extent to which an intervention is perceived to be a good fit with the participants’ value system. For this study, ethicality was related to the worldviews of women participating in the parent trial regarding taking medication; specific questions focused on using traditional medicine like herbs and Western medications from the health centre. While some women indicated that they used traditional medicines, most did not use these during pregnancy in fear of the harm it could potentially cause to their unborn child. Amongst others, herbal steam baths, paw-paw leaves, and lemon grass were common herbal remedies used by women at home as an initial treatment for malaria before seeking for medication at the health facility. These women expressed combining both traditional remedies and Western medication to treat malaria. An interviewed pregnant woman enrolled in the trial stated, “I got the flower of the pawpaw. I finished drinking it [...]. It helped a bit, then I went to the clinic and got Mala-1 [artemether-lumefantrine].” [ASTP035].

Most women used painkillers and/or went to the health centre when sick, so taking tablets during the clinical trial did fit with their value system. An interviewed pregnant woman enrolled in the trial stated, “I don’t think I will get herbs or whatever, but I need to come and talk with the nurses, and they prescribe anything for me to do, I will just do it.” [ASTP042]. Ethicality was also high among health workers who acknowledged that the intervention was a modification of an existing IPTp regimen currently used

for malaria in pregnancy in PNG and that women were already familiar with the concept of preventive treatment.

Intervention coherence

Intervention coherence relates to how participants understand the medication and clinical trial being administered. For this study, participants’ understanding of the parent trial and the medicines provided varied. Some participants had a basic understanding that the medication would protect them and their baby from malaria, and others understood additional details about killing parasites and protecting the baby in the womb. As stated by an interviewed pregnant trial participant, “The function of these medicines is to kill parasites.” [ASTP005]. While some women reported they were well informed about the medicine before they started taking it, others reported limited explanation or education. For example, some interviewed pregnant women involved in the trial expressed, “They have provided information about the medicine given, care of the baby and the mother. We were informed about all this. They have talked to us and have given us a document.” [ASTP001]. “They have explained very well to me. [...] I have fully understood what they have told me today.” [ASTP026]. Another interviewed pregnant trial participant stated, “I feel that they need to explain a bit more so we can have better understanding.” [ASTP023].

There were noted differences in understanding between women who had just enrolled in the study (first antenatal clinic visit) and those who were already enrolled and had taken multiple doses of IPTp-SP plus DP/DP-placebo. This suggests that intervention coherence increased throughout the clinical trial as participants were provided education at each antenatal clinic visit. There were also differences in understanding between first-time women and those who had previous pregnancies. Women with prior pregnancy experiences understood that IPTp and iron supplements are provided routinely at antenatal clinic and were necessary for their health and that of the baby.

Healthcare providers interviewed had clear knowledge and understood the rationale for adding DP to SP for IPTp. Healthcare providers were also aware that SP has non-antimalarial benefits that support the baby’s growth. Their knowledge of the trial medication was enriched from engaging with the clinical trial team and/or participants or information provided to them as part of their invitation to participate in an interview for this qualitative study. In addition, they were aware blood samples and placental biopsies were collected during the trial to investigate the effect of the medication on malaria parasites and adverse birth outcomes. As a policymaker stated, “So, my understanding, this is a trial that’s looking

at how effective the addition of the dihydroartemisinin-piperaquine to Fansidar [SP] that is in reducing rates of malaria in pregnancy and all the associated poor [birth] outcomes." [ASPM003].

The healthcare providers emphasized the need to educate women, communities, and health workers about this research and potential changes to IPTp policy for effective implementation and uptake. Educating and engaging health workers was central for both intervention coherence and potential future changes to IPTp guidelines and practices. A policymaker stated, "They [health workers] will say we don't have any training and why you are implementing the new things, and they will be a resistant. But if it's beneficial, I don't think there will be any resistance." [ASPM011].

Opportunity costs and benefits

The framework by Sekhon et al. includes opportunity costs related to the profits or values that must be given up to engage in an intervention. 'Benefits' emerged as a factor warranting further investigation through this analysis and were captured within this measure (Fig. 4b). While the original criteria focused solely on opportunity costs, the present analysis indicated that there was a range of benefits associated with engaging in the clinical trial that may influence adherence and participation. Women reported benefits of being part of the clinical trial, including additional staff meaning they do not have to wait at clinic, thorough checks of their baby, ultrasound scans, learning the position of the baby, and coverage of delivery bed fees, medicines, health record books, and ITNs. As stated in an interview by a postpartum woman involved in the trial, "Number one is the drugs they gave, number two is they check how the baby is lying and importantly is the [ultrasound] scan which they provided that motivates me to come join IMR's [Institute of Medical Research] study, that's all." [ASTP027].

Another interviewed pregnant trial participant stated, "From my view, I want to be in the study because of the medicine given to us and also as they thoroughly checked on us and that is why I am happy to be part of the study." [ASTP001]. Only one participant mentioned an opportunity cost associated with taking time away from work to go to the clinic to participate in the study.

Perceived effectiveness

Perceived effectiveness refers to the extent to which the intervention is perceived as likely to achieve its purpose. In this case, the perceived effectiveness of SP plus DP medication was high; most women reported that they did not get malaria or felt sick during this pregnancy and attributed this to the medication. An interviewed postpartum trial participant stated, "Maybe these drugs

I've been taking have been helping me and the baby, so I haven't been sick [with malaria]." [ASTP032]. Another interviewed pregnant trial participant expressed, "The medicine that I come to the clinic and get, I think that I haven't been sick because of these medicines." [ASTP004]. Moreover, most women affirmed they had been sleeping under the ITNs, apart from taking the trial medication and attributed the added benefits of using this malaria preventive measure.

An interviewed pregnant woman involved in the trial stated, "It is because I am drinking the medicine, and I am also sleeping under the mosquito net. It is protecting, preventing it [malaria]." [ASTP038]. Some multigravid women compared the effectiveness of the trial medication to the IPTp regimen they had received in their previous pregnancies, some reporting that they had frequently been sick with malaria during pregnancy.

An interviewed postpartum woman involved in the trial stated, "This is my second baby. With the first baby, I had a very severe malaria, I came and got admitted at Mugil [Health Centre] and I thought that with this second child it would be the same. I am going to get this same sick, malaria, but no. I joined this IMR's study [parent trial], and I was not sick until I had this baby." [ASTP029].

An interviewed woman who had withdrawn from the parent trial stated, "I thought that maybe I was getting the study drugs from the IMR [clinical trial], so I did not get malaria, but now I have left and stayed out, so I got malaria." [ASTP052].

Healthcare providers also perceived that SP plus DP could reduce the malaria burden in pregnancy and address the issue of malarial parasites resistance to SP. Healthcare providers were also concerned about the efficacy and effectiveness of SP being provided alone as an IPTp regimen in PNG. A policymaker stated, "Obviously, if the drug [SP] is not working, it's not working, we cannot do much about it. Except that at least in terms of like treatments, the first line [artemether-lumefantrine] that we use currently there are programmes in monitoring its efficacy and all that. But for SP we still have not been able to do [local] efficacy studies." [ASPM006].

Self-efficacy

Self-efficacy is defined as peoples' confidence that they can perform the behavior required by the intervention. Within the context of the parent trial, self-efficacy was high, and participants reported that they took the medication faithfully. An interviewed pregnant woman engaged in the trial stated, "I drank it. I drank it. I didn't throw any medicine away. I really made use of it." [ASTP001]. Another interviewed pregnant trial participant stated, "I usually take it faithfully at home. I haven't missed any." [ASTP010].

While some women indicated that they were not used to taking six tablets at once and had a history of vomiting when taking medicines, most persevered with taking study medications. An interviewed pregnant trial participant stated, “*That’s something that usually happens to me. Ever since I was young, I feel like vomiting when I take medicines.*” [ASTP005].

While trial participants reported high levels of self-efficacy, healthcare providers were concerned about the provision and uptake of the current IPTp-SP regimen in PNG. The frequency and uptake of the IPTp regimen depends on the women’s timing of ANC attendance and the number of antenatal clinic visits. Some women attend antenatal clinic late in the third trimester or only once during their pregnancy or come only for delivery. Some factors that influence IPTp provision as a directly observed therapy and this varied between health facilities, depending on the health workers’ workload or availability of resources, such as cups and/or clean water at the clinic, to support women in taking IPTp tablets.

As expressed by policymakers, “*At the moment, we are not really implementing the directly observed treatment of Fansidar [SP]. We give women and then we tell them to go and take it at home when we’re supposed to be seeing them taking it in front of us.*” [ASPM005]. “*So, you don’t know if they drink them or not. Some of them, if they have water with them, they will take it in the clinic, but most of them, they will take the [SP] packet home to drink. So, you just have to trust that they actually will drink it. But you never know.*” [ASPM001]. While healthcare providers were concerned about whether women were compliant in taking the IPTp regimen at home, mothers often wanted to take the drug at home because they may not have eaten in the morning or wanted to take the medication before sleep. These factors were deemed important to consider when aiming to maximize self-efficacy and compliance.

Family and community attitudes

An additional construct ‘family and community attitudes’ emerged from this study and was added as a new measure to the acceptability framework (Fig. 4b). Family and community attitudes encompass the perceptions and involvement of relatives as well as community members in the intervention. In this case, many women expressed that they were referred to the IMR and the parent trial by a family member or someone they knew from the village. As stated by an interviewed pregnant trial participant, “*I wasn’t supposed to come here [this clinic] but my in-law told me to come and [enroll] with the IMR clinic [clinical trial], so I came. She brought me here herself and enrolled me here.*” [ASTP002].

Another interviewed pregnant trial participant mentioned, “*There is this sister who works with IMR. She*

brought me here. She knew so, she told me, I will take you to IMR group.” [ASTP004]. Additionally, an interviewed postpartum woman involved in the trial stated, “*I was [at home], one of my aunties was their helper [study community reporter] so she went and talked about it [the clinical trial]. So, me and my husband were happy to see the baby [on ultrasound].*” [ASTP009].

Apart from family and community members, some husbands were supportive in engaging with their pregnant partners and allowing them to join the clinical trial for their ANC. An interviewed pregnant woman enrolled in the trial stated, “*I was interested, then my husband agreed, and he said, ‘let’s go.’ He said, ‘first you go [to the clinic], you will join IMR [clinical trial].*” [ASTP020]. This relationality was important for building trust and increasing acceptability and adherence to study intervention. This is significant in terms of adapting frameworks for acceptability to fit with the PNG context and other settings with similar social/familial relationality in the Pacific or elsewhere.

Discussion

The provision and uptake of IPTp-SP plus DP/DP-placebo in the context of a clinical trial in PNG was acceptable among users and providers in this study. Both women and health workers valued the perceived benefits of the novel IPTp regimen to prevent malaria and malaria-associated adverse pregnancy outcomes. Trial participants accepted the practical aspects of the new IPTp regimen, including the tablets size, number and treatment days and drug-associated side effects were uncommonly reported. Healthcare providers were concerned about the effective implementation and uptake of IPTp-SP plus DP outside a clinical trial. The enabling factors that more broadly increased the acceptability of the new IPTp regimen included ANC education and awareness, and the newly identified framework domains: i) benefits of healthcare provision including ultrasound, and other medicines for parent trial participants; and ii) family and community attitudes, which were influenced by engagement with the current trial and other previous clinical research.

The acceptability of IPTp-SP plus DP/DP-placebo was high amongst participants. Whilst tablet size, appearance, number and multiple dosing were of some concern, these practical aspects did not hinder women from taking their initial SP plus DP/DP-placebo dose or the subsequent DP/DP-placebo doses. In multi-country clinical trials providing DP plus azithromycin for IPTp to pregnant women or DP plus mefloquine for uncomplicated malaria treatment in non-pregnant patients, there were no reported issues with the practical aspects of administering these regimens [47, 48]. However, their

acceptability was not specifically assessed. In the present study, some trial participants were hesitant to take six tablets at once. Several interviewees raised concerns over the appearance of DP/DP-placebo tablets, specifically their blue colouration, which may have arisen as women may not be accustomed to this colour or could be due to yet-to-be explored cultural factors. In non-pregnant hospitalized patients, preference to specific tablet colour, size and shape were factors influential to medicines uptake [49]. The dislike for blue colouration in the current study may be an important finding for manufacturers, who may wish to alter the colour of DP tablets to increase acceptability in this context. However, in settings like Papua, Indonesia, where DP has been used as the first-line treatment for clinical malaria over a decade, patients appear accustomed to the colour and associated “blue pills” (DP) with effective treatment for malaria [50]. In addition, healthcare providers suggested to combine SP and DP to reduce the number of pills that need to be taken, or to reduce tablet size, to enhance acceptability. Enhanced formulations of anti-malarials including DP have been shown to improve uptake and acceptability in relation to malaria treatment in children [51]. The formulation, number of tablets and their appearance can be critical to their acceptability and evaluation of these aspects for anti-malarials administered as IPTp or treatments in pregnant women must be considered in future studies.

Side effects associated with administering the IPTp regimen (SP plus DP or DP-placebo) were uncommon and manageable and did not substantially influence acceptability. Only a small number of IDI participants reported nausea, vomiting or dizziness. This aligns with findings from clinical trials comparing IPTp-SP with DP, or DP plus azithromycin, in which most women tolerated study drugs well [24, 47]. In other studies, IPTp-SP was associated with vomiting, nausea, weakness, and dizziness with the first dose, and these side effects decreased with subsequent treatment courses [34, 35, 52]. In the present study, side effects mostly occurred after the initial dose taken on day one of the first antenatal clinic visit and not often on subsequent treatment courses. Some women who had nausea or vomited in the current study associated this with taking study medication on an empty stomach, mirroring reports from women randomized to SP or DP for IPTp in a clinical trial in Kenya [36]. Some trial participants related these side effects to their experiences when taking any type of tablet. The present study was unable to evaluate differences in tolerability by trial arm as it was conducted closed-label, but similar clinical trials comparing SP to DP alone, or to DP plus azithromycin, reported comparable or minor differences in tolerability across study arms [24, 34, 35, 47].

In support of the perceptions of women, healthcare providers understood the beneficial aspects of the new medication and its effects on placental malaria and adverse birth outcomes that are prevalent in this setting [19, 40, 41]. The new IPTp regimen was perceived to protect the women and her unborn baby and prevent malaria-associated adverse pregnancy outcomes, which was a motivator for participation in the parent trial and uptake of the IPTp regimen. Perceived healthcare benefits for the women and their baby were key drivers of acceptability in trials of DP for IPTp or intermittent screening and treatment in pregnancy [36, 53], which aligns with findings of the present study. Regular ANC education, previous experience of IPTp and prior use of anti-malarials in pregnancy improved acceptance of trial medications in the current study. Furthermore, the engagement of community and family members with the clinical trial alongside trial participants, health workers and community volunteers helped to build trust and increase recruitment and acceptability. In contrast, evidence elsewhere has shown that relatives and community members as well as pregnant women often had negative attitudes towards ANC and IPTp [54]. The education for family and community members seen in this study increased awareness and appeared to improve acceptability, which is important for the PNG context [42] and other similar malaria-endemic settings. To improve IPTp provision and uptake, healthcare programmes should engage with family and community members.

Healthcare providers were optimistic that evidence provided from the clinical trial could critically inform malaria treatment practice in PNG, but emphasized the need to educate women, health workers and communities on the broad benefits of IPTp, and more specifically on the intricacies of IPTp-SP plus DP, to enable effective implementation and uptake of this medication outside of a clinical trial. The acceptability of the new IPTp regimen was assessed in a clinical trial context and may differ in routine antenatal clinic settings. This aligns with findings from similar research in other malaria-endemic settings where healthcare providers of different cadres acknowledged the need for education to enable implementation [36]. Furthermore, healthcare providers were concerned about health system barriers, particularly supply chains and barriers to access of antenatal clinic to receive IPTp. Similar views were also raised in other clinical trials providing DP for IPTp or intermittent screening and treatment in pregnancy [36, 53].

The participants' positive feelings about SP plus DP/DP-placebo in this study may have likely been influenced by the level of care provided at antenatal clinic visits through the parent trial infrastructure. All trial participants perceived parent trial staff as open and friendly

with caring attitudes when attending to them, and some reported reduced waiting time at the clinic. Others complained of the delay in ANC processes, which was attributed to participation in the parent trial. In addition, trial participants were motivated about the perceived benefits of ultrasound, which was provided as part of the parent trial protocol. Women's attitudes and feelings in accepting the IPTp regimen were further enhanced through healthcare benefits, including good supply of anti-malarials, provision of health record books and ITNs and coverage of delivery fees as part of the clinical trial, as especially noted by multigravid women. The availability of free, quality healthcare and helpful attitudes of the parent trial staff have extensively influenced the acceptability of the new medication among women, reflecting findings observed in other similar clinical trials elsewhere [36, 55]. This shows that interventions are acceptable if combined with good healthcare and highlights the difficulty in separating the new intervention (SP plus DP) from the antenatal clinic context when assessing the acceptability of an intervention. Hence, this demonstrates the importance of a holistic approach to understanding all factors influencing acceptability and uptake [36]. Future pilot implementation studies are needed to confirm acceptability in a 'real life' setting, alongside evaluations of program effectiveness and women's adherence to a proposed novel IPTp regimen. For example, a pilot study in Papua, Indonesia was conducted to assess the effectiveness of IPTp-DP delivered through ANC services in a real-life setting (ClinicalTrials.gov NCT05294406). Such information could support National Malaria Control Programmes in effectively implementing this IPTp regimen and be relevant to policy recommendations from the WHO.

IDIs and FGDs included a wide range and large number of participants. The study included women participating in the parent trial who were interviewed pre-intervention, during intervention and post-intervention as well as other women with experience of pregnancy and IPTp. Apart from women, a variety of policymakers across national, provincial and district levels and health workers involved with primary, secondary and tertiary healthcare services were considered. This ensured the analysis captured a wide range of experiences and perspectives. The qualitative data allowed us to critically examine all components of the theoretical framework of acceptability including the addition of constructs relevant to the local context that may be relevant to other similar malaria-endemic settings, particularly in the Pacific. Expanding the theoretical framework based on additional constructs emerging from study findings (Fig. 4b) emphasized the importance of enabling factors for users that can build trust and influence their participation, adherence, and acceptability of healthcare interventions.

There were some limitations to this qualitative study. As qualitative studies are focused on rigor rather than generalizability, the study findings may not be representative of other malaria-endemic areas in PNG. Further studies from other malaria-endemic areas in PNG may be needed to validate the findings of this study. However, sufficient participants within the study setting were recruited to reach saturation [45], which was reflected when no new themes were emerging from the analysis. As the clinical trial was blinded, the present qualitative enquiry could not determine the potential impacts of side effects of DP on acceptability. Nevertheless, side effects did not emerge as a major deterrent and study medications were identical in terms of number of tablets, treatment days, and treatment course intervals, although these findings may be subject to recall and social desirability bias.

Conclusions

In the context of a clinical trial in PNG, IPTp-SP plus DP was acceptable. Users and providers accepted DP among IPTp-SP plus DP/DP-placebo, and participants expressed positive feelings about the new IPTp regimen. Prior exposure and knowledge of preventive treatment and broader healthcare benefits received through the parent trial, positively influenced the acceptability of SP plus DP. The realities of supply chains, adherence to and implementation of IPTp-SP plus DP outside of a clinical trial setting were of concern to healthcare providers, who highlighted the need for educational activities to raise awareness amongst women, communities and health workers and enable implementation.

Abbreviations

ANC	Antenatal care
DP	Dihydroartemisinin-piperazine
FGD	Focus group discussion
IDI	In-depth interview
IMR	Institute of Medical Research
IPTp	Intermittent preventive treatment in pregnancy
ITN	Insecticide-treated bed net
PNG	Papua New Guinea
SP	Sulfadoxine-pyrimethamine
WHO	World Health Organization

Supplementary Information

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Additional file 1

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Author contributions

EL, HU, KT, SP and SR designed the study. EL, AA, AM, NN, JB, and ML collected and prepared the data. EL, SP and HU analyzed and interpreted the data. EL wrote the first draft of the manuscript. All authors read, reviewed and finalized the manuscript.

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Availability of data and materials

The data is available upon request from the authors.

Declarations

Ethics approval and consent to participate

Ethical approvals for this study were obtained from the Charles Darwin University Human Research Ethics Committee (H22094), the Human Research Committee of the Northern Territory Department of Health and Menzies School of Health Research (2021-4107), the PNG IMR Institutional Review Board (2113), the Madang Provincial Health Authority Research Ethics Committee (04.21), and Medical Research Advisory Committee of PNG National Department of Health (22.10). All participants provided written informed consent for this study. Women involved in the parent trial also provided written informed consent, independent of participation in the clinical trial. Methods used in participants recruitment, data collection, storage, processing, and analysis were carried out according to the Declaration of Helsinki, the Principles of Good Clinical Practice and PNG regulatory guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Reddy V, Weiss DJ, Rozier J, ter Kuile FO, Dellicour S. Global estimates of the number of pregnancies at risk of malaria from 2007 to 2020: a demographic study. *Lancet Glob Health*. 2023;11:e40–7.
- Desai M, ter Kuile FO, Nosten F, McGready R, Asamoah K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7:93–104.
- Brabin BJ, Romagosa C, Abdelgalil S, Menendez C, Verhoeff FH, McGready R, et al. The sick placenta—the role of malaria. *Placenta*. 2004;25:359–78.
- Mayor A, Moro L, Aguilar R, Bardaji A, Cisteró P, Serra-Casas E, et al. How hidden can malaria be in pregnant women? Diagnosis by microscopy, placental histology, polymerase chain reaction and detection of histidine-rich protein 2 in plasma. *Clin Infect Dis*. 2012;54:1561–8.
- Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. *Lancet Infect Dis*. 2018;18:e107–18.
- Rogerson SJ, Hviid L, Duffy PE, Leke RF, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. *Lancet Infect Dis*. 2007;7:105–17.
- Kattenberg JH, Ochodo EA, Boer KR, Schallig HD, Mens PF, Leeftang MM. Systematic review and meta-analysis: rapid diagnostic tests versus placental histology, microscopy and PCR for malaria in pregnant women. *Malar J*. 2011;10:321.
- Umbers AJ, Unger HW, Rosanas-Urgell A, Wangnapi RA, Kattenberg JH, Jally S, et al. Accuracy of an HRP-2/panLDH rapid diagnostic test to detect peripheral and placental *Plasmodium falciparum* infection in Papua New Guinean women with anaemia or suspected malaria. *Malar J*. 2015;14:412.
- WHO. Policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). Geneva, World Health Organization, 2013. Available from: <https://www.who.int/publications/item/WHO-HTM-GMP-2014.4> [accessed 1 July 2024].
- WHO. Guidelines for malaria. Geneva, World Health Organization, 2023. Available from: <https://iris.who.int/handle/10665/373339> [accessed 21 July 2024].
- Eisele TP, Larsen DA, Anglewicz PA, Keating J, Yukich J, Bennett A, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis*. 2012;12:942–9.
- Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA*. 2013;309:594–604.
- Desai M, Gutman J, Taylor SM, Wiegand RE, Khairallah C, Kayentao K, et al. Impact of Sulfadoxine-pyrimethamine resistance on effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight. *Clin Infect Dis*. 2016;62:323–33.
- Naidoo I, Roper C. Mapping 'partially resistant', 'fully resistant', and 'super resistant' malaria. *Trends Parasitol*. 2013;29:505–15.
- Desai M, Hill J, Fernandes S, Walker P, Pell C, Gutman J, et al. Prevention of malaria in pregnancy. *Lancet Infect Dis*. 2018;18:e119–32.
- van Eijk AM, Larsen DA, Kayentao K, Koshy G, Slaughter DEC, Roper C, et al. Effect of *Plasmodium falciparum* sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. 2019;19:546–56.
- Chaturvedi R, Chhibber-Goel J, Verma I, Gopinathan S, Parvez S, Sharma A. Geographical spread and structural basis of sulfadoxine-pyrimethamine drug-resistant malaria parasites. *Int J Parasitol*. 2021;51:505–25.
- Sundararaman SA, Odom John AR. Prevention of malaria in pregnancy: the threat of sulfadoxine-pyrimethamine resistance. *Front Pediatr*. 2022;10:966402.
- Unger HW, Acharya S, Arnold L, Wu C, van Eijk AM, Gore-Langton GR, et al. The effect and control of malaria in pregnancy and lactating women in the Asia-Pacific region. *Lancet Glob Health*. 2023;11:e1805–18.
- Barnadas C, Senn N, Iga J, Timinao L, Javati S, Malau E, et al. *Plasmodium falciparum* and *Plasmodium vivax* genotypes and efficacy of intermittent preventive treatment in Papua New Guinea. *Antimicrob Agents Chemother*. 2014;58:6958–61.
- Koleala T, Karl S, Laman M, Moore BR, Benjamin J, Barnadas C, et al. Temporal changes in *Plasmodium falciparum* anti-malarial drug sensitivity in vitro and resistance-associated genetic mutations in isolates from Papua New Guinea. *Malar J*. 2015;14:37.

22. Gonzalez R, Mombo-Ngoma G, Ouedraogo S, Kakolwa MA, Abdulla S, Accrombessi M, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Med*. 2014;11: e1001733.
23. Madanitsa M, Barsosio CH, Minja TR, Mtove G, Kavishe AR, et al. Effect of monthly intermittent preventive treatment with dihydroartemisinin-piperazine with and without azithromycin versus monthly sulfadoxine-pyrimethamine on adverse pregnancy outcomes in Africa: a double-blind randomised, partly placebo-controlled trial. *Lancet*. 2023;401:1020–36.
24. Desai M, Gutman J, L'Lanziva A, Otieno K, Juma E, Kariuki S, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperazine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet*. 2015;386:2507–19.
25. Kajubi R, Ochieng T, Kakuru A, Jagannathan P, Nakalembe M, Ruel T, et al. Monthly sulfadoxine-pyrimethamine versus dihydroartemisinin-piperazine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial. *Lancet*. 2019;393:1428–39.
26. Kakuru A, Jagannathan P, Muhindo MK, Natureeba P, Awori P, Nakalembe M, et al. Dihydroartemisinin-piperazine for the prevention of malaria in pregnancy. *N Engl J Med*. 2016;374:928–39.
27. Mlugu EM, Minzi O, Kamuhabwa AAR, Akillu E. Effectiveness of intermittent preventive treatment with dihydroartemisinin-piperazine against malaria in pregnancy in Tanzania: a randomized controlled trial. *Clin Pharmacol Ther*. 2021;110:1478–89.
28. Roh ME, ter Kuile FO, Rerolle F, Glymour MM, Shiboski S, Gosling R, et al. Overall, anti-malarial, and non-malarial effect of intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine on birthweight: a mediation analysis. *Lancet Glob Health*. 2020;8:e942–53.
29. Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine-pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clin Infect Dis*. 2017;64:1043–51.
30. Waltmann A, McQuade ETR, Chinkhumba J, Operario DJ, Mzembe E, Itoh M, et al. The positive effect of malaria IPTp-SP on birthweight is mediated by gestational weight gain but modifiable by maternal carriage of enteric pathogens. *EBioMedicine*. 2022;77: 103871.
31. Benjamin JM, Moore BR, Salman S, Page-Sharp M, Tawat S, Yadi G, et al. Population pharmacokinetics, tolerability, and safety of dihydroartemisinin-piperazine and sulfadoxine-pyrimethamine-piperazine in pregnant and nonpregnant Papua New Guinean women. *Antimicrob Agents Chemother*. 2015;59:4260–71.
32. Hughes E, Imperial M, Wallender E, Kajubi R, Huang L, Jagannathan P, et al. Piperazine exposure is altered by pregnancy, HIV, and nutritional status in Ugandan women. *Antimicrob Agents Chemother*. 2020;64:e01013–e1020.
33. National Department of Health. Papua New Guinea National Malaria Treatment Policy. 2009.
34. Clerk CA, Bruce J, Affipunguh PK, Mensah N, Hodgson A, Greenwood B, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. *J Infect Dis*. 2008;198:1202–11.
35. Tagbor H, Bruce J, Browne E, Randal A, Greenwood B, Chandramohan D. Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet*. 2006;368:1349–56.
36. Hill J, Hoyt J, Achieng F, Ouma P, L'Lanziva A, Kariuki S, et al. User and provider acceptability of intermittent screening and treatment and intermittent preventive treatment with dihydroartemisinin-piperazine to prevent malaria in pregnancy in Western Kenya. *PLoS ONE*. 2016;11: e0150259.
37. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res*. 2017;17:88.
38. Müller I, Bockarie M, Alpers M, Smith T. The epidemiology of malaria in Papua New Guinea. *Trends Parasitol*. 2003;19:253–9.
39. WHO. World malaria report 2022. Geneva, World Health Organization, 2022. Available from: <https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022> [accessed 22 October 2023].
40. Mueller I, Rogerson S, Mola GD, Reeder JC. A review of the current state of malaria among pregnant women in Papua New Guinea. *P N G Med J*. 2008;51:12–6.
41. Lufele E, Umbers A, Ordi J, Ome-Kaius M, Wangnapi R, Unger H, et al. Risk factors and pregnancy outcomes associated with placental malaria in a prospective cohort of Papua New Guinean women. *Malar J*. 2017;16:427.
42. Kura S, Vince J, Crouch-Chivers P. Male involvement in sexual and reproductive health in the Mendi district, Southern Highlands province of Papua New Guinea: a descriptive study. *Reprod Health*. 2013;10:46.
43. Valley LM, Homiehombo P, Kelly AM, Valley A, Homer CS, Whittaker A. Exploring women's perspectives of access to care during pregnancy and childbirth: a qualitative study from rural Papua New Guinea. *Midwifery*. 2013;29:1222–9.
44. Pascoe S. Community Engagement Toolkit: Milne Bay Provincial Health Authority, Papua New Guinea. 2016.
45. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant*. 2018;52:1893–907.
46. Bernard H. Research methods in anthropology: qualitative and quantitative approaches. Oxford: Alta Mira Press; 2006.
47. Madanitsa M, Barsosio HC, Minja DTR, Mtove G, Kavishe RA, Dodd J, et al. Effect of monthly intermittent preventive treatment with dihydroartemisinin-piperazine with and without azithromycin versus monthly sulfadoxine-pyrimethamine on adverse pregnancy outcomes in Africa: a double-blind randomised, partly placebo-controlled trial. *Lancet*. 2023;401:1020–36.
48. van der Pluijm RW, Tripura R, Hoglund RM, Pyae Phyo A, Lek D, Ul Islam A, et al. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated *Plasmodium falciparum* malaria: a multicentre, open-label, randomised clinical trial. *Lancet*. 2020;395:1345–60.
49. Overgaard AB, Højsted J, Hansen R, Møller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm World Sci*. 2001;23:185–8.
50. Rahmalia A, Poespoprodjo JR, Landuwulung CUR, Ronse M, Kenangalem E, Burdam FH, et al. Adherence to 14-day radical cure for *Plasmodium vivax* malaria in Papua, Indonesia: a mixed-methods study. *Malar J*. 2023;22:162.
51. Bélard S, Ramharther M, Kurth F. Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children. *Cochrane Database Syst Rev*. 2020;12:CD009568.
52. Pell C, Meñaca A, Chatio S, Hodgson A, Tagbor H, Pool R. The acceptability of intermittent screening and treatment versus intermittent preventive treatment during pregnancy: results from a qualitative study in Northern Ghana. *Malar J*. 2014;13:432.
53. Almond D, Madanitsa M, Mwapasa V, Kalilani-Phiri L, Webster J, ter Kuile F, et al. Provider and user acceptability of intermittent screening and treatment for the control of malaria in Malawi. *Malar J*. 2016;15:574.
54. Cardona-Arias JA. Synthesis of qualitative evidence on malaria in pregnancy, 2005–2022: a systematic review. *Trop Med Infect Dis*. 2023;8:235.
55. Smith LA, Jones C, Adjei RO, Antwi GD, Afrah NA, Greenwood B, et al. Intermittent screening and treatment versus intermittent preventive treatment of malaria in pregnancy: user acceptability. *Malar J*. 2010;9:18.

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