BMJ Global Health

Cost-effectiveness of community-based distribution of intermittent preventive treatment of malaria in pregnancy in Madagascar, Mozambique, Nigeria, and the Democratic Republic of Congo

Laia Cirera ,[1] Charfudin Sacoor,[2] Martin Meremikwu,[3] Louise Ranaivo,[4] Manu F Manun'Ebo,[5] Clara Pons-Duran,[1] Dachi Arikpo ,[3] Maximo Ramirez,[1] Francesco Ramponi,[1] Antia Figueroa-Romero,[1] Raquel Gonzalez ,[1,2] Christina Maly,[6] Elaine Roman,[6] Elisa Sicuri ,[1,7] Franco Pagnoni,[1] Clara Menéndez[2]

To cite: Cirera L, Sacoor C, Meremikwu M, *et al*. Cost-effectiveness of community-based distribution of intermittent preventive treatment of malaria in pregnancy in Madagascar, Mozambique, Nigeria, and the Democratic Republic of Congo. *BMJ Glob Health* 2023;**8**:e010238. doi:10.1136/bmjgh-2022-010238

Handling editor Lei Si

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2022-010238).

LC, CS, MM, LR and MFM'E contributed equally.

Received 23 July 2022
Accepted 5 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Laia Cirera;
laiacirerac@gmail.com

ABSTRACT

Introduction Malaria in pregnancy is a major driver of maternal and infant mortality in sub-Saharan Africa. The WHO recommends the administration of intermittent preventive treatment with sulfadoxine pyrimethamine (IPTp-SP) at antenatal care (ANC) visits. Despite being a highly cost-effective strategy, IPTp-SP coverage and uptake remains low. A pilot project was conducted to assess the cost-effectiveness (CE) of community-based delivery of IPTp (C-IPTp) in addition to ANC delivery to increase IPTp uptake in the Democratic Republic of Congo (DRC), Madagascar (MDG), Mozambique (MOZ) and Nigeria (NGA).

Methods Costs and CE estimates of C-IPTp were calculated according to two scenarios: (1) costs in 'programmatic mode' (ie, costs if C-IPTp was to be implemented by national health systems) and (2) costs from the pilot project. The effectiveness of C-IPTp was obtained through estimates of the averted disability-adjusted life-years (DALYs) associated with maternal clinical malaria and anaemia, low birth weight and neonatal mortality.

Results Net incremental costs of C-IPTp ranged between US$6138–US$47 177 (DRC), US$5552–US$31 552 (MDG), US$10 202–US$53 221 (MOZ) and US$667–US$28 645 (NGA) per 1000 pregnant women, under scenarios (1) and (2), respectively. Incremental cost-effectiveness ratios (ICERs) ranged between US$15–US$119 in DRC, US$9–US$53 in MDG, US$104–US$543 in MOZ and US$2–US$66 in NGA per DALY averted, under scenarios (1) and (2), respectively. ICERs fall below the WHO recommended CE threshold based on the gross domestic product per capita.

Conclusion Findings suggest that C-IPTp is a highly cost-effective intervention. Results can inform policy decisions on adopting and optimising effective interventions for preventing malaria in pregnancy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The cost-effectiveness (CE) of community health worker (CHW)-based initiatives for delivering malaria interventions has been assessed previously.

⇒ A study from Uganda showed that community delivery of intermittent preventive treatment was a cost-effective alternative strategy for increasing the uptake of two doses of sulfadoxine-pyrimethamine (IPTp2) (as was previously recommended by WHO).

WHAT THIS STUDY ADDS

⇒ We provide new evidence on the CE of delivering three or more IPTp doses (IPTp3+) through CHWs in addition to antenatal care (ANC) delivery, in hard-to reach areas of four sub-Saharan Africa (SSA) countries.

⇒ The incremental cost-effectiveness ratios (ICERs) for C-IPTp, ranged between US$15–US$119 in Democratic Republic of Congo, US$9–US$53 in Madagascar, US$104–US$543 in Mozambique and US$2–US$66 in Nigeria per disability-adjusted life-year averted, when considering costs in 'programmatic mode' and costs from the pilot implementation project, respectively.

⇒ The ICERs fell below the WHO recommended CE threshold based on the gross domestic product per capita in all project areas.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Community delivery of IPTp has been shown to be a highly cost-effective strategy that can complement the routine delivery of IPTp at ANC clinics.

⇒ Our study supports the implementation of community-based delivery strategies to optimise malaria prevention among pregnant women in hard-to-reach areas in SSA.

INTRODUCTION

Despite the increased access to malaria prevention tools achieved in the last decade, malaria continues to be a significant cause of morbidity and mortality in endemic countries, especially in sub-Saharan Africa (SSA).[1] Pregnant women are at higher risk of infection, which can lead to adverse consequences for both themselves and their fetus, including maternal anaemia, premature birth and low birth weight (LBW).[2–4]

The WHO strategy for preventing malaria in pregnancy (MiP) across SSA consists of effective case management, the use of insecticide-treated bed nets,[1] and since 1998 the administration of intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP).[5 6] Since 2012, the administration of IPTp has been recommended at each scheduled antenatal care (ANC) visit beginning as early as possible in the second trimester, at least 1 month apart and until the end of pregnancy, ensuring at least three IPTp administrations over the gestation.[7 8]

Economic evaluations conducted alongside clinical trials on IPTp delivered through the ANC clinics have shown that the intervention is highly cost-effective and leads to significant reductions in clinical malaria, anaemia, LBW and even neonatal mortality.[9–11] However, the proportion of women receiving at least three doses of IPTp is still low (32% on average).[1] This low uptake may be explained by several factors, including misleading perceptions of the effects of SP by both health staff and pregnant women, and stock-outs of the drug.[12–14] High household costs—both direct (eg, out-of-pocket medical expenses, transportation) and indirect (opportunity costs of the time lost due to access to care)—associated with malaria control in pregnancy may be additional barriers to IPTp uptake.[15–17]

Delivery of essential health services by community health workers (CHWs) has been identified as an effective strategy to increase coverage of health interventions and improve children's health outcomes compared with routine distribution at health facilities (HFs) alone[18–20] CHWs have also proven to be successful in improving access to malaria prevention strategies for both children and adults,[21–23] and CHW-based programmes for malaria control have been shown to be highly cost-effective. Home management of uncomplicated malaria by CHWs in Zambia was 36% more cost-effective than standard care at HFs.[24]

With regard to malaria prevention in pregnancy, a study in Uganda evaluated the delivery of IPTp-SP through CHWs (C-IPTp) compared with delivery at ANC clinics alone among 2700 participants. The study showed that community distribution increased access, improved IPTp2 uptake and was highly cost-effective.[25]

Community-based health programmes may provide good value for money for several reasons.[26 27] Since CHWs live in the communities they serve, they are generally more accessible, trusted and accepted by the community compared with clinic-based health staff, all of which facilitate interventions uptake. In addition, expanding health services provision through community-based strategies (in addition to routine delivery at health clinics), does not involve any additional structural costs, and can translate into potential cost savings for the health system given their impact in reducing the incidence of disease and the associated treatment costs. Running costs related to CHW interventions often include training, supplies, equipment, incentives or salaries (if they are not volunteers) and a proportion of salaried staff time to monitor and supervise CHW's activities. With high-impact services at a low incremental cost, CHW programmes reach larger pockets of the population that would remain otherwise underserved.

Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP) is a project focused on C-IPTp to prevent MiP as a complement to SP delivery through routine ANC visits.[28] The TIPTOP project was implemented from 2018 to 2022 in 12 rural districts in four SSA countries, the Democratic Republic of Congo (DRC), Madagascar (MDG), Mozambique (MOZ) and Nigeria (NGA). In each country, intervention districts were representative of poor and hard-to-reach rural areas in each country.

The effectiveness evaluation of the TIPTOP project showed that C-IPTp delivery significantly increased the proportion of women receiving three or more IPTp doses (IPTp3+) in all project areas. In DRC, IPTp3+ increased from 21.21% at baseline to 65.23% at endline, in MDG the increase was from 27.87% to 74.86%, in NGA from 11.45% to 62.69%, and in MOZ from 52.73% to 58.55%, respectively.[29]

In this component of the TIPTOP study, we aimed to assess the cost-effectiveness (CE) of C-IPTp in project intervention districts in addition to its delivery at the ANC clinics, compared with distributing IPTp at the ANC clinics alone (standard delivery).

METHODS

Study context

In each project country, after consultation with the local Ministry of Health (MoH), three districts were selected based on the following criteria: (1) high levels of malaria transmission, (2) having in place an IPTp policy and (3) the presence of a functional CHW programme. C-IPTp implementation was in two phases; during phase I, four districts (one per country) started C-IPTp implementation. About 1 year later, phase II began with the expansion of C-IPTp to eight additional districts (two per country) (see online supplemental figure S1).

The package of interventions deployed under the project consisted of the following: (1) selection, training and supervision of CHWs to deliver IPTp; (2) updating the knowledge and skills of ANC clinics health staff as trainers and supervisors of the CHWs; (3) training on new reporting tools for CHWs and HFs staff to monitor C-IPTp and (4) promotion of community awareness and sensitisation for C-IPTp. Further details on project

setting, interventions and population characteristics are provided elsewhere.[28 30]

Cost estimation

The costs of C-IPTp were assessed by taking into consideration the intervention's delivery costs, as well as the system's foregone treatment costs due to a reduction in the burden of malaria.

C-IPTp delivery costs were estimated by using a micro-costing approach or ingredients-based costing. Data on project key delivery activities, from 2018 to beginning 2022, were gathered from implementation partners in each country (ie, costing scenario in 'TIPTOP mode'). To that end, regular meetings and field visits were held during project implementation to assess and quantify the items, their frequency and corresponding unit costs used for key delivery activities. The procurement department in each country provided unit costs and quantities (number of units) of purchased goods across the period of study, which were expressed in the equivalent local currency (Congolese franc in DRC; Malagasy ariary in MDG; Metical in MOZ and Naira in NGA) and then converted to US$. For imported goods, unit costs were disaggregated by importation tax and in-country delivery costs.

C-IPTp delivery costs were discounted, annualised and expressed in constant 2018 US$.[31–33] Only costs of the activities directly related to C-IPTp administration were considered. Administrative and coordination costs incurred by the organisation in charge of the implementation at their headquarters, as well as research activity costs (ie, census of pregnant women, drug resistance monitoring, anthropological and economic studies) were excluded.

To generate useful information for policy-makers on the sustainability of C-IPTp, delivery costs in 'programmatic mode' were also estimated. Project implementation data were complemented with information provided by MoH staff on the frequency of activities, items and inputs that would likely be required if C-IPTp was implemented by the MoH. Unit costs were adjusted to those paid by the MoH (eg, salaries and transport allowances) and the use of existing capital goods within the public health system were taken into consideration (ie, vehicles, warehouses and health structures).

Assuming that in 'programmatic mode' several activities related to C-IPTp implementation will be integrated with other community-based programmes, we allocated resources to C-IPTp based on the estimated time CHWs would devote to administering C-IPTp as a share of their total activities. These estimates were obtained from interviews with CHWs' supervisors in each intervention district, which provided figures based on direct observation of workers' time devoted to different tasks.

To estimate the potential health system cost savings, a facility-based survey was conducted between 2020 and 2021 to better understand the costs associated to treating MiP. Information on the use of resources to treat MiP was gathered through a questionnaire administered to HF staff from randomly selected HFs in project intervention areas. A total of 133 key focal staff from 133 HFs (30% of total HFs) were interviewed (online supplemental table S1). Recurrent costs (such as personnel salaries and medical supplies) and capital costs (eg, utilities and running costs) were considered. Reference prices for drugs, tests and vaccines were taken from the WHO and the Global Fund procurement prices records.[34 35] Total admission costs were calculated by multiplying the cost per inpatient bed day for the average number of admission days (online supplemental tables S2 and S3). Estimates of cost per inpatient bed day were obtained from WHO.[36] Further details on costs associated with MiP in project intervention districts have been published elsewhere.[37]

Effectiveness

Household surveys (HHS) were conducted before, during and after C-IPTp delivery, in order to measure the change in the proportion of women receiving three or more IPTp doses (IPTp3+) during their last pregnancy. Results from the HHS showed that between baseline and endline surveys, IPTp3+ coverage increased by 11.0% in MOZ, 168.6% in MDG, 207.5% in DRC and 447.5% in NGA, respectively (online supplemental table S4).[29]

Improvement in IPTp3+ coverage was modelled on health outcomes for pregnant women and newborns as follows: (A) cases of clinical MiP and malaria-related deaths averted; (B) maternal anaemia cases at delivery and related deaths averted, (C) LBW deliveries averted and (D) neonatal deaths averted. Evidence on IPTp3+ efficacy to prevent maternal malaria, anaemia at delivery, LBW and neonatal deaths was retrieved from the literature[11 38–42] (see online supplemental table S5).

Impacts on disease-specific health outcomes for both mothers and newborns were converted into disability-adjusted life-years (DALYs) averted.[33] DALYs were calculated based on standard measures of disease duration and impact on health-related quality of life, by using disability weights from the Global Burden of Disease estimates[43] and applying country-specific life expectancies.[33]

Cost-effectiveness analysis

The CE analysis was conducted from the health provider perspective and considered C-IPTp delivery costs in both 'TIPTOP mode' and 'programmatic mode'. C-IPTp net intervention costs (per 1000 pregnant women) were calculated as the difference between C-IPTp delivery costs, and the health system costs-savings associated with the reduction in treatments of clinical malaria episodes. The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the net incremental cost of C-IPTp by the total incremental DALYs averted due to the reduction in the number of maternal malaria episodes, anaemia at delivery, LBW and neonatal deaths.

The CE of C-IPTp was assessed by comparing ICER estimates to threshold recommended by the WHO, based on

1 (highly cost-effective) and 3 (cost-effective) times the GDP per capita in each country,[33] as well as alternative thresholds based on countries' opportunity cost.[44]

A deterministic sensitivity analysis was conducted, where model parameters such as IPTp3+ coverage, SP drug price, SP protective efficacy, incidence of maternal malaria and neonatal mortality rates, were varied to assess their impact on the ICERs (see online supplemental table S6). Results were graphically presented in tornado diagrams. Considering that project C-IPTp effectiveness might be reduced in 'programmatic mode' implementation, a threshold analysis for a potential decrease in IPTp3+ coverage was conducted to investigate the cut-off values beyond which the intervention would no longer be cost-effective.

A probabilistic sensitivity analysis (PSA) was conducted by assigning probability distribution functions to key model inputs and running 1000 Monte Carlo iterations (online supplemental table S7). The PSA results are presented in the CE acceptability curves, which show the probability of the intervention being cost-effective for different values of the CE thresholds.

We used Stata V.17.0 to analyse the data and Microsoft Excel 2019 to run the Monte Carlo simulations and conduct the PSA.

Patient and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Costs of C-IPTp delivery per 1000 pregnant women in 'TIPTOP mode' were US$32 492 in MDG, US$35 174 in NGA, US$53 389 in MOZ and US$53 558 in DRC (table 1). The main cost drivers were monitoring and evaluation activities, and CHW monthly transport allowance to attend supervision meetings at the HFs.

Table 2 shows C-IPTp delivery costs per 1000 pregnant women in 'programmatic mode', equivalent to US$6492 in MDG, US$7196 in NGA, US$10 369 in MOZ and US$12 519 in DRC (see online supplemental table S8 for details on costing inputs).

Table 1 Costs of community-based distribution of intermittent preventive treatment of malaria in pregnancy (C-IPTp) in 'TIPTOP mode', 2018–2022

	C-IPTp delivery costs in 'TIPTOP mode' (US$ 2018)				
Activity	**DRC**	**MDG**	**MOZ**	**NGA**	**Notes**
Personnel	151 402	102 691	184 370	176 414	Essential staff for C-IPTp delivery (project coordinator, programme officer, community officer, M&E focal point) contracted over study period (2018–2022)
CHW materials and tools	254 394	96 765	193 729	85 347	Material includes: T-shirt, cap, backpack, waterproof jackets (to be renewed annually), register books, referral forms, summary form (provided on a monthly basis).
CHW training and refresher training	309 810	202 468	188 393	300 518	Annual training of new CHWs and refreshment of old CHWs conducted together.
Training of trainers and health service providers	207 507	108 162	173 836	187 574	Annual training to health professionals and CHWs' supervisors
CHW incentives	365 728	281 951	498 102	392 304	Incentives are provided to CHWs for attending monthly supervision visits
Supervision visits	228 172	227 892	220 362	233 799	Routine monthly supervision visits held at provincial, district and community levels
Monitoring and evaluation	429 798	293 674	464 749	449 361	Monthly monitoring meetings at provincial, district and community level; monitoring workshop and tools. Routine activities along project implementation.
Sensitisation campaigns	152 891	161 947	87 338	104 563	Advocacy meetings, educational workshop, SBCC campaigns and community mobilisation meetings. Routine activities along project implementation
Total cost	2 099 703	1 475 550	2 010 880	1 929 881	
Cost per 1000 PW	53 558	32 492	53 389	35 174	

Costs in constant US$ 2018.
CHW, community health workers; DRC, Democratic Republic of Congo; MDG, Madagascar; M&E, Monitoring and Evaluation; MOZ, Mozambique; NGA, Nigeria; PW, pregnant women; SBCC, Social and Behaviour Change Communication; TIPTOP, Transforming Intermittent Preventive Treatment for Optimal Pregnancy.

Table 2 Costs of community-based distribution of intermittent preventive treatment of malaria in pregnancy (C-IPTp) in 'programmatic mode', 2018–2022

	C-IPTp delivery costs in 'programmatic mode' (US$ 2018)				
Activity	**DRC**	**MDG**	**MOZ**	**NGA**	**Notes**
CHW material and tools	200 399	108 756	75 923	122 795	Includes basic CHW material, registers and distributed drugs
CHW training and refresher training	175 500	90 534	177 718	132 874	Annual training of new CHWs and refreshment of old CHWs conducted together. Integrated with other health promotion activities of CHWs (ie, nutrition, HIV, wash).
Training of trainers and health service providers	29 527	36 536	34 767	75 116	Annual training to health professionals and CHWs' supervisors.
Governmental salary	0	0	36 049	0	Subsidies provided to CHWs on a monthly basis
Supervision visits	85 380	58 985	66 109	64 038	Integrated provincial (quarterly) and district (monthly) supervision visits for CHWs
Total costs	490 808	313 078	492 066	476 070	
Total costs per 1000 PW	12 519	6492	10 369	7196	

CHW, community health workers; DRC, Democratic Republic of Congo; HIV, human immunodeficiency virus; MDG, Madagascar; MOZ, Mozambique; NGA, Nigeria; PW, pregnant women.

Online supplemental table S8 provides further details on items, frequency and unit cost estimates for each activity implemented in 'programmatic mode'.

Health system costs per outpatient treatment of MiP were estimated to be US$3.61 in MDG, US$4.09 in NGA, US$4.68 in MOZ and US$4.69 in DRC (online supplemental table S2). Costs per admission case of MiP were estimated to be US$63.33 in MDG, US$83.70 in MOZ, US$92.64 in NGA and US$101.41 in DRC (online supplemental table S3).

C-IPTp incremental net cost per 1000 pregnant women, obtained by aggregating intervention costs and health system cost-savings, ranged between US$667–US$28 645 in NGA, US$5552–US$31 552 in MDG, US$6138–US$47 177 in DRC and US$10 202–US$53 221 in MOZ, under both cost scenarios in 'programmatic mode' and in 'TIPTOP mode', respectively (table 3).

C-IPTp implementation averted 98 in MOZ, 396 in DRC, 435 in NGA and 591 in MDG per 1000 pregnant women (online supplemental table S9). The resulting ICERs ranged between US$2–US$66 in NGA, US$9–US$53 in MDG, US$15–US$119 in DRC and US$104–US$543 in MOZ, for delivery costs under 'programmatic mode' and 'TIPTOP mode', respectively (table 3).

In 'programmatic mode' ICERs fell below the WHO recommended CE threshold based on 1–3 times the GDP per capita (The GDP per capita was US$449 in MOZ, US$496 in MDG, US$557 in DRC and US$2097 in NGA according to World Bank estimates (https://data.worldbank.org)). In 'TIPTOP mode', the costs and resulting ICERs increased, however, the intervention still remained cost-effective in all project countries (For DRC, MDG and NGA, the ICER was below the high CE threshold (one time the GDP per capita), and for MOZ, the ICER was

Table 3 Costs and cost-effectiveness of community-based distribution of intermittent preventive treatment of malaria in pregnancy (C-IPTp), 2018–2022

	Programmatic mode (per 1000 PW)				TIPTOP mode (per 1000 PW)			
	DRC	**MDG**	**MOZ**	**NGA**	**DRC**	**MDG**	**MOZ**	**NGA**
Incremental costs (US$ 2018 per 1000 PW)								
C-IPTp delivery costs	12 519	6492	10 369	7196	53 558	32 492	53 389	35 174
Health system cost-savings	6381	940	167	6529	6381	940	167	6529
Net incremental C-IPTp costs	6138	5552	10 202	667	47 177	31 552	53 221	28 645
DALYs averted per 1000 PW	396	591	98	435	396	591	98	435
ICER (cost/DALY averted)	15	9	104	2	119	53	543	66

Costs in constant US$ 2018.
DALYs, disability-adjusted life-years; DRC, Democratic Republic of Congo; ICER, incremental cost-effectiveness ratio; MDG, Madagascar; MOZ, Mozambique; NGA, Nigeria; PW, pregnant women; TIPTOP, Transforming Intermittent Preventive Treatment for Optimal Pregnancy.

below the CE threshold (three times the GDP per capita) but above the high CE threshold (one time the GDP per capita)) (online supplemental table S10).

The one-way deterministic sensitivity analysis showed that the ICERs were extremely sensitive to epidemiological parameters associated to neonatal outcomes (ie, neonatal mortality rate and SP efficacy in reducing neonatal mortality), as well as to variations in IPTp3+ coverage across study sites (online supplemental table S6, figure 1). On the other hand, the threshold analysis showed that, even in the situation of decreased effectiveness, C-IPTp would remain cost-effective if at least 24%, 11%, 40% and 10% of the observed effectiveness is achieved (ie, number of DALYs averted) in DRC, MDG, MOZ and NGA, respectively.

Table 4 reports the CIs for ICER estimates obtained from the PSA. In 'TIPTOP mode', these are US$55 (95% CI US$52 to US$57) per DALY averted in MDG, US$67 (95% CI US$65 to US$70) in NGA, US$122 (95% CI US$117 to US$126) in DRC and US$555 (95% CI US$532 to US$578) in MOZ. In 'programmatic mode', the overall costs and ICERs were reduced, translating into an ICER per DALY averted of US$2 (95% CI US$3 to US$7) in NGA, US$10 (95% CI US$9 to US$11) in MDG, US$16 (95% CI US$15 to US$17) in DRC and US$106 (95% CI US$125 to US$141) in MOZ.

DISCUSSION

In this economic evaluation, we have assessed the CE of C-IPTp in hard-to-reach areas of DRC, MDG, MOZ and NGA. The intervention was found to be a cost-effective malaria control strategy in all study countries, with ICER values that fell below the WHO recommended CE threshold of three times the GDP per capita.

The observed variation of ICERs across countries may be explained by several factors, such as disparities in the epidemiology and burden of malaria, differences in the effectiveness of the intervention in increasing IPTp3+ coverage, variations in local input costs as well as in other health systems and community-based schemes features. The ICER associated with C-IPTp in NGA was the lowest among all countries included in the study, which is likely due to a low IPTp3+ coverage at baseline and a significant increase immediately after the start of the intervention in a context of a high incidence of malaria. This led to an increase in IPTp3+ coverage, which translated into a high number of averted maternal malaria episodes and DALYs, and therefore, high health system cost savings. By contrast, the ICER in MOZ was found to be the highest of all study countries. This may be explained by the high costs of the CHW programme in the country, since CHWs receive a monthly salary and incentives to undertake many other duties. Moreover, their training period is the largest of all project countries and therefore more costly. In addition, there was a limited marginal impact of C-IPTp on IPTp3+ coverage, partially explained by a high baseline IPTp coverage and a low ratio of CHWs per pregnant woman.[29]

The ICER results show C-IPTp to be more cost-effective and intervention costs significantly lower when costs are calculated in 'programmatic mode' rather than in 'TIPTOP mode' (online supplemental table S10). This is because the pilot project supported all activities needed to ensure that C-IPTp was effectively implemented, such as CHW monthly incentives, which are unlikely to be sustainable in real-life situations (ie, when C-IPTp is implemented by the government, or in 'programmatic mode'). In addition, in 'programmatic mode' other CHW-related activities, such as monthly supervision visits and training, would be conducted as part of other community-based health programmes that CHWs are also responsible for (not exclusively for C-IPTp), and therefore, would not count as added costs.

The analysis was conducted from the perspective of the health system; however, the incremental net costs and ICERs would be further reduced if households' cost savings resulting from averted episodes of maternal malaria were considered. Details on the economic burden of malaria on households in project areas have been analysed and discussed elsewhere.[37]

Our results align with available evidence showing that malaria interventions delivered by CHWs are generally cost-effective.[24 25 45 46] However, a direct comparison of our estimates with other interventions should be done with caution, since the epidemiological contexts, outcomes, and programmes may differ. As suggested in other studies evaluating the TIPTOP project, countries' specificities should be considered when assessing C-IPTp implementation.[47] Thus, bearing in mind the contextual factors is essential to compare and contrast our results with evidence from the literature.

In this analysis, the impact of three or more doses of IPTp-SP on maternal anaemia and clinical malaria, and neonatal mortality was modelled using the results from clinical trials using two or more doses of IPTp-SP versus placebo.[39 42] In the case of LBW, we used the protective efficacy rate shown in a study using two versus three doses of IPTp- SP.[40] Therefore, the effectiveness estimates should be considered as a lower bound of the true effectiveness of the intervention.

We estimated the number of clinical malaria episodes during pregnancy by using self-reported data from pregnant women in intervention areas.[37] While not ideal due to its susceptibility to bias, this approximation is unlikely to affect the CE substantially since the surrogate measure of clinical malaria contributed less than 5% to the total DALYs averted.

The WHO recommended CE thresholds based on the GDP per capita have been subject to criticism when used to judge the CE of healthcare interventions. Alternative thresholds based on countries' 'opportunity cost' have been proposed.[44 48] Recommendations based on CE did not change when using these thresholds, except for MOZ.

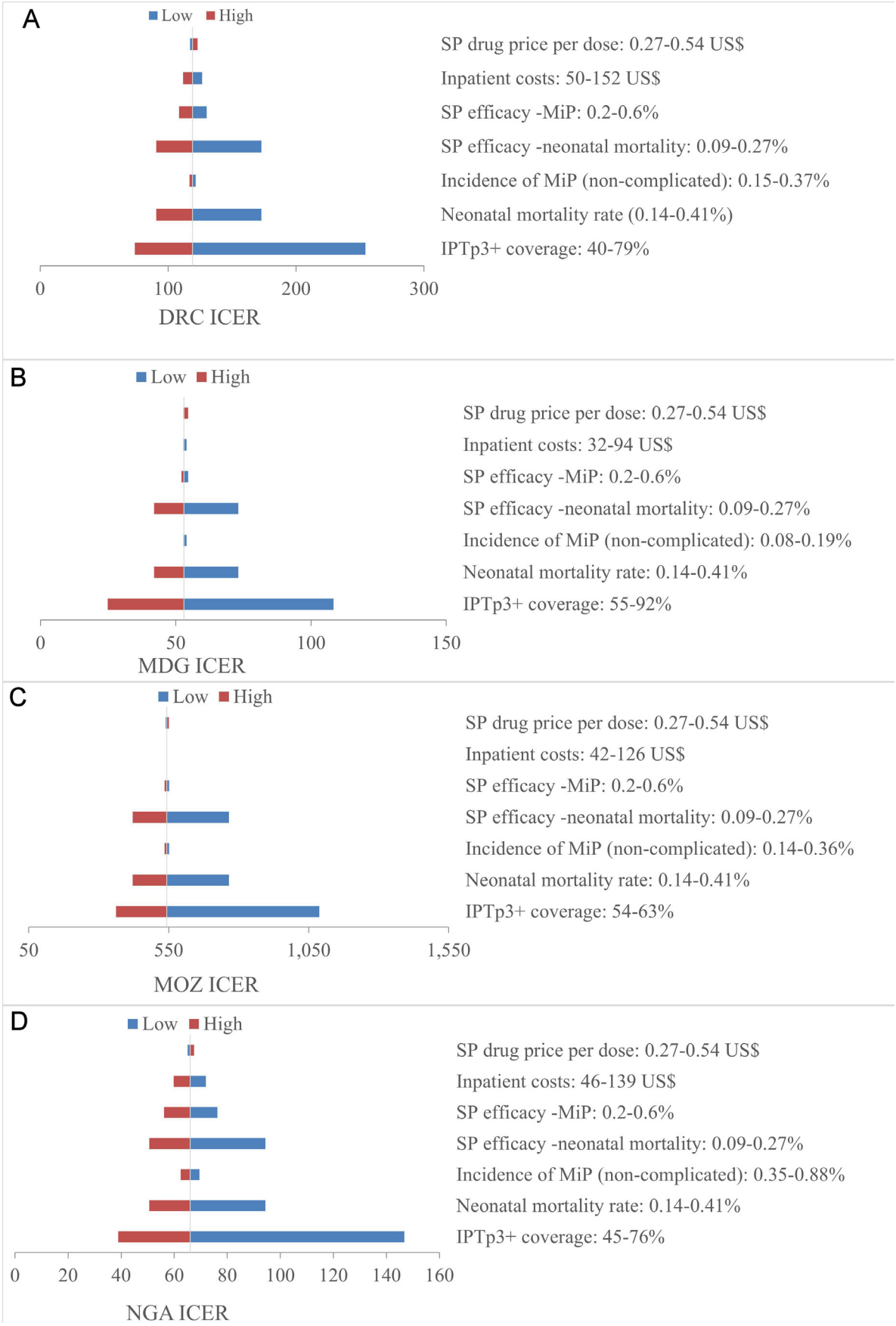

Figure 1 Tornado diagram on incremental cost-effectiveness ratio (ICER) in (A) the Democratic Republic of Congo (DRC), (B) Madagascar (MDG), (C) Mozambique (MOZ) and (D) Nigeria (NGA). MiP, malaria in pregnancy; SP, sulfadoxine-pyrimethamine.

Table 4 Probabilistic costs and cost-effectiveness of community-based distribution of intermittent preventive treatment of malaria in pregnancy (C-IPTp), 2018–2022

	Programmatic mode (per 1000 PW)						TIPTOP mode (per 1000 PW)					
	Net INCR cost (2018 US$)		DALYs averted		ICER (2018 US$)		Net INCR cost (2018 US$)		DALYs averted		ICER (2018 US$)	
Country	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean
DRC	(5942–6687)	6314	(389–417)	403	(15–17)	16	(46 865–47 721)	47 293	(389–417)	403	(117–126)	122
MDG	(5484–5620)	5552	(578–625)	599	(9–11)	10	(31 344–31 755)	31 549	(578–625)	599	(52–57)	55
MOZ	(10 055–10 307)	10 181	(96–103)	99	(102–111)	106	(52 821–53 613)	53 217	(96–103)	99	(532–578)	555
NGA	(551–1177)	864	(427–457)	442	(1–3)	2	(28 397–29 097)	28 747	(427–457)	442	(65–70)	67

Costs in constant US$ 2018.
DALYs, disability-adjusted life-years; DRC, Democratic Republic of Congo; ICER, incremental cost-effectiveness ratio; INCR, Incremental; MDG, Madagascar; MOZ, Mozambique; NGA, Nigeria; PW, pregnant women; TIPTOP, Transforming Intermittent Preventive Treatment for Optimal Pregnancy.

The costs in 'programmatic mode' aimed to reflect the actual C-IPTp costs with the intervention delivered and administered by the government. However, actual costs by the time governments decide to implement C-IPTp may differ from the estimates presented in this study. In addition, effectiveness shown in this analysis may not be achieved if the intervention is implemented by the government without the economic and technical support of international donors. To ensure efficient distribution of C-IPTp by the government, and therefore, maximise effectiveness, C-IPTp should be integrated with other community programmes already operative within the MoH. Active engagement and acceptability of community key stakeholders would be additional conditions for C-IPTp sustainability, scalability and optimal effectiveness.[49]

Finally, to take into consideration uncertainty around model parameters and evaluate the robustness of the

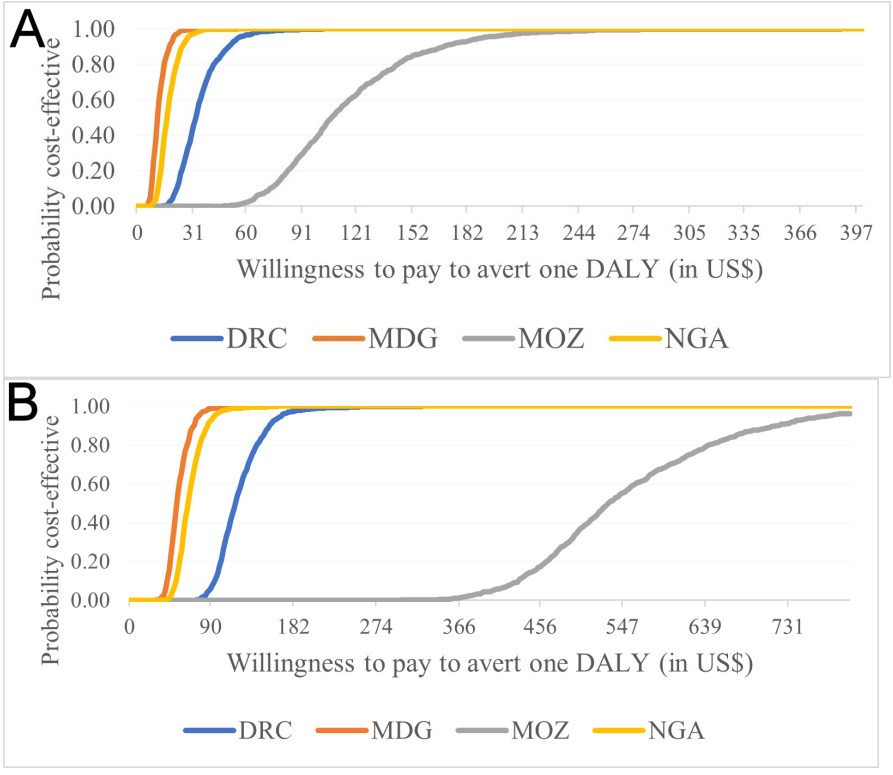

Figure 2 Cost-effectiveness (CE) acceptability curve based on (A) 'programmatic mode' costs and (B) 'TIPTOP mode' costs. DALY, disability-adjusted life-year; DRC, Democratic Republic of Congo; MDG, Madagascar; MOZ, Mozambique; NGA, Nigeria; TIPTOP, Transforming Intermittent Preventive Treatment for Optimal Pregnancy.

results, sensitivity analyses were carried out. The findings remained robust across a range of deterministic and PSA. While the government's willingness to pay is unknown and will depend on country-specific preferences and resource availability, the CE acceptability curves (figure 2) show that the probability for C-IPTp to be cost-effective at a theoretical willingness to pay equal to the GDP per capita (online supplemental table S10) would be close to 100% in DRC, MDG and NGA.

Furthermore, we undertook a threshold analysis on the effectiveness of the intervention and ascertained that the intervention would remain cost-effective if at least 10% (NGA), 11% (MDG), 24% (DRC) and 40% (MOZ) of the effectiveness was achieved. This suggests that C-IPTp would remain cost-effective even if implemented in less favourable context and socioeconomic conditions, such as those that could be faced when implemented by national governments.

It can be assumed that C-IPTp has mostly benefited women living in hard-to-reach areas, who otherwise would have not been reached by the routine delivery system, thereby improving equity in access to healthcare. Including equity concerns in the CE analysis would likely further improve the ICER of the intervention.[50–52]

Conclusion

This study showed that C-IPTp may be a cost-effective malaria control intervention when integrated into routine governmental programmes, in diverse settings and epidemiological contexts in SSA. These results can help policy-makers make decisions on scaling up C-IPTp in similar contexts and should be considered to improve malaria prevention in pregnant women, especially in hard-to-reach settings of sub-Saharan countries.

Author affiliations
[1]Maternal, Child and Reproductive Health Initiative, Barcelona Institute for Global Health, Barcelona, Spain
[2]Manhiça Health Research Center, Manhiça, Mozambique
[3]Cross River Health and Demographic Surveillance System, University of Calabar, Calabar, Nigeria
[4]Malagasy Associates for Numerical Information and Statistical Analysis (MANISA), Antananarivo, Madagascar
[5]Bureau d'Étude et de Gestion de l'Information Statistique (BEGIS), Kinshasa, Congo (the Democratic Republic of the)
[6]Jhpiego, Johns Hopkins University Affiliate, Baltimore, Maryland, USA
[7]Department of Health Policy, The London School of Economics and Political Science, London, UK

Acknowledgements We thank all the study participants for their time and contribution. We are also grateful to the four research teams and field data collectors in the study countries, for their role in coordinating the field data collection: le Bureau d'Étude et de Gestion de l'Information Statistique (BÉGIS) in the Democratic Republic of Congo; the Malagasy Associates for Numerical Information and Statistical Analysis (MANISA) in Madagascar; Centro de Investigação em Saúde (CISM) in Mozambique, and the Cross River Health and Demographic Surveillance System, University of Calabar (UNICAL) in Nigeria. Special thanks to ISGlobal colleagues and the Jhpiego finance team members for the technical support provided and the information shared. We also extend our gratitude to the MoH officials in intervention project areas for their knowledge and expertise provided.

Contributors Conceptualisation: LC, ES, FP and CM. Data curation: LC, CS, MM, LR, MFM, CP, DA, MR and CM. Formal analysis: LC, FR and ES. Data interpretation: all authors. Writing—original draft: LC. Writing—review and editing: all authors.LC is responsible for the overall content as guarantor.

Funding This work was supported by: UNITAID (2017–13-TIPTOP) through a subaward signed with Jhpiego (17-SBA-101); the Spanish Ministry of Science and Innovation through the 'Centro de Excelencia Severo Ochoa 2019–2023' Programme (CEX2018-000806-S) and the Generalitat de Catalunya through the CERCA Programme.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Study protocol and informed consents were approved by the Ethics Committee of the Hospital Clinic in Barcelona (CCI /051/AGO/2020) and the WHO ethics review board (ERC.0003384).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Laia Cirera http://orcid.org/0000-0002-1133-487X
Dachi Arikpo http://orcid.org/0000-0002-9035-9193
Raquel Gonzalez http://orcid.org/0000-0001-5487-801X
Elisa Sicuri http://orcid.org/0000-0002-2499-2732

REFERENCES

1 WHO. *World malaria report*. World Health Organization: Geneva, 2021.
2 Rogerson SJ, Hviid L, Duffy PE, *et al*. Malaria in pregnancy: pathogenesis and immunity. *Lancet Infect Dis* 2007;7:105–17.
3 Bardají A, Sigauque B, Bruni L, *et al*. Clinical malaria in African pregnant women. *Malar J* 2008;7:27.
4 Saito M, Briand V, Min AM, *et al*. Deleterious effects of malaria in pregnancy on the developing fetus: a review on prevention and treatment with Antimalarial drugs. *Lancet Child Adolesc Health* 2020;4:761–74.
5 WHO. *WHO expert committee on Malaria, twentieth report*. 1998. Available: https://apps.who.int/iris/handle/10665/42247
6 WHO. WHO regional office for Africa. A strategic framework forMalaria prevention and control during pregnancy in the African region. 2004. Available: https://www.afro.who.int/sites/default/files/2017-06/malaria_in_pregnancy_092004.pdf
7 WHO. Guidelines for the treatment of malaria. 2015. Available: https://www.who.int/malaria/publications/atoz/9789241549127/en
8 WHO. Intermittent preventive treatment Ofmalaria in pregnancy using Sulfadoxine-Pyrimethamine (Iptp-SP). 2012. Available: https://www.who.int/malaria/publications/atoz/who_iptp_sp_policy_recommendation/en
9 Wolfe EB, Parise ME, Haddix AC, *et al*. Cost-effectiveness of Sulfadoxine-Pyrimethamine for the prevention of malaria-associated low birth weight. *Am J Trop Med Hyg* 2001;64:178–86.
10 Conteh L, Sicuri E, Manzi F, *et al*. The cost-effectiveness of intermittent preventive treatment for malaria in infants in sub-Saharan Africa. *PLoS One* 2010;5:e10313.
11 Fernandes S, Sicuri E, Kayentao K, *et al*. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for

malaria during pregnancy in sub-Saharan Africa: a Modelling study of meta-analysis and cost data. *Lancet Glob Health* 2015;3:e143–53.
12 UNICEF. Antenatal care - UNICEF DATA. 2019. Available: http://data.unicef.org/topic/maternal-health/antenatal-care
13 Rassi C, Graham K, King R, *et al*. Assessing supply-side barriers to uptake of intermittent preventive treatment for malaria in pregnancy: a qualitative study and document and record review in two regions of Uganda. *Malar J* 2016;15:530:530.:.
14 Mubyazi GM, Bloch P, Byskov J, *et al*. Supply-related drivers of staff motivation for providing intermittent preventive treatment of malaria during pregnancy in Tanzania: evidence from two rural districts. *Malar J* 2012;11:48.
15 Onwujekwe O, Uguru N, Etiaba E, *et al*. The economic burden of malaria on households and the health system in Enugu state Southeast Nigeria. *PLoS One* 2013;8:e78362.
16 Alonso S, Chaccour CJ, Elobolobo E, *et al*. The economic burden of malaria on households and the health system in a high transmission District of Mozambique. *Malar J* 2019;18:360.
17 Klein MC, Harvey SA, Diarra H, *et al*. There is no free here, you have to pay": actual and perceived costs as barriers to intermittent preventive treatment of malaria in pregnancy in Mali. *Malar J* 2016;15:158.
18 Lehmann U, Sanders D. *Community health workers: What do we know about them*. Word Health Organization: Geneva, 2007.
19 Haines A, Sanders D, Lehmann U, *et al*. Achieving child survival goals: potential contribution of community health workers. *Lancet* 2007;369:2121–31.
20 Bari A, Sadruddin S, Khan A, *et al*. Community case management of severe pneumonia with oral Amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomised trial. *Lancet* 2011;378:1796–803.
21 Tine RCK, Ndiaye P, Ndour CT, *et al*. Acceptability by community health workers in Senegal of combining community case management of malaria and seasonal malaria Chemoprevention. *Malar J* 2013;12:467.
22 Greenwood B, Bojang K, Tagbor H, *et al*. Combining community case management and intermittent preventive treatment for malaria. *Trends Parasitol* 2011;27:477–80.
23 Bojang KA, Akor F, Conteh L, *et al*. Two strategies for the delivery of Iptc in an area of seasonal malaria transmission in the Gambia: a randomised controlled trial. *PLoS Med* 2011;8:e1000409.
24 Chanda P, Hamainza B, Moonga HB, *et al*. Relative costs and effectiveness of treating uncomplicated malaria in two rural districts in Zambia: implications for nationwide scale-up of home-based management. *Malar J* 2011;10:159.
25 Mbonye AK, Hansen KS, Bygbjerg IC, *et al*. Intermittent preventive treatment of malaria in pregnancy: the incremental cost-effectiveness of a new delivery system in Uganda. *Trans R Soc Trop Med Hyg* 2008;102:685–93.
26 Berman PA, Gwatkin DR, Burger SE. Community-based health workers: head start or false start towards health for all *Soc Sci Med* 1987;25:443–59.
27 Vaughan K, Kok MC, Witter S, *et al*. Costs and cost-effectiveness of community health workers: evidence from a literature review. *Hum Resour Health* 2015;13:71.
28 Pons-Duran C, Llach M, Sacoor C, *et al*. Coverage of intermittent preventive treatment of malaria in pregnancy in four sub-Saharan countries: findings from household surveys. *Int J Epidemiol* 2021;50:550–9.
29 González R, Manun'Ebo MF, Meremikwu M, *et al*. The impact of community delivery of intermittent preventive treatment of malaria in pregnancy on its coverage in four sub-Saharan African countries (Democratic Republic of the Congo, Madagascar, Mozambique, and Nigeria): a quasi-experimental Multicentre evaluation. *Lancet Glob Health* 2023;11:e566–74.
30 Enguita-Fernàndez C, Alonso Y, Lusengi W, *et al*. Trust, community health workers and delivery of intermittent preventive treatment of malaria in pregnancy: a comparative qualitative analysis of four sub-Saharan countries. *Glob Public Health* 2021;16:1889–903.
31 Drummond Met *al*. *Methods for the economic evaluation of health care programmes, 4th edn*. Oxford, UK: Oxford University Press, 2015.
32 WHO. *WHO guide to identifying the economic consequences of disease and injury, Department of Health Systems Financing Health Systems and Services*. Geneva, Switzerland, 2009.
33 WHO. *Making choices in health: guide to cost-effectiveness analysis*. Geneva, Switzerland, 2003.
34 Fund G. *The global fund: pooled procurement mechanism reference pricing*. 2020.
35 WHO. *World Health Organization vaccine price database*. 2020.
36 WHO. *WHO-CHOICE estimates of cost for inpatient and outpatient health service delivery*. 2010.
37 Cirera L, Sacoor C, Meremikwu M, *et al*. The economic costs of malaria in pregnancy: evidence from four sub-Saharan countries. *Gates Open Res* 2023;7:47.
38 Sicuri E, Bardají A, Nhampossa T, *et al*. Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in Southern Mozambique. *PLoS One* 2010;5:e13407.
39 Menéndez C, Bardají A, Sigauque B, *et al*. A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the Antenatal clinic. *PLoS One* 2008;3:e1934.
40 Kayentao K, Garner P, van Eijk AM, *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.
41 Menéndez C, Bardají A, Sigauque B, *et al*. Malaria prevention with Iptp during pregnancy reduces neonatal mortality. *PLoS One* 2010;5:e9438.
42 Eisele TP, Larsen DA, Anglewicz PA, *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.
43 World Health Organization. WHO methods and data sources for global burden of disease estimates 2000-2015. Geneve, Switzerland, 2017.
44 Woods B, Revill P, Sculpher M, *et al*. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016;19:929–35.
45 Patouillard E, Conteh L, Webster J, *et al*. Coverage, adherence and costs of intermittent preventive treatment of malaria in children employing different delivery strategies in Jasikan, Ghana. *PLoS One* 2011;6:e24871.
46 Conteh L, Patouillard E, Kweku M, *et al*. Cost effectiveness of seasonal intermittent preventive treatment using Amodiaquine & Artesunate or Sulphadoxine-Pyrimethamine in Ghanaian children. *PLoS One* 2010;5:e12223.
47 Alonso Yet *al*. Understanding the social dimensions of community delivery of Iptp: an anthropological study in 4 sub-Saharan countries. 2022.
48 Bertram MY, Lauer JA, De Joncheere K, *et al*. Cost – effectiveness thresholds: pros and cons. *Bull World Health Organ* 2016;94:925–30.
49 Alonso Y, Lusengi W, Manun'Ebo MF, *et al*. The social dimensions of community delivery of intermittent preventive treatment of malaria in pregnancy in Madagascar, Mozambique, Nigeria and the Democratic Republic of the Congo. *BMJ Glob Health* 2022;7:e010079.
50 Avanceña ALV, Prosser LA. Innovations in cost-effectiveness analysis that advance equity can expand its use in health policy. *BMJ Glob Health* 2022;7:e008140.
51 Avanceña ALV, Prosser LA. Examining equity effects of health interventions in cost-effectiveness analysis: A systematic review. *Value Health* 2021;24:136–43.
52 Cookson R, Mirelman AJ, Griffin S, *et al*. Using cost-effectiveness analysis to address health equity concerns. *Value Health* 2017;20:206–12.