



Cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperazine versus single screening and treatment for the control of malaria in pregnancy in Papua, Indonesia: a provider perspective analysis from a cluster-randomised trial

Lucy Paintain, Jenny Hill, Rukhsana Ahmed, Chandra Umbu Reku Landuwulang, Ansariadi Ansariadi, Jeanne Rini Poespoprodjo, Din Syafruddin, Carole Khairallah, Faustina Helena Burdam, Irene Bonsapia, Feiko O ter Kuile, Jayne Webster



Summary

Background Malaria infection during pregnancy is associated with serious adverse maternal and birth outcomes. A randomised controlled trial in Papua, Indonesia, comparing the efficacy of intermittent preventive treatment with dihydroartemisinin-piperazine with the current strategy of single screening and treatment showed that intermittent preventive treatment is a promising alternative treatment for the reduction of malaria in pregnancy. We aimed to estimate the incremental cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperazine compared with single screening and treatment with dihydroartemisinin-piperazine.

Methods We did a provider perspective analysis. A decision tree model was analysed from a health provider perspective over a lifetime horizon. Model parameters were used in deterministic and probabilistic sensitivity analyses. Simulations were run in hypothetical cohorts of 1000 women who received intermittent preventive treatment or single screening and treatment. Disability-adjusted life-years (DALYs) for fetal loss or neonatal death, low birthweight, moderate or severe maternal anaemia, and clinical malaria were calculated from trial data and cost estimates in 2016 US dollars from observational studies, health facility costings and public procurement databases. The main outcome measure was the incremental cost per DALY averted.

Findings Relative to single screening and treatment, intermittent preventive treatment resulted in an incremental cost of US\$5657 (95% CI 1827 to 9448) and 107·4 incremental DALYs averted (−719·7 to 904·1) per 1000 women; the average incremental cost-effectiveness ratio was \$53 per DALY averted.

Interpretation Intermittent preventive treatment with dihydroartemisinin-piperazine offers a cost-effective alternative to single screening and treatment for the prevention of the adverse effects of malaria infection in pregnancy in the context of the moderate malaria transmission setting of Papua. The higher cost of intermittent preventive treatment was driven by monthly administration, as compared with single-administration single screening and treatment. However, acceptability and feasibility considerations will also be needed to inform decision making.

Funding Medical Research Council, Department for International Development, and Wellcome Trust.

Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access Article under the CC BY-NC-ND 4.0 license.

Introduction

70% of all pregnancies in malaria-endemic regions globally are in the Asia-Pacific region, of which an estimated 6·4 million pregnancies (5·1% of the global total) occur annually in Indonesia, in areas with *Plasmodium falciparum* or *Plasmodium vivax* transmission.¹ Malaria infection in pregnancy is associated with serious adverse maternal and birth outcomes. The clinical effects of malaria infection in pregnancy depend upon the intensity of transmission, the malaria species, and the immunity in pregnant women. Indonesia has a high heterogeneity of risk of infection and malaria incidence across its 6000 inhabited islands.² Both

P falciparum and *P vivax* contribute to the burden of malaria infection in pregnancy in Indonesia and both infections are associated with severe maternal anaemia, fetal loss, and low birthweight.^{3–5}

The harmful effects of malaria infection in pregnancy are preventable, but the Asia-Pacific region has no regional prevention strategy; WHO recommendations for the region rely on passive case detection and case management alongside the use of long-lasting insecticidal nets.⁶ In 2012, Indonesia introduced a national screening policy for the prevention of malaria in pregnancy in malaria-endemic areas, the first country in Asia to do so. The single screening and treatment policy consists of screening all

Lancet Glob Health 2020;
8: e1524–33

Disease Control Department, London School of Hygiene and Tropical Medicine, London, UK (L Paintain MSc, Prof J Webster PhD); Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK (J Hill PhD, R Ahmed PhD, C Khairallah MSc, Prof F O ter Kuile PhD); Eijkman Institute for Molecular Biology, Jakarta, Indonesia (R Ahmed, C Umbu Reku Landuwulang MSc, A Ansariadi PhD, Prof D Syafruddin PhD); Department of Epidemiology, School of Public Health, Hasanuddin University, Makassar, Indonesia (A Ansariadi); Mimika District Health Authority, Timika, Papua, Indonesia (J Rini Poespoprodjo PhD, F H Burdam MD); Timika Malaria Research Program, Papuan Health and Community Development Foundation, Timika, Papua, Indonesia (J Rini Poespoprodjo, I Bonsapia, MD); Pediatric Research Office, Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (J Rini Poespoprodjo)

Correspondence to:
Lucy Paintain, Disease Control Department, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, United Kingdom
lucy.paintain@lshtm.ac.uk

Research in context

Evidence before this study

A randomised controlled trial of interventions for the prevention of malaria in pregnancy in Papua, Indonesia, found intermittent preventive treatment with dihydroartemisinin-piperazine to be a promising alternative to the current strategy of single screening and treatment. Acceptability and feasibility studies were also done in the same area as the trial to support policy decision making. These studies found that, although health providers and pregnant women widely accepted single screening and treatment, implementation was variable across different health facilities, particularly across different levels of facility. A change from screening and treatment strategies to preventive treatment would require a shift in attitude, particularly amongst health providers. Cost-effectiveness is another component of the policy decision-making process. This was the first trial of intermittent preventive treatment with dihydroartemisinin-piperazine in the Asia-Pacific region. A search of PubMed on June 4, 2020, with no date or language restrictions and using the search terms ("malaria" AND ("prevent*" OR "prevention") AND "pregnan*" AND ("asia" OR "pacific") AND ("economic" OR "economic evaluation" OR "cost-effect*")), confirmed that there are no published cost-effectiveness studies on preventive malaria infection in pregnancy interventions in the Asia-Pacific region.

Added value of this study

To our knowledge, this study is the first cost-effectiveness analysis of preventive strategies for malaria infection in

pregnancy in the Asia-Pacific region, complementing the evidence generated from the first randomised controlled trial of intermittent preventive treatment in Indonesia. Along with the acceptability and feasibility studies nested within the trial, the cost-effectiveness results provide a comprehensive package of evidence on an alternative strategy to the existing single screening and treatment policy.

Implications of all the available evidence

Intermittent preventive treatment, as an alternative to single screening and treatment, is efficacious and cost-effective from a provider perspective. There was more acceptance of single screening and treatment (standard of care) amongst health providers due to the long-standing culture of testing and treating for malaria. However, the implementation of single screening and treatment was variable across levels of health facility. Conversely, pregnant women reported that they welcomed the opportunity to prevent malaria infections during pregnancy through intermittent preventive treatment to protect themselves and their babies. Intermittent preventive treatment offers a cost-effective alternative to the current strategy of single screening and treatment for the prevention of the adverse effects of malaria infection in pregnancy in the context of the moderate malaria transmission setting of Papua, Indonesia. However, interventions to address provider and user acceptability should be considered alongside any future change in policy and costs and effects closely monitored.

pregnant women on their first antenatal care visit with either microscopy or a rapid diagnostic test and treatment of parasite-positive women with a first line antimalarial, followed by passive case detection and case management for the remainder of the pregnancy.⁷ High-grade resistance to sulfadoxine-pyrimethamine in Papua, Indonesia precludes the use of sulfadoxine-pyrimethamine for prevention or treatment of malaria.⁸

A three-arm, cluster-randomised, superiority trial (STOPMiP) was done in two sites in eastern Indonesia (Sumba island in Nusa Tenggara Province, and Mimika district in Papua Province) between May 16, 2013, and Nov 26, 2016.⁹ The trial compared the safety and efficacy of intermittent preventive treatment, consisting of monthly doses of an antimalarial in the second and third trimesters regardless of parasite positivity, and intermittent screening and treatment, consisting of screening at each scheduled antenatal care visit using a rapid diagnostic test and treatment with the first line antimalarial if parasite-positive, with the current single screening and treatment strategy for control of malaria infection in pregnancy in Indonesia. The first-line anti-malarial for second and third trimesters, dihydroartemisinin-piperazine,¹⁰ was used in all three groups. Cost-effectiveness, acceptability, and feasibility studies were done alongside the trial,¹¹⁻¹³ together with an evaluation of the implementation of

single screening and treatment.¹³ Intermittent preventive treatment was effective at reducing maternal malaria infection and maternal anaemia in Papua but not in Sumba. The effect of intermittent screening and treatment with dihydroartemisinin-piperazine compared with single screening and treatment was inconsistent. The authors concluded that the trial results do not support a role for intermittent screening and treatment with the current generation of standard rapid diagnostic tests or for intermittent preventive treatment in lower transmission areas in the Asia-Pacific region. However, intermittent preventive treatment provides an efficacious intervention in Papua and similar areas with moderate-to-high transmission in the region.¹⁰ In the accompanying single screening and treatment implementation feasibility study, around half of women were screened for malaria on their first visit to antenatal care. However, likelihood of malaria screening varied by level of health facility; screening was heavily skewed towards those accessing the community health centres with laboratory facilities (puskesmas) and poorly implemented at village-based health posts without microscopy (posyandus). In addition to the epidemiological, acceptability, and feasibility findings, the cost-effectiveness of alternative strategies for controlling malaria in pregnancy need to be understood. The aim of this study was to estimate the incremental

cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperazine compared with single screening and treatment with dihydroartemisinin-piperazine in Papua, Indonesia.

Methods

Study design and participants

We did a cost-effectiveness analysis comparing intermittent preventive treatment with dihydroartemisinin-piperazine with single screening and treatment with dihydroartemisinin-piperazine using data from a cluster randomised trial (STOPMiP). The trial enrolled 1290 women from the site in southern Papua, Indonesia. Details of the trial methods were published previously.¹⁰ In brief, the units of randomisation were 21 health facilities providing antenatal care services with more than ten new pregnancies per year and assigned (1:1:1) to intermittent preventive treatment, intermittent screening and treatment, or single screening and treatment. Women of all gravidities in the second or third trimester attending their first antenatal care clinic with a viable pregnancy of 16–30 weeks gestation were eligible for enrolment. Dihydroartemisinin-piperazine was used in all three groups. Recruitment began on May 16, 2013, and the last infant follow-up was completed on Nov 26, 2016. All

participants received a long-lasting insecticidal net at enrolment. The trial was registered with ISRCTN, number ISRCTN34010937.

The study received ethical approval from the Research Ethics Committees at the Eijkman Institute for Molecular Biology, Indonesia, and the Liverpool School of Tropical Medicine, UK. Endorsement was obtained from the Litbangkes (National Institutes of Health), Ministry of Health, Indonesia and deferral to the Liverpool School of Tropical Medicine Research Ethics Committees by the Research Ethics Committee of the London School of Hygiene and Tropical Medicine. Written, informed consent was obtained from each participant.

Outcomes

We included four trial outcomes in the mother or baby in the cost-effectiveness analysis: fetal loss or infant death by 6–8 weeks, low birthweight (<2500 g), moderate or severe anaemia (<9 g/dL), and clinical malaria during pregnancy. These outcomes were chosen based on clinical and economic importance and the availability of data for calculation of disability-adjusted life-years (DALYs). DALYs were calculated for each outcome in the intermittent preventive treatment and single screening and treatment trial groups.

	Base case	Range	Distribution for probabilistic sensitivity analysis	Source
Cost estimates				
Health worker time cost				
Mean number of administrations of single screening and treatment with dihydroartemisinin-piperazine per pregnancy	1	..	Point estimate	Ahmed et al (2019) ¹⁰
Administrations of single screening and treatment with positive rapid diagnostic test, n/N (%)	21/356 (5%)	..	Point estimate	Ahmed et al (2019) ¹⁰
Time taken to provide one administration of single screening and treatment (negative rapid diagnostic test), min*	23	17.3–28.8	Gamma	Observations
Time taken to provide one administration of single screening and treatment (positive rapid diagnostic test), min†	28	21–35	Gamma	Observations
Mean number of administrations of intermittent preventive treatment with dihydroartemisinin-piperazine per pregnancy	3.87	..	Point estimate	Ahmed et al (2019) ¹⁰
Time taken to provide one dose of intermittent preventive treatment, min‡	5	3.75–6.25	Gamma	Observations
Midwife's monthly cost of labour, 2016 US dollars	\$387.71	\$332.26–\$413.76	Gamma	Health facility costings
Drug costs				
Mean cost per dihydroartemisinin-piperazine administration, 2016 US dollars§	2.48	1.86–3.10	Gamma	Ahmed et al (2019) ¹⁰
Average rapid diagnostic test cost per administration, 2016 US dollars¶	0.86	0.65–1.08	Gamma	Ahmed et al (2019) ¹⁰
Other costs				
Reminder SMS or call for dihydroartemisinin-piperazine dose 2 and 3, 2016 US dollars	0.05	0.04–0.07	Gamma	Ahmed et al (2019) ¹⁰
Costs from consequences				
Cost per outpatient visit (excluding medical supplies), 2016 US dollars	9.23	7.38–12.30	Gamma	Health facility costings
Cost per inpatient day (excluding medical supplies), 2016 US dollars	69.34	55.47–92.46	Gamma	Health facility costings
Cost per paediatric inpatient day (excluding medical supplies), 2016 US dollars	69.34	55.47–92.46	Gamma	Health facility costings

(Table 1 continues on next page)

	Base case	Range	Distribution for probabilistic sensitivity analysis	Source
(Continued from previous page)				
DALY calculations				
Discount rate	0.03	0.00–0.05	Point estimate	Wilkinson (2016) ²⁰
Neonatal outcomes				
Life expectancy at birth, Indonesia (years)	69.72	68.5–70.95	Gamma	GBD Study (2010) ¹⁸
Length of disability—low birthweight, years	69.72	68.5–70.95	Gamma	Salomon et al (2012) ¹³
Disability weight—low birthweight	0.106	..	Point estimate	GBD Study (2004) ¹⁷
Maternal outcomes				
Mean age, years	26	..	Point estimate	Ahmed et al (2019) ¹⁰
Life expectancy for women aged 25–29 years, Indonesia, years	47.8	45.9–49.8	Gamma	GBD Study (2010) ¹⁸
Length of disability—malaria during pregnancy (5 days), years**	0.014	0.008–0.016	Gamma	Webster et al (2018) ¹³
Length of disability—anaemia during pregnancy (21 days), years	0.06	0.04–0.12	Gamma	Price et al (2001) ³⁴
Disability weight—infectious disease severe acute episode	0.133	0.088–0.19	Gamma	GBD Study (2017) ¹⁹
Disability weight—moderate anaemia	0.052	0.034–0.076	Gamma	GBD Study (2017) ¹⁹
Mortality estimates				
Case fatality rate for malaria during pregnancy	0.01%	..	Beta	Brabin et al (2001) ³⁵
Case fatality rate for moderate or severe anaemia during pregnancy	0.0033%	0.0026%–0.0045%	Beta	Sicuri et al (2010) ³⁶
Measures of effect (trial outcomes)				
Neonatal outcomes, per 1000 women				
Risk of fetal loss or infant death at 6–8 weeks				
Single screening and treatment group††	35.1	16.4–53.9	Beta	Ahmed et al (2019) ¹⁰
Intermittent preventive treatment group‡‡	33.0	12.9–53.1	Beta	Ahmed et al (2019) ¹⁰
Risk of low birthweight				
Single screening and treatment group	129.8	94.0–165.6	Beta	Ahmed et al (2019) ¹⁰
Intermittent preventive treatment group	115.2	77.1–153.4	Beta	Ahmed et al (2019) ¹⁰
Maternal outcomes, per 1000 women				
Risk of moderate or severe anaemia (<9 g/dL) at last antenatal care visit				
Single screening and treatment group	152.0	114.0–190.1	Beta	Ahmed et al (2019) ¹⁰
Intermittent preventive treatment group	96.3	61.1–131.5	Beta	Ahmed et al (2019) ¹⁰
Incidence of clinical malaria during pregnancy				
Single screening and treatment group	36.5	17.0–56.0	Beta	Ahmed et al (2019) ¹⁰
Intermittent preventive treatment group	6.3	0.0–14.9	Beta	Ahmed et al (2019) ¹⁰
DALY=disability-adjusted life-year. *Based on observations of the trial team: 3 min per woman for group information session, plus 5 min for preparation of rapid diagnostic test and 15 min waiting for the result. †Based on observations of the trial team: 3 min per woman for group information session, plus 5 min for preparation of rapid diagnostic test, 15 min waiting for the result, and a 5 min counselling the patient about the treatment need for a positive rapid diagnostic test. ‡Based on observations of the trial team: 3 min per woman for group information session, plus 2 min for directly observed therapy of first dose of dihydroartemisinin-piperazine. §Average dosing regimen of three tablets (40 mg dihydroartemisinin and 320 mg piperazine) per day for 3 days based on patient weight range 36–75 kg; purchasing cost, including shipping, transport, wastage (+25%); same dosing regimen for intermittent preventive treatment, and a course of treatment for women found to be positive in the single screening and treatment group. ¶Purchasing cost, including shipping, transport, wastage (+25%). Weighted mean based on the number of consultations per facility; range represents variation in unit cost assuming ±25% consultations. **Median number of days loss of income reported by pregnant women during exit interviews used as a proxy. ††In the single screening and treatment group, of the 13 fetal loss or infant deaths at 6–8 weeks, three were stillbirths (occurring after 28 weeks), two were miscarriages (occurring before 28 weeks), and eight were infant deaths. ‡‡In the Intermittent preventive treatment group, of the ten fetal losses or infant deaths at 6–8 weeks, four were stillbirths, one was a miscarriage, and five were infant deaths.				
Table 1: Input variables for the base case and probabilistic cost-effectiveness of alternative interventions for malaria in pregnancy in Papua, Indonesia				

Statistical analysis

We calculated fixed and variable costs to the provider of delivering the interventions and costs of the four consequences of malaria infection in pregnancy for mother and infant included in the analysis using a combination of step-down costing and micro-costing.^{14,15} We collected detailed cost data from seven antenatal care clinics in the Papua trial site between Feb 1 and

May 31, 2016. The clinics were selected to provide a range of facility sizes in terms of the number of staff and number of consultations; all provided preventive and curative outpatient services, and one provided inpatient services. We used step-down costing to estimate the unit cost per outpatient consultation, per adult inpatient day, and per paediatric inpatient day. We calculated the weighted mean for each unit cost, based

on the number of consultations at facilities providing each service.

Where available, we used data from the trial area to estimate the costs of intervention delivery and consequences.^{10,13} Where data for a parameter were not available for the trial area, we extracted suitable estimates from the published literature (table 1; appendix p 1). All costs are presented in 2016 US dollars using the official average annual exchange rate (US\$1=13 308 Indonesian Rupiahs).¹⁶

We did the cost-effectiveness analysis from the provider perspective, taking a lifetime horizon to show the lifelong (discounted) mortality effects of the consequences of malaria infection in pregnancy. We constructed separate but structurally identical decision trees for each of the four outcomes (appendix p 2).

We calculated DALYs for each outcome in each trial group separately using disability weights from the 2017, 2010, and 2004 Global Burden of Disease studies,^{17–19} local life expectancies, no age weighting, and 3% discounting.²⁰ We calculated total DALYs in each trial group by summing the DALYs from the four outcomes, combining mortality (years of life lost) and morbidity (years lived with disability) effects. In the base case, fetal loss and infant deaths were assigned the same number of DALYs. For the total DALY calculation, only the morbidity effect (years lived with disability) of low birthweight was included to avoid double counting infant deaths attributable to low birthweight.

We calculated the incremental cost-effectiveness ratio for a hypothetical cohort of 1000 women by dividing the incremental cost of intermittent preventive treatment versus single screening and treatment by the incremental DALYs averted by intermittent preventive treatment versus single screening and treatment.

In a deterministic sensitivity analysis, we varied key variables and model assumptions one at a time, using the minimum and maximum values of the parameter range to explore their relative contribution to uncertainty in the incremental cost-effectiveness ratio estimate. To assess the uncertainty of all variables and assumptions simultaneously, we did a probabilistic sensitivity analysis with 10 000 iterations, producing a point estimate and 95% CI based on percentiles for the difference in effects and costs and an average incremental cost-effectiveness ratio. Table 1 provides a summary of the costs and effects parameters included in the cost-effectiveness analysis. A suitable distribution and range for each parameter are given to show the variability of each parameter and to define the boundaries for the sensitivity analysis.²¹ We plotted the results of the sensitivity analysis on the cost-effectiveness plane. We calculated the probability of intermittent preventive treatment with dihydroartemisinin-piperaquine being cost-effective for three cost-effectiveness thresholds: low (US\$42), middle (\$249), and high (\$542) and plotted our results in a cost-effectiveness acceptability curve. The low and middle thresholds are historical WHO thresholds

of \$25 and \$150, and the high threshold is a country-specific estimate for Indonesia (\$535),²² all inflated to 2016 US dollars. We designed and ran the decision model in Microsoft Excel using Visual Basic for Applications to run the probabilistic sensitivity analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and, with JW, had final responsibility for the decision to submit for publication.

See Online for appendix

Results

We included data on 675 women included in STOPMIP (319 in the intermittent preventive treatment group and 356 in the single screening and treatment group). There were 35 fetal losses or infant deaths per 1000 women (95% CI 16–54) by 6–8 weeks in the single screening and treatment group and 33 per 1000 (13–53) in the intermittent preventive treatment group, 130 (94–166) and 115 (77–153) low-birthweight babies per 1000 women, 152 (114–190) and 96 (61–131) cases of moderate or severe maternal anaemia per 1000 women, and 37 (17–56), and 6 (0–15) episodes of clinical malaria during pregnancy per 1000 women (table 1). The frequency of all outcomes did not significantly differ between the two groups, except reduction in clinical malaria, which was significantly less common in the intermittent preventive treatment group.

The total cost per administration of single screening and treatment, including health worker time and supplies, was \$4.69 (95% CI 4.00–5.46) when the rapid

	Cost, 2016 US dollars (95% CI)
Intervention cost	
Total cost per administration of single screening and treatment if found positive	\$4.69 (4.00–5.46)
Total cost per administration of single screening and treatment if found negative	\$1.92 (1.59–2.27)
Total cost per administration of intermittent preventive treatment	\$2.76 (2.20–3.41)
Health provider cost of consequences	
Mean cost per low birthweight	\$48.54 (26.09–76.32)
Mean cost per fetal death or infant death 6–8 weeks	\$0.00
Mean cost per case of moderate or severe anaemia	\$15.60 (10.76–22.17)
Mean cost per case of clinical malaria during pregnancy	\$46.09 (33.50–62.21)
Cost per 1000 pregnant women	
Health provider cost of single screening and treatment, excluding consequences	\$2059.76 (1737.61–2423.50)
Health provider cost of intermittent preventive treatment, excluding consequences	\$10 694.29 (8503.71–13 207.42)
Health provider cost of single screening and treatment, including consequences	\$12 415.34 (8919.93–16 950.09)
Health provider cost of intermittent preventive treatment, including consequences	\$18 079.62 (14 175.65–22 731.77)

Table 2: Costs of intervention and consequences of malaria in pregnancy in Papua, Indonesia

	Single screening and treatment	Intermittent preventive treatment
Base case		
Δ DALYs—low birthweight	..	45.1
Δ DALYs—fetal loss or infant death 6–8 weeks	..	62.3
Δ DALYs—maternal anaemia	..	0.31
Δ DALYs—clinical malaria in pregnancy	..	0.08
Total DALY	1429.5	1321.7
Total cost, 2016 US dollars*	\$12 415	\$18 080
Δ Costs, 2016 US dollars*	..	\$5664
Δ DALYs	..	107.7
ICER, US dollars per DALY*	..	53
Probabilistic sensitivity analysis		
Δ DALYs (95% CrI)—low birthweight	..	45.6 (–117.6 to 205.5)
Δ DALYs (95% CrI)—fetal loss or infant death at 6–8 weeks	..	61.4 (–748.4 to 844.2)
Δ DALYs (95% CrI)—maternal anaemia	..	0.31 (0.02 to 0.73)
Δ DALYs (95% CrI)—clinical malaria in pregnancy	..	0.08 (0.03 to 0.15)
Total DALY (95% CrI)	1430.2 (944.2 to 2029.7)	1322.9 (812.7 to 1987.2)
Total cost (95% CrI), 2016 US dollars*	\$12 422 (8920 to 16 950)	\$18 079 (14 176 to 22 732)
Δ Costs (95% CrI), 2016 US dollars*	..	5657 (1827 to 9448)
Δ DALYs (95% CrI)	..	107.4 (–719.7 to 904.1)
Mean incremental cost-effectiveness ratio (95% CrI), US dollars per DALY*	..	53 (4 to –7)†

DALY=disability-adjusted life-year. CrI=credible interval *Includes provider costs from health consequences. †The 95% CrI varied from \$4 to to –\$7 per DALY averted; the latter representing a situation in which intermittent preventive treatment costs more and incurs more DALYs than single screening and treatment.

Table 3: Cost-effectiveness analysis, comparing intermittent preventive treatment with dihydroartemisinin-piperaquine with the existing policy of single screening and treatment in Papua, Indonesia

diagnostic test was positive and \$1.92 (1.59–2.27) if the rapid diagnostic test was negative; the total cost per administration of intermittent preventive treatment was \$2.76 (2.20–3.41; table 2).

The average cost of health consequences of malaria infection in pregnancy was \$48.54 (95% CI 26.09–76.32) for the short-term consequences per low-birthweight baby, \$15.60 (10.76–22.17) per case of moderate or severe maternal anaemia, and \$46.09 (33.50–62.21) per episode of clinical malaria during pregnancy.

The average cost per pregnant woman to deliver single screening and treatment was \$2.06 (95% CI 1.74–2.42) and to deliver intermittent preventive treatment was \$10.70 (8.50–13.21). This difference is largely driven by the greater number of administrations of intermittent preventive treatment per woman compared with single screening and treatment (3.87 vs 1.00). When the costs of consequences of malaria infection in pregnancy were included, the cost per 1000 pregnant women was \$12 415.34 (8919.93–16 950.09) for single screening and treatment, and \$18 079.62 (14 175.65–22 731.77) for intermittent preventive treatment (table 2). This amounts to intermittent preventive treatment costing on average around \$5.66

more per pregnant woman than single screening and treatment.

Compared with single screening and treatment, delivering intermittent preventive treatment to 1000 pregnant women led to 107.7 DALYs averted, of which 41.8% were due to low birthweight, 57.8% due to fetal loss or infant death by 6–8 weeks, and the remaining 0.4% due to maternal anaemia or clinical malaria. The incremental cost was \$5664 per 1000 women, and the incremental cost-effectiveness ratio was \$53 per DALY averted (table 3). Deterministic sensitivity analysis found that the cost-effectiveness of intermittent preventive treatment compared with single screening and treatment was most sensitive to the fetal loss or infant death effect measure, the discount rate used in the DALY calculations, and price of dihydroartemisinin-piperaquine (appendix pp 3–4). However, none of the parameter changes resulted in the incremental cost-effectiveness ratio increasing beyond the middle cost-effectiveness threshold.

The probabilistic sensitivity analysis for intermittent preventive treatment compared with single screening and treatment resulted in an incremental cost of \$5657 (95% CrI 1827 to 9448) and 107.4 incremental DALYs averted (–719.7 to 904.1) per 1000 women. The average incremental cost-effectiveness ratio was \$53 per DALY averted (figure 1; table 3). The 95% CrI around the mean incremental cost-effectiveness ratio varied from \$4 to to –\$7 per DALY averted; the latter representing a situation in which intermittent preventive treatment costs more and incurs more DALYs than single screening and treatment. The probability of intermittent preventive treatment falling below the cost-effectiveness threshold of \$42 and being considered highly cost-effective was 48%; the probability of falling below the cost-effectiveness threshold of \$249 was 59% or and below \$542 was 60% (figure 2).

Discussion

Our findings suggest that intermittent preventive treatment with dihydroartemisinin-piperaquine at a cost of \$53 per DALY averted offers a cost-effective alternative to the current policy of single screening and treatment in the moderate-malaria-transmission setting of Papua, Indonesia. Although intermittent preventive treatment incurred higher costs than single screening and treatment, it resulted in fewer DALYs. This cost per DALY compares favourably with the median cost per DALY averted by insecticide-treated nets (\$30), intermittent preventive treatment with sulfadoxine-pyrimethamine (\$27), and indoor residual spraying (\$160) reported by White et al²⁴ (all figures inflated to 2016 US dollars for comparison); no studies were found from the Asia-Pacific region that were eligible for inclusion in these estimates.

The wide 95% CI in the incremental DALYs averted and incremental costs estimated by the probabilistic sensitivity analysis should be noted. There are simulation points in the northwestern quadrant of the cost-effectiveness plane

and the uncertainty range of DALYs averted includes zero, indicating that, in some of the 10 000 iterations of the Monte Carlo model, intermittent preventive treatment incurred higher costs and resulted in more DALYs than single screening and treatment (ie, was more expensive and less effective). Although all four outcomes included in the cost-effectiveness analysis were less common in the intervention group than in the control group, only the reduction in clinical malaria between intermittent preventive treatment and single screening and treatment was statistically significant.

The cost-effectiveness acceptability curve presents the uncertainty in the model in an alternative format, showing the probability of intermittent preventive treatment falling below certain cost-effectiveness thresholds. To support decision-makers in choosing actions that are likely to lead to population health improvements, cost-effectiveness analyses should compare the additional health benefits of an intervention with the health likely to be lost elsewhere as a consequence of any additional costs (ie, the health opportunity costs). Cost-effectiveness thresholds are intended to represent these health opportunity costs; a number of options exist, each with advantages and disadvantages.²⁵ For example, the historic thresholds of \$25 and \$150 (adjusted in this study to \$42 and \$249) were based on affordability expectations and are widely used irrespective of the local context.²⁶ Another widely used threshold is 1–3 times a country's per capita GDP, essentially taking a human capital approach to valuing a person's life by the economic activity of individuals.²⁷ Ochalek et al²² argue that, with these demand-side cost-effectiveness thresholds of what health expenditure ought to be, there is no guarantee they will reflect actual health opportunity costs and their use, therefore, risks reducing, rather than improving, population health. They instead propose the use of supply-side thresholds of health opportunity costs given actual expenditure. Ochalek et al²² used econometric models analysing the effect of health expenditure on health outcomes from cross-country data to estimate supply-side cost-effectiveness thresholds for countries without empirical data; here we used their estimate for Indonesia of \$542. The probability of intermittent preventive treatment falling below the low cost-effectiveness threshold of \$42 was 48%; the probability of intermittent preventive treatment falling below the middle and high cost-effectiveness thresholds included in this analysis (\$249 and \$542) was consistent at around 60%, reflecting that above a cost-effectiveness threshold of around \$250, there is no additional increase in the probability of intermittent preventive treatment being cost-effective. Therefore, use of the considerably higher one-times per capita GDP threshold (\$3604 for Indonesia in 2016)¹⁶ would not increase the probability of intermittent preventive treatment being cost-effective in this analysis.

The uncertainty in the model should be noted. The trial was designed to detect a reduction in maternal or placental

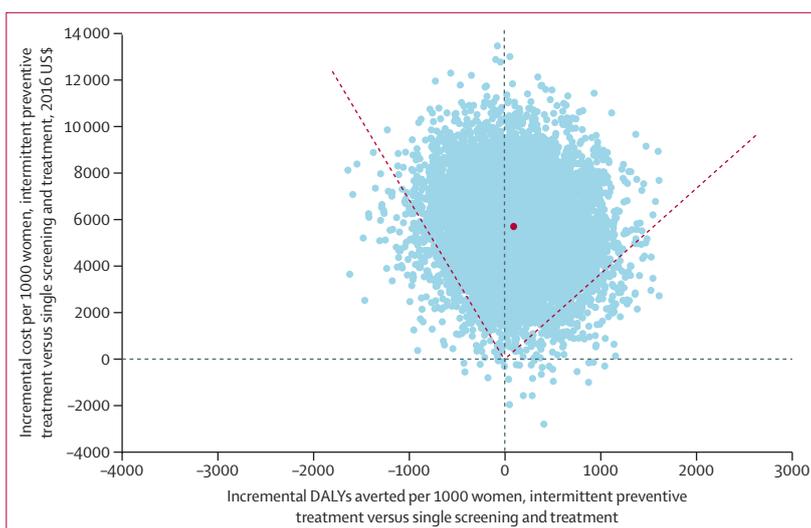


Figure 1: Cost-effectiveness plane of intermittent preventive treatment versus single screening and treatment in Papua, Indonesia

The graph displays results of Monte Carlo simulations with 10 000 iterations using the value ranges and distributions presented in table 1. The horizontal axis represents the difference in effect between intermittent preventive treatment and single screening and treatment and the vertical axis represents the difference in cost. The incremental cost-effectiveness ratio for each simulation is defined as the slope of the line from the origin to that datapoint. The red dot represents the mean incremental cost-effectiveness ratio (\$53 per DALY averted) at a mean cost of \$5657 and a mean of 107 DALYs averted. Because \$53 per DALY averted lies northeast of the origin and is a positive number, the new intervention is more effective but also more costly than the existing strategy. Datapoints falling northwest of the origin indicate the possibility that the new intervention is less effective and more costly than the existing strategy. Dashed lines indicate the 2.5th and 97.5th percentiles used to estimate the 95% CI for the incremental cost-effectiveness ratio. The lower bound of the 95% CI was \$4 per DALY averted, at a cost of \$2124 and 553 DALYs averted. The upper bound of the 95% CI was -\$7 per DALY averted, at a cost of \$3120 and -472 DALYs averted (i.e. health loss from the new strategy).

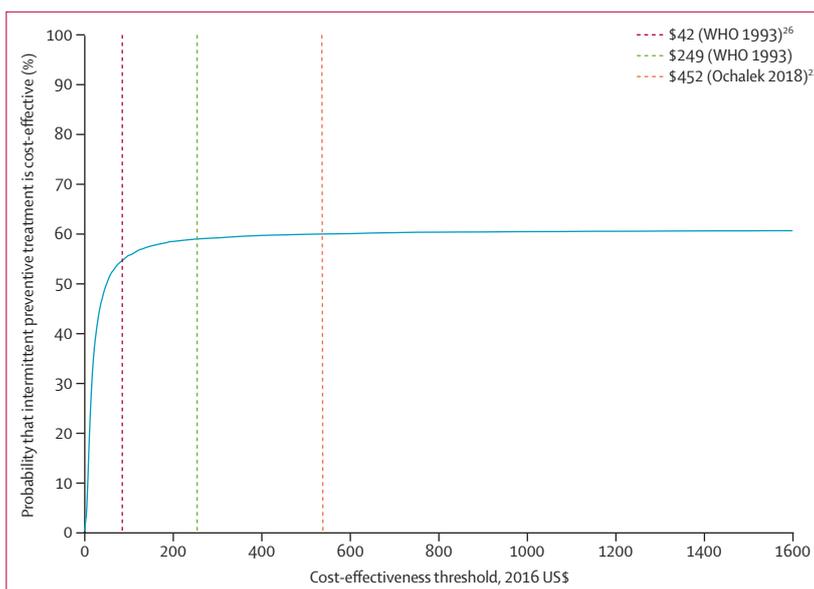


Figure 2: Cost-effectiveness acceptability curve of intermittent preventive treatment versus single screening and treatment in Papua, Indonesia

The curve shows the probability of intermittent preventive treatment being cost-effective at any given cost-effectiveness threshold value. The vertical dashed lines indicate three alternative cost-effectiveness thresholds.

malaria infection at delivery. It was not powered to detect statistically significant differences in the clinical outcomes included in this cost-effectiveness analysis, and the wide confidence interval in the effect size for some of these outcomes is reflected in the CI around the cost-effectiveness analysis.¹⁵ Cost-effectiveness analysis is valuable to decision-makers, as long as the uncertainty reflected by the results of the probabilistic sensitivity analysis is taken into account. In Papua, Indonesia, the malaria transmission intensity is similar to those in moderate malaria transmission areas in Africa where intermittent preventive treatment with sulfadoxine-pyrimethamine is implemented. It is biologically plausible that effective chemoprevention with monthly intermittent preventive treatment could reduce low birthweight and fetal or neonatal death in Papua when compared with single screening and treatment with low sensitivity rapid diagnostic tests.¹⁰ Therefore, although the cost per capita of delivering intermittent preventive treatment (\$10.70) is higher than the current strategy of single screening and treatment (\$2.06), it is a feasibly efficacious strategy for the chemoprevention of adverse pregnancy outcomes in the context of the moderate malaria transmission intensity found in Papua. Furthermore, the cost per capita of intermittent preventive treatment relates favourably to the total per capita annual health expenditure of \$112 in Indonesia.²³ Although sulfadoxine-pyrimethamine is a cheaper drug than dihydroartemisinin-piperaquine, use of sulfadoxine-pyrimethamine for intermittent preventive treatment is not an option in Papua owing to high-grade resistance.^{28,29}

Fetal deaths were allocated the same number of years of life lost as infant deaths. The incremental cost-effectiveness ratio was very sensitive to this assumption, particularly owing to the small numbers of events in each group and the high proportional contribution of infant outcomes to the total DALYs. However, the majority of these fetal losses were stillbirths, taking place at 28 weeks gestation or later and we took this approach to acknowledge the value of the loss of a baby late in pregnancy as supported by the 2016 *Lancet* Series on Ending Preventable Stillbirths,³⁰ which advocates for the recognition of the full impact of stillbirth and the need for improved measurement and reporting.

Our model had several limitations. Although the effect parameters used were from an intention-to-treat analysis rather than per protocol, efficacy outcomes from a controlled trial will still be better than results achievable under routine conditions. For example, although around 90% of women in Papua attend antenatal care clinics at least once, only 45% of women make at least four antenatal care visits.³¹ In contrast, women in our study received on average 3.9 administrations of intermittent preventive treatment. It would be possible to model the change in costs of varying numbers of administrations of intermittent preventive treatment, because we know the unit costs per administration. However, there are no data

on how efficacy would be affected by varying the number of administrations, and hence the number of courses administered in our trial were used. A similar limitation applies to the low sensitivity of the rapid diagnostic tests used. It would be useful to explore the effects of increasing the proportion of rapid diagnostic tests that were positive as a proxy for more sensitive rapid diagnostic tests in future. However, it is not possible to predict the resulting change in efficacy given the available evidence.

Our analysis presents the provider perspective only. Taking a societal perspective would capture the full costs associated with the delivery of the interventions and the consequences of malaria infection in pregnancy, including the direct and indirect costs of seeking and receiving care. However, estimating the medical costs of malaria infection in pregnancy to the provider or household, particularly low birthweight and fetal or neonatal loss, is challenging due to the wide variation in treatment required and would have increased uncertainty in the model estimates. Despite intermittent preventive treatment requiring monthly dosing compared with one administration of single screening and treatment, the monthly doses align with the antenatal care schedule, and would therefore, in theory, not require extra visits or incur incremental costs to households. However, as previously discussed, only 45% of women made at least four antenatal care visits in Papua, which suggests interventions to increase antenatal care attendance might be needed, which would incur additional costs to providers and households. This could be an area for future research.

Decisions about a change in policy for the prevention of malaria infection in pregnancy will be based on multiple factors in addition to effectiveness and cost-effectiveness, including equity, ethics, acceptability, feasibility and a range of other factors affecting the political economy. Studies done in the same area as ours found that the existing strategy of single screening and treatment was acceptable to health providers but being implemented inconsistently.^{11,13} Investigation of the acceptability of intermittent screening and treatment or intermittent preventive treatment as alternatives to the existing strategy found that there was more acceptance of intermittent screening and treatment among health providers due to the long-standing culture of testing and treating for malaria. Conversely, pregnant women were accepting of all three interventions used in the trial and reported that they welcomed the opportunity to prevent malaria infections during pregnancy through intermittent preventive treatment to protect themselves and their babies.¹² Concerns about the presumptive use of dihydroartemisinin-piperaquine during pregnancy were however revealed during the trial; a higher proportion of participants withdrew consent in the intermittent preventive treatment group (14% compared with 2% in the single screening and treatment group and 0% in the

intermittent screening and treatment group).¹⁰ Although the occurrence of adverse events was similar across trial groups, the larger number of withdrawals in the intermittent preventive treatment group reflects women's concerns about side-effects and taking medications when they are pregnant while they do not have any symptoms of malaria. The withdrawals occurred in certain clusters often led by one influential woman. Similarly, although adherence to the full dose of dihydroartemisinin-piperaquine was high (90%) in the trial setting, adherence will probably be lower under routine conditions.³² Interventions to encourage uptake and correct implementation of any new policy will increase the potential impact of the intervention when delivered under routine conditions, and the costs of these interventions should be factored into future cost-effectiveness analyses.

Intermittent preventive treatment is likely to offer a cost-effective alternative to the current strategy of single screening and treatment for the prevention of the adverse effects of malaria infection in pregnancy in the context of moderate malaria transmission in Papua, Indonesia. Interventions to address provider and user acceptability should be considered alongside any future change in policy and costs and effects closely monitored.

Contributors

LP designed the cost-effectiveness model. JH and JW designed the study. CURL, AA, FHB, and IB acquired the costs data. RA and CK provided the trial data. LP and CK analysed the data. LP, JH, RA, FOTK, and JW interpreted the data. LP wrote the first draft of the manuscript. All authors critically revised subsequent drafts of the paper. JH, RA, JRP, DS, FOTK, and JW obtained funding. JH and JW supervised the study.

Declaration of interests

We declare no competing interests.

Data sharing

All individual-participant data collected during this trial will be available to access after de-identification. Data and documents, including the study protocol and statistical analysis plan, will be available. Data access will be provided to researchers after a proposal has been approved by an independent review committee identified for this purpose.

An agreement on how to collaborate will be reached based on any overlap between the proposal and any ongoing efforts. Data will be available beginning at 3 months after publication of this Article. Proposals should be directed to feiko.terkuile@lstmed.ac.uk; to gain access, data requesters will need to sign a data access agreement, and the de-identified database will be transferred by email.

Acknowledgments

This work was supported by a grant from the UK Medical Research Council, Department for International Development, and Wellcome Trust Joint Global Health Trials Scheme (100024) to the Liverpool School of Tropical Medicine. We thank Silke Fernandes, Kara Hanson, and the Economic Evaluation group of the London School of Hygiene and Tropical Medicine for valuable discussions about the model and methods and would also like to acknowledge the fieldworkers and participants in Indonesia.

References

- Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med* 2010; **7**: e1000221.
- Elyazar IR, Hay SI, Baird JK. Malaria distribution, prevalence, drug resistance and control in Indonesia. *Adv Parasitol* 2011; **74**: 41–175.
- Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; **7**: 93–104.
- Nosten F, McGready R, Simpson JA, et al. Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet* 1999; **354**: 546–49.
- Rijken MJ, McGready R, Boel ME, et al. Malaria in pregnancy in the Asia-Pacific region. *Lancet Infect Dis* 2012; **12**: 75–88.
- WHO. Global technical strategy for malaria, 2016–2030. Geneva: World Health Organisation, 2015.
- Indonesian Ministry of Health. Antenatal care for prevention and treatment of malaria in pregnancy. Jakarta: Indonesian Ministry of Health, 2013.
- Poespoprodjo JR, Fobia W, Kenangalem E, et al. Treatment policy change to dihydroartemisinin-piperaquine contributes to the reduction of adverse maternal and pregnancy outcomes. *Malar J* 2015; **14**: 272.
- Ahmed R, Poespoprodjo JR, Syafruddin D, et al. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin-piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. *Lancet Infect Dis* 2019; **19**: 973–87.
- Indonesian Ministry of Health. The national guidelines for malaria treatment and management in Indonesia. Jakarta: Indonesian Ministry of Health, 2013.
- Hill J, Landuwulang CUR, Ansariadi, et al. Evaluation of the national policy of single screening and treatment for the prevention of malaria in pregnancy in two districts in Eastern Indonesia: health provider perceptions. *Malar J* 2018; **17**: 309.
- Hoyt J, Landuwulang CUR, Ansariadi, et al. Intermittent screening and treatment or intermittent preventive treatment compared to current policy of single screening and treatment for the prevention of malaria in pregnancy in Eastern Indonesia: acceptability among health providers and pregnant women. *Malar J* 2018; **17**: 341.
- Webster J, Ansariadi, Burdam FH, et al. Evaluation of the implementation of single screening and treatment for the control of malaria in pregnancy in Eastern Indonesia: a systems effectiveness analysis. *Malar J* 2018; **17**: 310.
- Conteh L, Walker D. Cost and unit cost calculations using step-down accounting. *Health Policy Plan* 2004; **19**: 127–35.
- Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for economic evaluation of health care programmes, 3rd edn. Oxford: Oxford University Press, 2005.
- International Monetary Fund. International Financial Statistics. International Monetary Fund, 2019. <https://data.world.imf/international-financial-statistics> (accessed April 1 2019).
- WHO. Global burden of disease 2004 update: disability weights for diseases and conditions. World Health Organization, 2004. http://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf (accessed June 15, 2019).
- Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2010 (GBD 2010) Life Expectancy and Healthy Life Expectancy 1970–2010. Global Burden of Disease Collaborative Network, 2010. <http://ghdx.healthdata.org/record/ihme-data/gbd-2010-life-expectancy-and-healthy-life-expectancy-1970-2010> (accessed June 15, 2019).
- Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Disability Weights. Global Burden of Disease Collaborative Network, 2018. <http://ghdx.healthdata.org/record/ihme-data/gbd-2017-disability-weights> (accessed June 15, 2019).
- Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative reference case for economic evaluation: an aid to thought. *Value Health* 2016; **19**: 921–28.
- Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.
- Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health* 2018; **3**: e000964.
- WHO. World Health Organization global health expenditure database. World Health Organization, 2019. <http://apps.who.int/nha/database/ViewData/Indicators/en> (accessed June 15, 2019).
- White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions—a systematic review. *Malar J* 2011; **10**: 337.

- 25 Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. *Pharmacoeconomics* 2009; **27**: 903–17.
- 26 WHO. Investing in health research and development: report of the ad hoc committee on health research relating to future intervention options. Geneva: World Health Organization, 1996.
- 27 WHO. WHO-CHOICE: choosing Interventions that are cost-effective. World Health Organization, 2019. <https://www.who.int/choice/cost-effectiveness/en/> (accessed June 15, 2019).
- 28 Ratcliff A, Siswanto H, Kenangalem E, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. *Lancet* 2007; **369**: 757–65.
- 29 Ratcliff A, Siswanto H, Kenangalem E, et al. Therapeutic response of multidrug-resistant *Plasmodium falciparum* and *P. vivax* to chloroquine and sulfadoxine-pyrimethamine in southern Papua, Indonesia. *Trans R Soc Trop Med Hyg* 2007; **101**: 351–59.
- 30 Heazell AEP, Siassakos D, Blencowe H, et al. Stillbirths: economic and psychosocial consequences. *Lancet* 2016; **387**: 604–16.
- 31 Mimika District Health Office. 2017 Annual Health Profile Report. Mimika District Health Office, 2017.
- 32 Oduro AR, Chatio S, Beeri P, et al. Adherence to dihydroartemisinin-piperaquine treatment among patients with uncomplicated malaria in northern Ghana. *J Trop Med* 2019; **2019**: 5198010.
- 33 Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2129–43.
- 34 Price RN, Simpson JA, Nosten F, et al. Factors contributing to anemia after uncomplicated falciparum malaria. *Am J Trop Med Hyg* 2001; **65**: 614–22.
- 35 Brabin BJ, Hakimi M, Pelletier D. An analysis of anemia and pregnancy-related maternal mortality. *J Nutr* 2001; **131**: 604S–15S.
- 36 Sicuri E, Bardaji A, Nhampossa T, et al. Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in southern Mozambique. *PLoS One* 2010; **5**: e13407.