Title

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

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Abstract

Background

Malaria is an important cause of adverse pregnancy outcomes. A randomised controlled trial in Papua, Indonesia, on the efficacy of intermittent-preventive-treatment (IPT) with dihydroartemisinin-piperaquine (DP) compared to the current strategy of single screening-and-treatment (SST) with DP showed that IPT-DP is a promising alternative to SST-DP for the reduction of malaria in pregnancy (MiP). A cost-effectiveness analysis comparing IPT-DP to SST-DP was conducted.

Methods

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 1,000 women who received IPT-DP or SST-DP. Disability-adjusted life years (DALYs) for fetal loss/neonatal death, low birthweight, moderate/severe maternal anaemia, and clinical malaria were calculated from trial data and cost estimates from observational studies, health facility costings and public procurement databases. Costs are presented in 2016 US dollars. The main outcome measure was the incremental cost per DALY averted.

Findings

Relative to SST-DP, IPT-DP resulted in an incremental cost of USD 5,657 (95% CI: 1,827, 9,448) and 107·4 incremental DALYs averted (-719·7, 904·1) per 1,000 women; the average incremental cost-effectiveness ratio (ICER) was USD 53/DALY averted.

Interpretation

IPT-DP offers a cost-effective alternative to the current strategy of SST-DP for the prevention of the adverse effects of MiP in the context of the moderate malaria transmission setting of Papua. Higher cost of IPT-DP was driven by monthly-administration, as compared with single-administration SST. However, acceptability and feasibility considerations will also be needed to inform decision making.

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Research in context

Evidence before this study

A randomised controlled trial of interventions for the prevention of malaria in pregnancy (MiP) in Papua, Indonesia found intermittent preventive treatment with dihydroartemisinin-piperaquine (IPT-DP) to be a promising alternative to the current strategy of single screening and treatment (SST-DP). Acceptability and feasibility studies were also conducted 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 important component of the policy decision-making process. This was the first IPT-DP trial in the Asia-Pacific region, and a search of PubMed confirmed that there are no published cost-effectiveness studies on preventive MiP interventions in the Asia-Pacific region.

Added value of this study

To our knowledge, this study is the first cost-effectiveness analysis of MiP preventive strategies in the Asia-Pacific region, complementing the evidence generated from the first randomised controlled trial of IPT-DP 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 screen and treat policy.

Implications of all the available evidence

IPT-DP, as an alternative to SST-DP, is efficacious and cost-effective from a provider perspective. There was more acceptance of SST-DP (standard of care) amongst health providers due to the long-standing culture of testing and treating for malaria. However, the implementation of SST-DP was variable across levels of health facility. Conversely, pregnant women reported that they welcomed the opportunity to prevent malaria infections during pregnancy through IPT-DP to protect themselves and their babies. IPT-DP offers a cost-effective alternative to the current strategy of SST-DP for the prevention of the adverse effects of MiP 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.

Background

Over two thirds (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* and/or *Plasmodium vivax* transmission.[1] Malaria infection in pregnancy (MiP) is associated with serious adverse maternal and birth outcomes. The clinical effects of MiP depend upon the intensity of transmission, the malaria species and the level of immunity in pregnant women. Indonesia has a high heterogeneity of risk of infection and malaria incidence across its 6,000 inhabited islands.[2] Both *P. falciparum* and *P. vivax* contribute to the burden of MiP in Indonesia and both infections are associated with severe maternal anaemia, fetal loss and low birth weight (LBW).[3-5]

The harmful effects of MiP are preventable, yet the Asia-Pacific region has no regional prevention strategy; current World Health Organisation (WHO) recommendations for the region rely on passive case detection and case management alongside the use of long-lasting insecticidal nets (LLINs).[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 (SST) policy consists of screening all pregnant women on their first antenatal care (ANC) visit with either microscopy or a rapid diagnostic test (RDT) and treatment of parasite positive cases with the first line antimalarial; this is followed by passive case detection and case management for the remainder of the pregnancy.[7] High-grade resistance to sulfadoxine-pyrimethamine (SP) in Papua, Indonesia precludes the use of SP for prevention or treatment of malaria.[8] At the time of this study, the first-line antimalarial was quinine in the first trimester, and dihydroartemisinin-piperaquine (DP) in the second and third trimesters.[9]

A three-arm cluster-randomised controlled superiority trial was conducted in two sites in Eastern Indonesia (Sumba island in Nusa Tenggara Province, and Mimika district in Papua Province) between May 2013 and November 2016.[10] The trial compared the safety and efficacy of intermittent preventive treatment (IPT), consisting of monthly doses of an antimalarial in the second and third trimesters regardless of parasite positivity, and intermittent screening and treatment (IST), consisting of screening at each scheduled ANC visit using an RDT and treatment with the first line antimalarial if parasite-positive, versus the current SST strategy for control of MiP in Indonesia. DP was used in all three arms. Cost-effectiveness, acceptability and feasibility studies were conducted alongside the trial,[11-13] together with an evaluation of the implementation of SST-DP.[13] IPT-DP was effective at reducing maternal malaria infection and maternal anaemia in Papua but not in Sumba. The effect of IST-DP compared to SST-DP was inconsistent. The authors concluded that the trial results do not support a role for IST-DP with the current generation of standard RDTs or for IPT-DP in lower transmission areas in the Asia-Pacific region. However, IPT-DP provides an efficacious intervention in Papua and similar areas with moderate-to-high transmission in the region.[10] In the accompanying SST-DP implementation feasibility study, it was found that approximately half of women were successfully screened for malaria on their first visit to ANC. However, this 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*).
Here we report the results of a cost-effectiveness analysis of IPT-DP compared to the current SST-DP policy for the control of MiP in Indonesia. The outcomes and costs for the analysis focus on Papua, Indonesia, where the trial results[10] suggest there is a plausible benefit of IPT-DP as an alternative to SST-DP in this setting.

Methods

Trial setting

The trial enrolled a total of 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 ANC services with more than ten new pregnancies per year and assigned (1:1:1) to either IPT, IST or SST. Women of all gravidities in the second or third trimester attending their first ANC clinic with a viable pregnancy between 16-30 weeks gestation were eligible for enrolment Dihydroartemisinin-piperaquine was used in all three trial arms. Recruitment began in May 2013, and the last infant follow-up was completed in November 2016. All participants received an LLIN at enrolment. The trial was registered with ISRCTN (ISRCTN34010937).

Effects

We included four trial outcomes in the mother or baby in the cost-effectiveness analysis: (i) fetal loss or infant death by 68 weeks; (ii) low birthweight (LBW) (<2500g); (iii) moderate/severe anaemia (<9g/dl); and (iv) 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 IPT-DP and SST-DP trial arms.

Costs

We calculated fixed and variable costs to the provider of delivering the interventions and costs of the four consequences of MiP to 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 ANC clinics in the Papua trial site between February and May 2016. The clinics were purposively 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, 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; further details in appendix p1). All costs are presented in 2016 USD using the official average annual exchange rate (1 USD = 13,308 Indonesian Rupiahs).[16]

Analysis and modelling

We conducted the cost-effectiveness analysis from the provider perspective, taking a lifetime horizon to show the lifelong (discounted) mortality effects of the consequences of MiP. We constructed separate but structurally identical decision trees for each of the four outcomes (appendix p2, using the LBW decision tree as an example).

We calculated DALYs for each outcome in each trial arm separately using disability weights from the 2017, 2010 and 2004 global burden of disease (GBD) studies,[17-19] local life expectancies, no age weighting, and 3% discounting.[20] We calculated total DALYs in each trial arm by summing the DALYs from the four outcomes, combining mortality (years of life lost, YLL) and morbidity (years lived with disability, YLD) 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 (YLD) of LBW was included to avoid double counting infant deaths attributable to LBW.

We calculated the incremental cost-effectiveness ratio (ICER) for a hypothetical cohort of 1,000 women by dividing the incremental cost of IPT-DP versus SST-DP by the incremental DALYs averted by IPT-DP versus SST-DP.

We varied key variables and model assumptions in a deterministic sensitivity analysis to explore their relative contribution to uncertainty in the ICER estimate. To assess the uncertainty of all variables and assumptions simultaneously, we conducted a probabilistic sensitivity analysis (PSA) with 10,000 iterations, producing a point estimate and 95% confidence interval (CI) based on percentiles for the difference in effects and costs and an average ICER. 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 demonstrate the variability of each parameter and to define the boundaries for the PSA.[21] We plotted the PSA results on the cost-effectiveness plane. We calculated the probability of IPT-DP being cost-effective for three cost-effectiveness thresholds (CET): low (USD 42), middle (USD 249), and high (USD 542) and plotted our results in a cost-effectiveness acceptability curve. The low and middle thresholds are historical WHO thresholds of USD 25 and USD 150, and the high threshold is a country-specific estimate for Indonesia (USD 535)[22], all inflated to 2016 USD. We designed and ran the decision model in Microsoft Excel using Visual Basic for Applications to run the PSA.

Ethics

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

Role of the funding source

The funding institution had no role in the study design, data collection, analysis and interpretation, or preparation, review, or approval of the paper. LP had full access to all data in the model and takes full responsibility for the integrity of the data and the model as well as the accuracy of all analyses. LP and JW had final responsibility for the decision to submit for publication.

Results

Efficacy

In the SST-DP and IPT-DP arms there were respectively: 35 (95% CI: 16, 54) and 33 (13, 53) fetal loss or infant deaths by 6-8 weeks; 130 (94,166) and 115 (77, 153) LBW babies; 152 (114, 190) and 96 (61, 131) cases of moderate/severe maternal anaemia; and 37 (17, 56), and 6 (0, 15) episodes of clinical malaria during pregnancy, per 1,000 women (Table 1). All outcomes were less common in the IPT-DP arm than SST-DP arm. However, only the reduction in clinical malaria was statistically significant.

Costs

The total cost per administration of SST-DP, including health worker time and supplies, was USD 4·69 (4·00, 5·46) when the RDT was positive and USD 1·92 (1·59, 2·27) if the RDT was negative; the total cost per administration of IPT-DP was USD 2·76 (2·20, 3·41) (Table 2).

The average cost of health consequences of MiP was USD 48·54 (26·09, 76·32) for the short-term consequences per LBW baby, USD 15·60 (10·76, 22·17) per case of moderate/severe maternal anaemia, and USD 46·09 (33·50, 62·21) per episode of clinical malaria during pregnancy.

The average cost per pregnant woman to deliver SST-DP was USD 2·06 (1·74, 2·42) and to deliver IPT-DP was USD 10·70 (8·50, 13·21). This difference is largely driven by the greater number of administrations of IPT-DP per woman compared to SST-DP (3.87 versus 1, respectively). When the costs of consequences of MiP were included, the cost per 1,000 pregnant women was USD 12,415·34 (8,919·93, 16,950·09) for SST-DP, and USD 18,079·62 (14,175·65, 22,731·77) for IPT-DP (Table 2). This amounts to IPT-DP costing on average around USD 5.66 more per pregnant woman than SST-DP, respectively.

Cost-effectiveness

Compared to SST-DP, delivering IPT-DP to 1,000 pregnant women led to 107·7 DALYs averted of which 41·8% were due to LBW, 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. With an incremental cost of USD 5,664 per 1,000 women, this gave an ICER of USD 53 per DALY averted (Table 3). Deterministic sensitivity analysis found that the cost-effectiveness of IPT-DP compared to SST-DP was most sensitive to the fetal loss/infant death effect measure, the discount rate used in the DALY calculations, and price of DP (appendix p3-4). However, none of the parameter changes resulted in the ICER increasing beyond the middle CET.

The probabilistic sensitivity analysis for IPT-DP compared to SST-DP resulted in an incremental cost of USD 5,657 (1,827, 9,448) and 107·4 incremental DALYs averted (-719·7, 904·1) per 1,000 women; the average ICER was USD 53 per DALY averted (Table 3 and Figure 1). The probability of IPT-DP falling below the CET of USD 42 and being considered highly attractive was 48%; the probability of falling below the CET of USD 249 or USD 542 and being considered cost-effective was 59% or 60%, respectively (Figure 2).

Discussion

Our findings suggest that IPT-DP at a cost of USD 53 per DALY averted offers a cost-effective alternative to the current policy of SST-DP in the moderate malaria transmission setting of Papua, Indonesia. Although IPT-DP incurred higher costs than SST-DP, it resulted in fewer DALYs. This cost per DALY compares favourably with the median cost per DALY averted by insecticide-treated nets (USD 30), IPT-SP (USD 27) and indoor residual spraying (USD 160) reported by White et al (all figures inflated to 2016 USD for comparison); note that no studies were found from the Asia-Pacific region that were eligible for inclusion in these estimates.[24]

It is important to note the wide 95% CI in the incremental DALYs averted and incremental costs estimated by the PSA. There are simulation points in the north-western 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 IPT-DP incurred higher costs and resulted in more DALYs than SST (i.e. was more expensive and less effective). This reflects that although all four outcomes included in the cost-effectiveness analysis were less common in the intervention arm compared to the control arm, only the reduction in clinical malaria between IPT-DP and SST-DP was statistically significant.

The CEAC presents the uncertainty in the model in an alternative format, showing the probability of IPT-DP falling below certain cost-effectiveness thresholds. To support decision-makers to choose actions that are likely to lead to population health improvements, cost-effectiveness analysis should

involve comparing the additional health benefits of an intervention with the health likely to be lost elsewhere as a consequence of any additional costs, i.e. the health opportunity costs. CETs 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 USD 25 or USD 150 (adjusted here to 2016 USD 42 and USD 249, respectively) 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 in valuing a person's life by the economic activity of individuals.[27] Ochalek *et al.* argue that with these "demand-side" CETs 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 levels of expenditure.[22] Ochalek *et al.* use econometric models analysing the effect of health expenditure on health outcomes from cross-country data to estimate "supply-side" CETs for countries without empirical data; here we have used their estimate for Indonesia of USD 542.[22] The probability of IPT-DP falling below the low CET of USD 42 was 48%; the probability of IPT-DP falling below the middle and high CETs included in this analysis (USD 249, USD 542) was consistent at around 60%, reflecting that above a CET of around USD 250, there is no additional increase in the probability of IPT-DP being cost-effective. Therefore, use of the considerably higher one-times per capita GDP threshold (USD 3,604 for Indonesia in 2016)[16] would not increase the probability of IPT-DP being cost-effective in this analysis.

The uncertainty in the model is important. The trial was designed to detect a reduction in maternal or placental malaria infection at delivery. It was not powered to detect statistically significant differences in the clinical outcomes included in this CEA, and the wide confidence interval in the effect size for some of these outcomes is reflected in the confidence interval around the CEA.[15] CEA is valuable to decision-makers, as long as the uncertainty reflected by the results of the PSA is taken into account. In Papua, Indonesia, the levels of malaria transmission are similar to those in moderate malaria transmission areas in Africa where IPT with SP is implemented. It is biologically plausible that effective chemoprevention with monthly IPT-DP could reduce LBW and fetal/neonatal death in Papua when compared to SST-DP with low sensitivity RDTs.[10] Therefore, although the cost per capita of delivering IPT-DP (USD 10·70) is higher than the current strategy of SST-DP (USD 2·06), it is a feasibly efficacious strategy for the chemoprevention of adverse pregnancy outcomes in the context of the levels of malaria transmission found in Papua. Furthermore, the cost per capita of IPT-DP relates favourably to the total per capita annual health expenditure of USD 112 in Indonesia.[23] Although SP is a cheaper drug than DP, use of SP for IPT is not an option in Papua, Indonesia due to high-grade resistance.[28,29]

Fetal deaths were allocated the same number of years of life lost as neonatal deaths. The ICER was very sensitive to this assumption, particularly due to the small numbers of events in each arm 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, which advocates for the recognition of the full impact of stillbirth and the need for improved measurement and reporting.[30]

Our model had a number of limitations. Although the effect parameters used were from an intention to treat analysis rather than per protocol, the use of efficacy outcomes from a controlled trial setting will still be higher than results achievable under routine conditions. For example, although attendance of at least one ANC clinic is around 90% in Papua, only 45% of women make at least four

ANC visits.[31] In contrast, women in the trial received on average 3.9 administrations of IPT-DP. It would be possible to model the change in costs of varying numbers of administrations of IPT-DP. However, there is no data on how this would affect the efficacy, and hence the number of courses administered in the trial were used. A similar limitation applies to the low sensitivity of the RDTs used. It would be useful to explore the impact of increasing the proportion of RDTs that were positive as a proxy for more sensitive RDTs 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 MiP, including the direct and indirect costs of seeking and receiving care. However, estimating the medical costs to the provider or household of MiP, particularly LBW and fetal/neonatal loss is challenging due to the wide variation in treatment required and would have increased uncertainty in the model estimates. Despite IPT-DP requiring monthly dosing compared to one administration of SST-DP, the monthly doses align with the ANC 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 ANC visits in Papua, which suggests interventions to increase ANC attendance may be needed that 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 MiP will be based on multiple factors in addition to effectiveness and cost-effectiveness, including equity, ethics, acceptability and feasibility and a range of other factors affecting the political economy. Studies conducted in the same area as the trial found that the existing strategy of SST-DP was acceptable to health providers but being implemented inconsistently.[11,13] Investigation of the acceptability of IST-DP or IPT-DP as alternatives to the existing strategy found that there was more acceptance of IST-DP amongst 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 IPT-DP to protect themselves and their babies.[12] Concerns about the presumptive use of DP during pregnancy were however revealed during the trial: a higher proportion of participants withdrew consent in the IPT arm (14% compared to 0% and 2% SST arm, respectively).[10] This tended to follow the women having minor adverse events such as nausea, vomiting or headache after taking DP. The withdrawals occured in certain clusters often led by one influential woman. Although the occurrence of adverse events was similar across trial arms, the higher withdrawal rate in the IPT-DP arm reflects women's concerns about side effects and taking medications when they are pregnant while they do not have any symptoms of malaria. Similarly, although adherence to the full dose of DP was high (90%) in the trial setting, it is likely that adherence will be lower under routine conditions.[32] Interventions to encourage uptake and correct implementation of any new policy will be important, and the costs of these interventions should be factored into future cost-effectiveness analyses.

IPT-DP is likely to offer a cost-effective alternative to the current strategy of SST-DP for the prevention of the adverse effects of MiP 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. JW and JH designed the study. CL, A, FHB and IB acquired the costs data. RA and CK provided the trial data. LP and CK analysed the data. LP, JH, JW, RA and FtK

interpreted the data. LP wrote the first draft of the manuscript. All authors critically revised subsequent drafts of the paper. FtK, RA, JP, DS, JH and JW obtained funding. JW and JH supervised the study.

Declaration of interests

We declare no competing interests.

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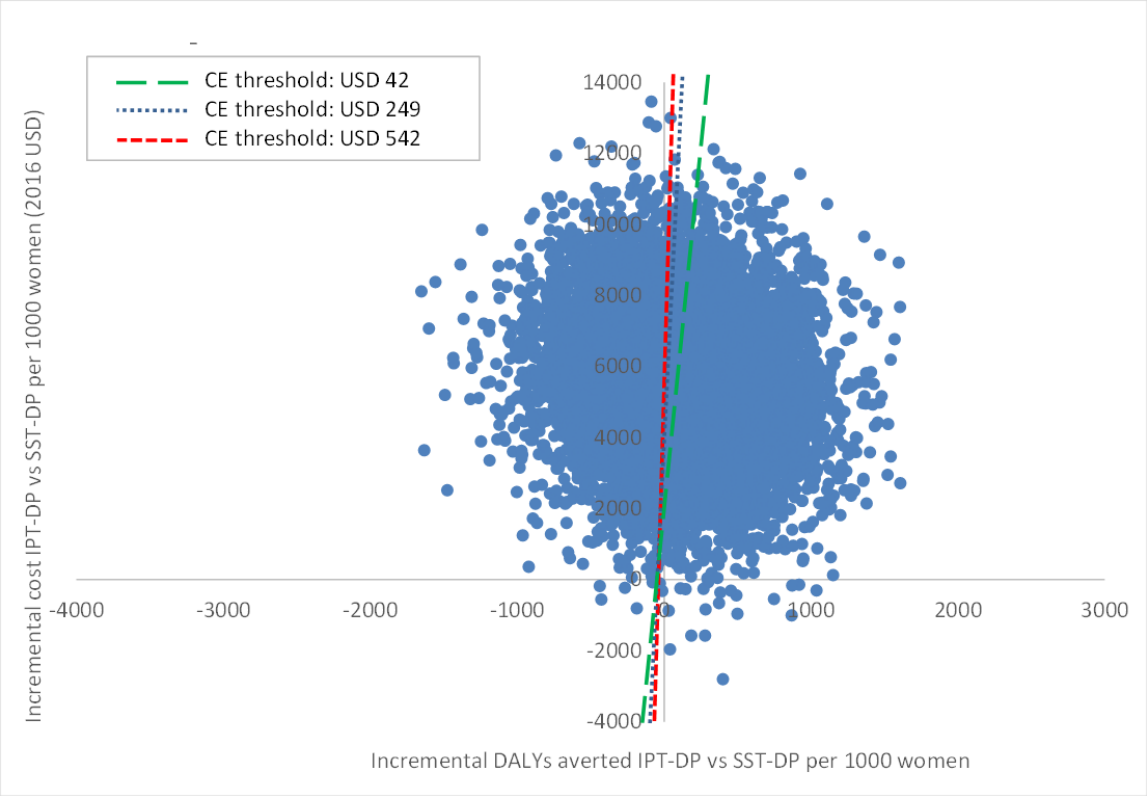
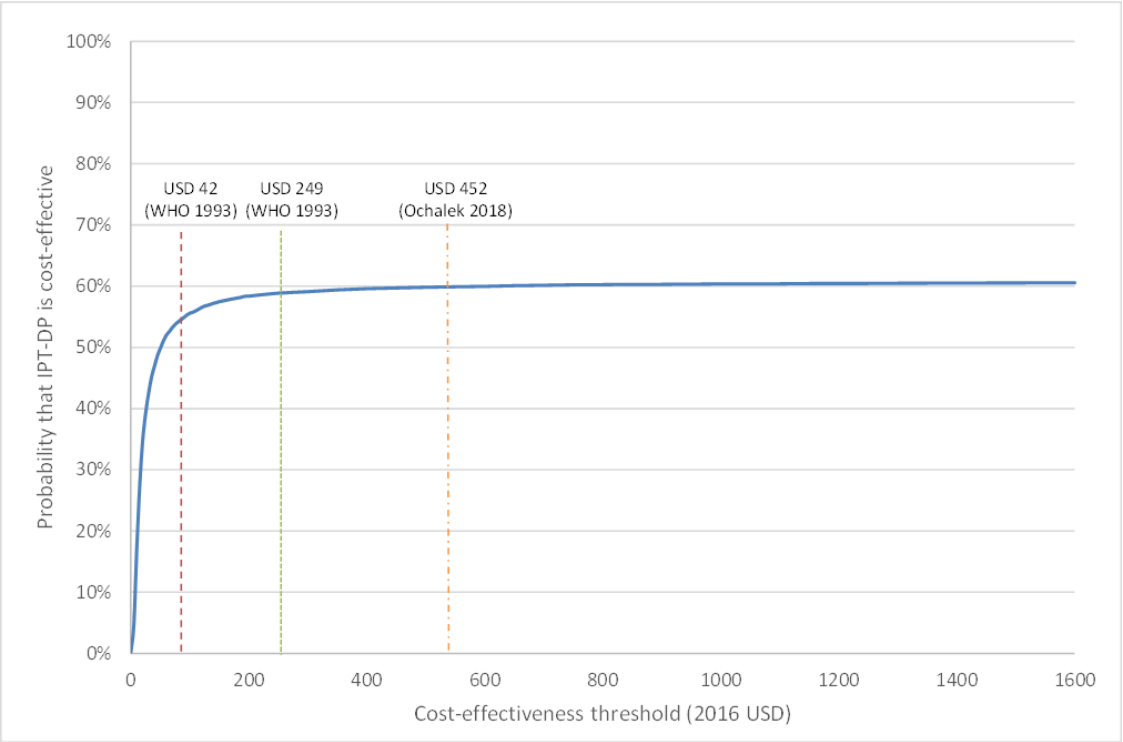
Figures

Figure 1: Cost-effectiveness plane of IPT-DP versus SST-DP in Papua Indonesia.



Graphs display 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 IPT-DP and SST-DP and the vertical axis represents the difference in cost. Points that lie in the top right (northeast) quadrant of the cost-effectiveness plane indicate the new intervention is more effective but also more costly than the existing strategy. The dotted lines represent different cost-effectiveness (CE) thresholds; the area to the right of the dotted lines is the region of cost-effectiveness.

Figure 2: Cost-effectiveness acceptability curve of IPT-DP versus SST-DP in Papua Indonesia.



The curve shows the probability of IPT-DP being cost-effective at any given cost-effectiveness threshold (CET) value. The vertical dashed lines indicate three alternative CET thresholds.

Table 1: Input variables for the base case and probabilistic cost-effectiveness of alternative MiP interventions in Papua, Indonesia

Parameter	Base case	Low	High	Distribution for PSA	Source
Cost estimates					
Health worker time cost					
Average number of administrations of SST-DP per pregnancy	1	..	..	Point estimate	Ahmed et al (2019)[10]
% administrations of SST-DP with +ve RDT	5·0% (21/356)	..	..	Point estimate	Ahmed et al (2019)[10]
Time taken to provide one administration of SST-DP (RDT-ve) (minutes) [i]	23	17·3	28·8	Gamma	Observations
Time taken to provide one administration of SST-DP (RDT+ve) (minutes) [ii]	28	21	35	Gamma	Observations
Average number of administrations of IPT-DP per pregnancy	3·87	..	..	Point estimate	Ahmed et al (2019)[10]
Time taken to provide one dose of IPT-DP (mins)[iii]	5	3·75	6·25	Gamma	Observations
Midwife's monthly cost of labour (USD 2016)	387·71	332·26	413.76	Gamma	Health facility costings
Drug costs					
Average DP cost per administration (USD 2016)[iv]	2·48	1·86	3·10	Gamma	Ahmed et al (2019)[10]
Average RDT cost per administration (USD 2016)[v]	0·86	0·65	1·08	Gamma	Ahmed et al (2019)[10]
Other costs					
Reminder SMS/call for DP dose 2 & 3 (USD 2016)	0·05	0·04	0·07	Gamma	Ahmed et al (2019)[10]
Costs from consequences					
Cost per OP visit (excluding medical supplies) (USD 2016)[vi]	9·23	7·38	12·30	Gamma	Health facility costings
Cost per IP day (excluding medical supplies) (USD 2016)[vi]	69·34	55·47	92·46	Gamma	Health facility costings
Cost per paediatric IP day (excluding medical supplies) (USD 2016)[vi]	69·34	55·47	92·46	Gamma	Health facility costings
DALY calculations					
Discount rate	0·03	0	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 – LBW (years)	69·72	68·5	70·95	Gamma	Salomon et al (2012)[33]
Disability weight – LBW	0·106	..	..	Point estimate	GBD Study (2004)[17]

Table 1: Input variables for the base case and probabilistic cost-effectiveness of alternative MiP interventions in Papua, Indonesia

Parameter	Base case	Low	High	Distribution for PSA	Source
Maternal outcomes					
Average age (years)	26	..	..	Point estimate	Ahmed et al (2019)[10]
Life expectancy women aged 25-29 years, Indonesia	47·8	45·9	49·8	Gamma	GBD Study (2010)[18]
Length of disability – malaria during pregnancy (5 days)[vii]	0·014	0·008	0·016	Gamma	Webster et al (2018)[13]
Length of disability – anaemia during pregnancy (21 days)	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 – anaemia: moderate	0·052	0·034	0·076	Gamma	GBD Study (2017)[19]
Mortality estimates					
CFR malaria during pregnancy (%)	0·01	..	..	Beta	Brabin et al (2001)[35]
CFR moderate/severe anaemia during pregnancy (%)	0·0033	0·0026	0·0045	Beta	Sicuri et al (2010)[36]
Measures of effect (trial outcomes)					
Neonatal outcomes					
Risk of fetal loss/infant death 6-8w, per 1000 women					
SST-DP arm [viii]	35·1	16·4	53·9	Beta	Ahmed et al (2019)[10]
IPT-DP arm [ix]	33·0	12·9	53·1		
Risk of LBW, per 1000 women					
SST-DP arm	129·8	94·0	165·6	Beta	Ahmed et al (2019)[10]
IPT-DP arm	115·2	77·1	153·4		
Maternal outcomes					
Risk of moderate/severe anaemia (<9g/dl) at last ANC visit, per 1000 women					
SST-DP arm	152·0	114·0	190·1	Beta	Ahmed et al (2019)[10]
IPT-DP arm	96·3	61·1	131·5		
Incidence of clinical malaria during pregnancy, per 1000 women					
SST-DP arm	36·5	17·0	56·0	Beta	Ahmed et al (2019)[10]
IPT-DP arm	6·3	0	14·9		

ANC = antenatal care; CFR = case fatality rate; DALY = disability-adjusted life year; DP = dihydroartemisinin-piperaquine; IP = inpatient; IPT = intermittent preventive treatment; LBW = low birth weight; OP = outpatient; RDT = rapid diagnostic test; SST = single screening and treatment. [i]Based on observations of the trial team: 3 minutes per woman for group information session, plus 5 minutes for RDT preparation and 15 minutes waiting for the result; [ii]Based on observations of the trial team: 3 minutes per woman for group information session, plus 5 minutes for RDT preparation, 15 minutes waiting for the result and a further 5 minutes counselling the patient about the treatment need for a positive RDT; [iii]Based on observations of the trial team: 3 minutes per woman for group information session plus 2 minutes for directly observed

Table 1: Input variables for the base case and probabilistic cost-effectiveness of alternative MiP interventions in Papua, Indonesia

Parameter	Base case	Low	High	Distribution for PSA	Source

therapy of first dose of DP; [iv]Average dosing regimen of 3x 40/320mg tablets x 3 days based on patient weight range 36-75kg; purchasing cost, including shipping, transport, wastage (+25%); same dosing regimen for IPT-DP, and a course of treatment for women found to be positive in the SST-DP arm; [v]Purchasing cost, including shipping, transport, wastage (+25%); [vi]Weighted mean based on the number of consultations per facility; range represents variation in unit cost assuming ±25% consultations; [vii]Median number of days loss of income reported by pregnant women during exit interviews used as a proxy; [viii]In the SST-DP arm, of the 13 fetal loss or infant deaths 6-8w, 3 were stillbirths (occurring after 28 weeks); 2 were miscarriages (occurring before 28 weeks); and 8 were infant deaths; [ix]In the IPT-DP arm, of the 10/303 fetal loss or infant deaths 6-8w , 4 were stillbirths; 1 was a miscarriage; and 5 were infant deaths.

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

Type	Cost parameter	Cost in 2016 USD (95% CI)
Intervention cost		
	Total cost per admin of SST-DP if found positive	4·69 (4·00, 5·46)
	Total cost per admin of SST-DP if found negative	1·92 (1·59, 2·27)
	Total cost per admin of IPT-DP	2·76 (2·20, 3·41)
Health provider cost of consequences		
	Total average cost per LBW	48·54 (26·09, 76·32)
	Total average cost per fetal death/infant death 6-8 weeks	0
	Total average cost per case of moderate/severe anaemia	15·60 (10·76, 22·17)
	Total average cost per case of clinical malaria during pregnancy	46·09 (33·50, 62·21)
Cost per 1000 pregnant women		
	Health provider cost of SST-DP, excluding consequences	2,059·76 (1,737·61, 2,423·50)
	Health provider cost of IPT-DP, excluding consequences	10,694·29 (8,503·71, 13,207·42)
	Health provider cost of SST-DP, including consequences	12,415·34 (8,919·93, 16,950·09)
	Health provider cost of IPT-DP, including consequences	18,079·62 (14,175·65, 22,731·77)

DP = dihydroartemisinin-piperaquine; IPT = intermittent preventive treatment; RDT = rapid diagnostic test; SST = single screening and treatment.

Table 3: Cost-effectiveness analysis, comparing IPT-DP to the existing policy of SST-DP in Papua, Indonesia`

	SST-DP	IPT-DP
Base case		
Δ DALYs - LBW	··	45·1
Δ DALYs - fetal loss or infant death 6-8w	··	62·3
Δ DALYs - maternal anaemia	··	0·31
Δ DALYs – clinical malaria in pregnancy	··	0·08
Total DALY	1,429·5	1,321·7
Total cost* (2016 USD)	12,415	18,080
Δ Costs* (2016 USD)	··	5,664
Δ DALYs	··	107·7
ICER* (USD/DALY)	··	53
Probabilistic sensitivity analysis		
Δ DALYs - LBW	··	45·6 (-117·6, 205·5)
Δ DALYs - fetal loss or infant death 6-8w	··	61·4 (-748·4, 844·2)
Δ DALYs - maternal anaemia	··	0·31 (0·02, 0·73)
Δ DALYs – clinical malaria in pregnancy	··	0·08 (0·03, 0·15)
Total DALY	1,430·2 (944·2, 2,029·7)	1,322·9 (812·7, 1,987·2)
Total cost* (2016 USD)	12,422 (8,920, 16,950)	18,079 (14,176, 22,732)
Δ Costs* (2016 USD)	··	5,657 (1,827, 9,448)
Δ DALYs	··	107·4 (-719·7, 904·1)
Average ICER* (USD/DALY)	··	53

DALY = disability-adjusted life years; ICER = incremental cost-effectiveness ratio; LBW = low birth weight.*includes provider costs from health consequences