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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

Silke Fernandes, Elisa Sicuri, Kassoum Kayentao, Anne Maria van Eijk, Jenny Hill, Jayne Webster, Vincent Were, James Akazili, Mwayi Madanitsa, Feiko O ter Kuile, Kara Hanson

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See Comment page e116

London School of Hygiene & Tropical Medicine, Keppel Street, London, UK (S Fernandes MSc, J Webster PhD, Prof K Hanson ScD); **ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic-Universitat de Barcelona, Barcelona, Spain** (E Sicuri PhD); **Liverpool School of Tropical Medicine, Liverpool, UK** (K Kayentao MD, A M van Eijk PhD, Jenny Hill PhD, Prof F O ter Kuile PhD); **Malaria Research and Training Centre, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy and Dentistry, University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali** (K Kayentao); **KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya** (V Were MSc, F O ter Kuile); **Navrongo Health Research Centre, Navrongo, Ghana** (J Akazili PhD); **and College of Medicine, University of Malawi, Blantyre, Malawi** (M Madanitsa MD)

Correspondence to: Silke Fernandes, Faculty of Population Health and Policy, Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London WC1H 9SH, UK **silke.fernandes@lshtm.ac.uk**

Summary

Background In 2012, WHO changed its recommendation for intermittent preventive treatment of malaria during pregnancy (IPTp) from two doses to monthly doses of sulfadoxine-pyrimethamine during the second and third trimesters, but noted the importance of a cost-effectiveness analysis to lend support to the decision of policy makers. We therefore estimated the incremental cost-effectiveness of IPTp with three or more (IPTp-SP3+) versus two doses of sulfadoxine-pyrimethamine (IPTp-SP2).

Methods For this analysis, we used data from a 2013 meta-analysis of seven studies in sub-Saharan Africa. We developed a decision tree model with a lifetime horizon. We analysed the base case from a societal perspective. We did deterministic and probabilistic sensitivity analyses with appropriate parameter ranges and distributions for settings with low, moderate, and high background risk of low birthweight, and did a separate analysis for HIV-negative women. Parameters in the model were obtained for all countries included in the original meta-analysis. We did simulations in hypothetical cohorts of 1000 pregnant women receiving either IPTp-SP3+ or IPTp-SP2. We calculated disability-adjusted life-years (DALYs) for low birthweight, severe to moderate anaemia, and clinical malaria. We calculated cost estimates from data obtained in observational studies, exit surveys, and from public procurement databases. We give financial and economic costs in constant 2012 US$. The main outcome measure was the incremental cost per DALY averted.

Findings The delivery of IPTp-SP3+ to 1000 pregnant women averted 113·4 DALYs at an incremental cost of $825·67 producing an incremental cost-effectiveness ratio (ICER) of $7·28 per DALY averted. The results remained robust in the deterministic sensitivity analysis. In the probabilistic sensitivity analyses, the ICER was $7·7 per DALY averted for moderate risk of low birthweight, $19·4 per DALY averted for low risk, and $4·0 per DALY averted for high risk. The ICER for HIV-negative women was $6·2 per DALY averted.

Interpretation Our findings lend strong support to the WHO guidelines that recommend a monthly dose of IPTp-SP from the second trimester onwards.

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Introduction

Malaria during pregnancy can lead to poor health outcomes in both mother and child.[1] In 2007, 32 million pregnant women were at risk of malaria infection in sub-Saharan Africa.[2] The prevention and consequences of diseases and their related treatments during pregnancy are generally complex from an epidemiological, public health, and economic perspective because both the mother and her unborn baby are often affected. *Plasmodium falciparum* infection in pregnant women in sub-Saharan Africa is most importantly associated with maternal anaemia, perinatal mortality, and low birthweight caused by intrauterine growth restriction and prematurity, especially in women pregnant for the first or second time.[1] At present, the control of malaria during pregnancy consists of intermittent preventive treatment during pregnancy (IPTp) with sulfadoxine-pyrimethamine, the provision of insecticide-treated bednets, and effective case management of clinical malaria.[3] Findings from several economic evaluations have shown that two doses of IPTp with sulfadoxine-pyrimethamine (IPTp-SP) versus case management only or placebo is highly cost effective.[4–6] However, the emergence and spread of strains of *P falciparum* resistant to sulfadoxine-pyrimethamine has led to rising concerns about the ongoing effectiveness of IPTp-SP.[7]

After an expert meeting in June, 2012, WHO recommended that all pregnant women, unless receiving co-trimoxazole prophylaxis, should receive IPT-SP monthly from their second trimester onwards.[8,9] The clinical evidence behind this decision was provided in a meta-analysis by Kayentao and colleagues[10] that

compared three or more doses versus two doses of IPTp-SP. Their findings suggested that receiving three or more doses (weighted mean of actual doses received was 2·79) of IPTp-SP were associated with higher birthweight and a lower risk of low birthweight (relative risk=0·80, 95% CI 0·69–0·94) than were two doses of IPTp-SP (weighted mean of actual doses received was 1·65). The results of the meta-analysis were consistent and did not show evidence for heterogeneity, despite studies being done in areas of varying levels of sulfadoxine-pyrimethamine resistance.[10]

In addition to the epidemiological evidence, it is crucial for policy makers to understand the cost-effectiveness and cost drivers of any new regimen.

We aimed to estimate the incremental cost-effectiveness of IPTp-SP comparing three or more (SP3+) doses with two (SP2) doses. Our cost-effectiveness model incorporated primary and secondary endpoints (low birthweight, anaemia, and maternal parasitaemia) in Kayentao and colleagues' meta-analysis.[10]

Methods

Study design

Details of the study setting, population, and intervention for each trial included in this analysis are reported elsewhere.[10] Kayentao and colleagues[10] previously synthesised data from seven trials done in six countries (Burkina Faso, Kenya, Malawi [two trials], Mali, Tanzania, and Zambia). Four studies included all pregnant women irrespective of the number of pregnancies they had had, whereas recruitment for the remaining three was restricted to women who were pregnant for the first or second time only. Four studies included women with or without HIV, the study in Zambia included only those with HIV, and the two west African trials did not screen for HIV status. The malaria transmission settings were either holoendemic (five trials) or hyperendemic (two trials). The trials were done between 1994 and 2008, with six taking place between 2002 and 2008. The average age of women enrolled in the trials was 22·8 years, excluding the Tanzanian trial for which data were unavailable.[10]

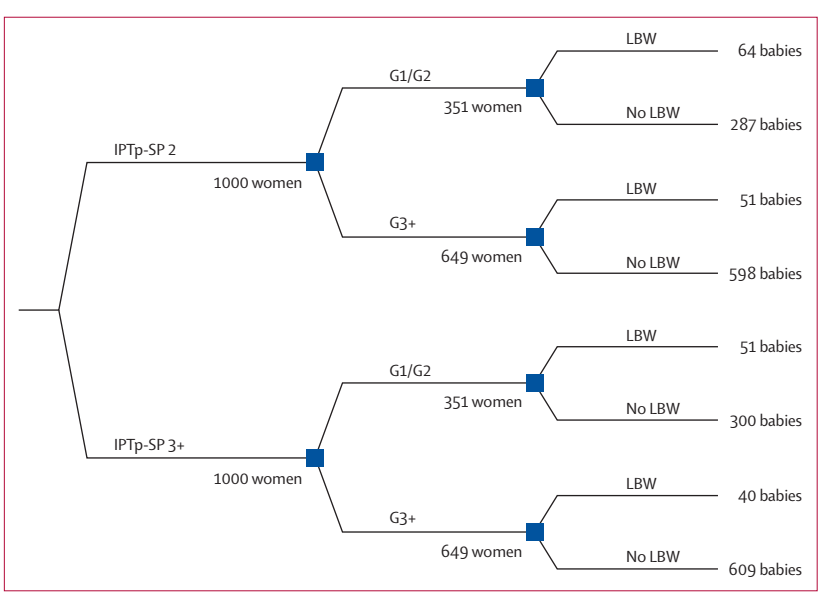

Figure 1: **The decision tree**

The decision tree model shows the example for LBW. All numbers are the results published by Kayentao and colleagues.[10] The example shown here is representative of a setting with moderate LBW risk and included all pregnant women independent of HIV status (positive, negative, unknown). The same structure was used for severe anaemia and clinical malaria. LBW=low birthweight. IPTp-SP=intermittent preventive treatment with sulfadoxine-pyrimethamine. SP2=two doses of IPTp-SP during pregnancy. SP3+=three or more doses of IPTp-SP during pregnancy. G1/G2=women who have had one or two pregnancies. G3+=women who have had three or more pregnancies.

Effects

4345 (69%) of 6281 women in the meta-analysis were pregnant for either the first or second time, a proportion higher than that occurring in the general population in the six countries.[11–16] We therefore used the baseline risks and measures of effects stratified by gravidity listed by Kayentao and colleagues.[10] We considered for inclusion in the model only statistically significant outcomes (p value ≤0·05) in either of the gravidae subgroup results. Data for clinical malaria were not available so, as a surrogate measure, we used maternal peripheral parasitaemia multiplied by the proportion of pregnant women with parasitaemia who had documented fever in high to medium transmission areas (7%; 107 of 1563).[17] There was no difference in the risk of serious adverse events between the SP3+ and SP2 group. Additionally, evidence from large-scale passive surveillance in Blantyre District, Malawi, suggests that adverse reactions to sulfadoxine-pyrimethamine (eg, Steven-Johnson syndrome) were rare (1·7 cases per 100 000 exposures in adults).[18]

The final cost-effectiveness model included low birthweight, moderate to severe maternal anaemia (haemoglobin <80 g/L, 70 g/L, or 60 g/L), and clinical malaria as outcomes. The relative risks were estimated with random effects log binomial regression models as described by Kayentao and colleagues.[10] We used the median baseline risk in the SP2 group and the relative risk for each outcome of interest to calculate the intervention-group risk. Outcomes were not stratified by HIV status, but the cost-effectiveness of IPTp-SP3+ for HIV-negative women was explored in a sensitivity analysis.

Costs

We included the variable cost to the health provider and household in the model, but excluded the fixed costs such as training, dissemination or policy change of extending an existing intervention to a higher frequency of dosing, because they were regarded as negligible. We excluded cost savings due to averting clinical outcomes from this analysis because data were not available. We calculated economic costs (including indirect cost of time spent travelling to and waiting at the health

facility) and financial costs and expressed them in constant 2012 US$ by using the local consumer price index[19] and average 2012 exchange rates.[20] All cost data collection was approved by the Institutional Review Board of the London School of Hygiene & Tropical Medicine and by the institution or country in which the data were collected.

The health provider costs comprise the cost of sulfadoxine-pyrimethamine and the value of nurses' time to administer IPTp-SP. For details about how costs were estimated, see the appendix. Household costs included the direct (transport) and indirect (value of time spent travelling to and waiting at the health facility) costs of women attending antenatal care at least three times during the second and third trimester versus twice, and the arbitrary assumption was made that 25% of the costs (direct and indirect) of these visits were attributed to IPTp-SP (varied to 0% and 100% in deterministic sensitivity analysis; appendix).

Statistical analysis and modelling

We adopted a societal perspective (which takes into account the cost of the intervention to the health provider but also the additional cost to the recipient of the intervention) because attendance at antenatal care is inadequate in many settings and therefore the cost to households of increasing the number of visits could be substantial. We developed separate but structurally identical decision tree models (figure 1) with a lifetime horizon for each outcome because data for concurrence of outcomes were unavailable. To model the cost-effectiveness in a population with a gravidity distribution representative of the six countries,

See Online for appendix

	Base	New value (% change compared with base case)	Incremental cost	Incremental DALYs	Incremental cost-effectiveness ratio	% change
Base case	NA	NA	825·7	113·4	7·3	NA
Simultaneously change relative risk: all outcomes (all gravidae), lower value	NA	All low	825·7	225·6	3·7	–49·7%
Simultaneously change relative risk: all outcomes (all gravidae), higher value	NA	All high	825·7	15·4	53·7	637·1%
Simultaneously change relative risk: low birthweight (all gravidae), lower value	NA	All low	825·7	223·3	3·7	–49·2%
Simultaneously change relative risk: low birthweight (all gravidae), higher value	NA	All high	825·7	16·3	50·7	595·7%
Low and high background risk of low birthweight (G1/G2 and G3+), lower value	NA	All low	825·7	45·8	18·0	147·5%
Low and high background risk of low birthweight (G1/G2 and G3+), higher value	NA	All high	825·7	218·3	3·8	–48·0%
Increase antenatal care visits and IPTp-SP doses in SP3+ group	2·79	4·0	1585·1	113·7	14·0	92·0%
Relative risk low birthweight G3+ 95% CI, lower value	0·79	0·49 (–38·0%)	825·7	186·6	4·4	–39·2%
Relative risk low birthweight G3+ 95% CI, higher value	0·79	1·00 (26·6%)	825·7	62·2	13·3	82·3%
Nurses monthly cost of labour: min and max meta-analysis countries , lower value	542·76	101·93 (–81·2%)	427·9	113·4	3·8	–48·2%
Nurses monthly cost of labour: min and max meta-analysis countries, higher value	542·76	1243·30 (129·1%)	1457·8	113·4	12·9	76·6%
Relative risk low birthweight G1/G2 95% CI, lower value	0·80	0·68 (–15·0%)	825·7	150·1	5·5	–24·5%
Relative risk low birthweight G1/G2 95% CI, higher value	0·80	0·95 (18·8%)	825·7	67·5	12·2	68·0%
Discount rate, lower value	0·03	0·00 (–100·0%)	825·7	239·0	3·5	–52·5%
Discount rate , higher value	0·03	0·05 (66·7%)	825·7	78·0	10·6	45·3%
Disability weight low birthweight , lower value	0·11	0·05 (–50·0%)	825·7	79·4	10·4	42·8%
Disability weight low birthweight, higher value	0·11	0·16 (50·0%)	825·7	147·4	5·6	–23·1%
Sulfadoxine-pyrimethamine drug price, lower value	0·20	0·10 (–50·0%)	709·2	113·4	6·3	–14·1%
Sulfadoxine-pyrimethamine drug price, higher value	0·20	0·41 (100·0%)	1058·6	113·4	9·3	28·2%
Low birthweight attributable mortality risk, lower value	6·9%	3·5% (–50·0%)	825·7	91·2	9·1	24·4%
Low birthweight attributable mortality risk, higher value	6·9%	10·4% (50·0%)	825·7	157·8	5·2	–28·2%
Average health-care worker time per administration of sulfadoxine-pyrimethamine 95% CI, lower value	8·31	6·59 (–20·7%)	724·4	113·4	6·4	–12·3%
Average health-care worker time per administration of sulfadoxine-pyrimethamine 95% CI, higher value	8·31	10·03 (20·7%)	927·0	113·4	8·2	12·3%
Percentage of household costs attributed to intermittent preventive treatment, lower value	25%	0% (–100·0%)	722·7	113·4	6·4	–12·5%
Percentage of household costs attributed to intermittent preventive treatment, higher value	25%	100% (300·0%)	1134·6	113·4	10·0	37·4%
Changes to structural model assumptions						
Intervention delivered to primigravidae and secundigravidae only	NA	NA	825·7	178·4	4·6	–36·4%
HIV-negative only	NA	NA	825·7	139·0	5·9	–18·4%
Health provider perspective	NA	NA	722·7	113·4	6·4	–12·5%
Direct cost only	NA	NA	752·4	113·4	6·6	–8·9%

DALY=disability-adjusted life year. NA=not applicable.

Table 1: **Deterministic sensitivity analysis—parameter inputs and results**

each arm was stratified into women pregnant for the first or second time (G1/G2) and those pregnant for the third or more time (G3+). Subsequently we modelled the efficacy of the intervention in a population with the gravidity distribution (G1/G2 *vs* G3+) as found in the most recent Demographic and Health Survey from the six countries.[11–16]

We calculated disability-adjusted life-years (DALYs) averted in each arm for each outcome separately and in total. When available, we used disability weights from the 2010 Global Burden of Disease (GBD) study; otherwise we used 2004 GBD study estimates.[21,22] We calculated DALYs with a 3% discount rate,[23] as per conventional practice, with no age weighting (appendix). We calculated the incremental cost-effectiveness ratio for a hypothetical cohort of 1000 women by dividing the incremental cost of the intervention by the incremental DALYs averted.

In the deterministic sensitivity analysis, we varied key variables and model assumptions to assess their relative contributions to uncertainty (table 1, figure 2). The 95% CI for all relative risk estimates in the G3+ subgroup included the value one.[10] However, because no epidemiological evidence exists to suggest that more doses of IPTp-SP could result in higher numbers of low birthweight, severe anaemia, or maternal malaria cases, we capped the upper estimates of relative risks at 1·00 in the deterministic sensitivity analysis.

To gauge the robustness and uncertainty of all estimates and assumptions simultaneously, we did a probabilistic sensitivity analysis (ie, Monte Carlo simulation) using 10 000 iterations, producing a point estimate and 95% CIs for the difference in effects and costs based on percentiles and an average incremental cost-effectiveness ratio. In the probabilistic sensitivity analyses, we used all value ranges as reported in the meta-analysis so it would explicitly reflect the results published by Kayentao and colleagues, representative of a setting with moderate risk of low birthweight. We used commonly used cost-effectiveness guidelines to assign an appropriate distribution to each parameter.[24] Finally, we calculated the probability of IPTp-SP3+ being cost effective for three frequently applied policymaker willingness-to-pay thresholds and plotted our results in a cost-effectiveness acceptability curve.[25] We refer to these thresholds as low (US$39·72), middle (US$238·33), and high (US$756·09; appendix).

We repeated the probabilistic sensitivity analyses described above for settings with a low or high low-birthweight risk by imputing the minimum (for low risk) or maximum (for high risk) value of the baseline risk range of low birthweight in both subgroups as presented by Kayentao and colleagues in place of the assumed control group risk (baseline risk in the SP2 group, representative of a setting with moderate risk).

IPTp-SP is contraindicated for women receiving cotrimoxazole prophylaxis.[26] We therefore also did a probabilistic sensitivity analysis for HIV-negative women. We changed baseline risks and relative risks for all outcomes and subgroups to those reported by Kayentao and colleagues for HIV-negative women.

We used STATA (version 12.0) for analysis of observational, exit survey, and Demographic and Health Survey data. We used Microsoft Excel 2013 for the decision tree model in the probabilistic sensitivity analysis using Visual Basic for Applications.

Role of the funding source

The funding institution had no role in the model design and development, data collection, analysis and interpretation, or preparation, review, or approval of the paper. SF and ES had full access to all data in the model and take full responsibility for integrity of the

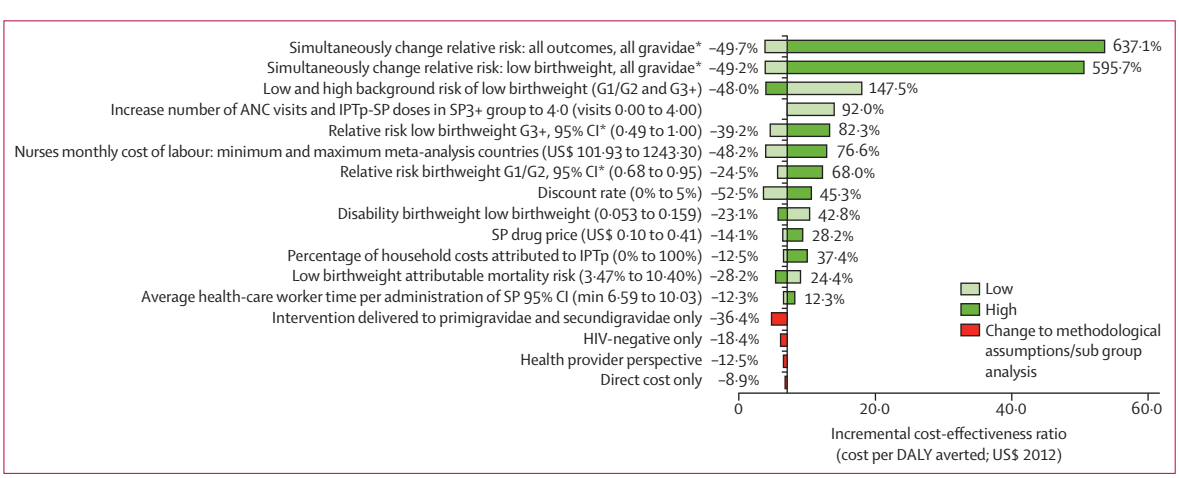

Figure 2: **Tornado diagram—deterministic sensitivity analysis**

The variable ranges imputed for each variable are shown in parentheses. The light green bars show the direction and magnitude of change in the incremental cost-effectiveness ratio, when the input variable is set to its minimum value; the dark green bars show the direction and magnitude of change when the input variable is set to its maximum. See appendix for more information. ANC=antenatal care. DALY=disability-adjusted life-years. G1/G2=Women who have had one or two pregnancies. G3+=women who have had three or more pregnancies. IPTp-SP=intermittent preventive treatment with sulfadoxine-pyrimethamine. SP=sulfadoxine-pyrimethamine. SP2=two doses of IPTp-SP during pregnancy. SP3+=three or more doses of IPTp-SP during pregnancy. *Relative risk capped at one, see methods and appendix..

	Base case (low,high)	Distribution for probabilistic sensitivity analysis	Source
Cost estimates			
Health-care worker time cost			
Health-care worker time per IPTp-SP administration (min; 95% CI)	8·31 (6·59–10·03)	Gamma	Observational studies (Ghana, Kenya, Malawi)*
Number of doses in SP2 group	1·65	Point estimate	Kayentao et al (2013)[10]
Number of doses in SP3+ group	2·79	Point estimate	Kayentao et al (2013)[10]
Nurses' monthly cost of labour (US$2012; 95% CI)	542·76 (373·94–711·58)	Gamma	Ministry of Health data†
Drug cost			
Average SP price per administration (US$2012; 95% CI)	0·20 (0·19–0·22)	Lognormal	International procurement databases‡
Household cost			
Antenatal care visit direct cost (US$2012; 95% CI)	0·47 (0·42–0·53)	Gamma	Exit surveys Mali (N=778, Kenya=613)
Antenatal care visit indirect cost (US$2012; 95% CI)	1·17 (1·13–1·21)	Gamma	Exit surveys Mali (N=778, Kenya=613)
DHS data analysis			
Percentage women in DHS with 0 antenatal care visits (95% CI)	8·40 (8·15–8·65)	Dirichlet	DHS meta-analysis countries§
Percentage of women in DHS with one antenatal care visit (95% CI)	3·90 (3·72–4·07)	Dirichlet	DHS meta-analysis countries§
Percentage of women in DHS with two ANC visits (95% CI)	12·78 (12·48–13·09)	Dirichlet	DHS meta-analysis countries§
Percentage of women in DHS with three or more antenatal care visits (95% CI)	74·92 (74·53–75·32)	Dirichlet	DHS meta-analysis countries§
Proportion G1/G2 women in meta-analysis countries (95% CI)	35·10 (34·05–36·14)	Beta	DHS meta-analysis countries§
DALY calculations			
Discount rate r (range)	0·03 (0·00–0·05)	Point estimate	Assumption
Average age (years)	22·83	Point estimate	Kayentao et al (2013)¶[10]
Life expectancy for women aged 20–24 years (95% CI)	47·24 (41·79–51·51)	Lognormal	Wang et al (2010)‖,[27]
Life expectancy at birth (95% CI)	57·96 (52·91–64·80)	Lognormal	Wang et al (2010)‖,[27]
Length disability: malaria during pregnancy (3·5 days; range 2–6)	0·010 (0·005–0·016)	Gamma	Assumption
Length disability: malaria-related anaemia (21 days; range 14–42)	0·06 (0·04–0·12)	Gamma	Price et al (2001)[28]
Length disability: low birthwieght (95% CI)	57·96 (52·91–64·80)	Lognormal	Wang et al (2010)[27]
Disability weight infectious disease: severe acute episode (95% CI)	0·21 (0·14–0·30)	Lognormal	Salomon (2010)[21]
Disability weight maternal anaemia: moderate (95% CI)	0·06 (0·04–0·09)	Lognormal	Salomon et al (2010)[21]
Disability weight low birthweight	0·11	Point estimate	World Health Organization[22]
Mortality estimates			
Low birthweight attributable neonatal mortality risk (95% CI)	6·93% (4·36–9·50)	Beta	Marchant et al (2012)[29]
Case fatality rate: malaria during pregnancy (95% CI)	0·33% (0·26–0·45)	Beta	Sicuri et al (2010)[5]
Case fatality rate: moderate to severe anaemia in pregnancy	1·0%	Beta	Brabin el al (2001)[30]
Measures of effect: primary and secondary endpoints used in model			
Low birthweight			
G1/G2: ACR per 1000 pregnant women (range)	181·00 (51·00–231·00)	Point estimate**	Kayentao et al (2013)[10]
G1/G2: relative risk (95% CI)	0·80 (0·68–0·95)	Lognormal	Kayentao et al (2013)[10]
G3+: ACR per 1000 pregnant women (range)	78·00 (42·00–212·00)	Point estimate**	Kayentao et al (2013)[10]
G3+: Relative risk (95% CI)	0·79 (0·49–1·27††)	Lognormal	Kayentao et al (2013)[10]
Moderate to severe maternal anaemia (<80 g/L,<70 g/L, or <60 g/L)			
G1/G2: ACR per 1000 pregnant women (range)	36·00 (0·00–65·00)	Point estimate**	Kayentao et al (2013)[10]
G1/G2: relative risk (95% CI)	0·60 (0·36–0·99)	Lognormal	Kayentao et al (2013)[10]
G3+: ACR per 1000 pregnant women (range)	14·00 (0·00–63·00)	Point estimate**	Kayentao et al (2013)[10]
G3+: relative risk (95% CI)	1·18 (0·56–2·48††)	Lognormal	Kayentao et al (2013)[10]
Maternal parasitaemia			
G1/G2: ACR per 1000 pregnant women (range)	130·00 (20·00–359·00)	Point estimate**	Kayentao et al (2013)[10]
G1/G2: relative risk (95% CI)	0·54 (0·37–0·80)	Lognormal	Kayentao et al (2013)[10]
G3+: ACR per 1000 pregnant women (range)	31·00 (00·00–263·00)	Point estimate**	Kayentao et al (2013)[10]
G3+: relative risk (95% CI)	0·97 (0·75–1·24††)	Lognormal	Kayentao et al (2013)[10]
Proportion of parasitaemic pregnant women with documented fever (%; 95% CI)	0·07 (0·03–0·38)	Beta	Van Eijk and colleagues‡‡,[17]

(Table 2 continues on next page)

	Base case	Distribution for probabilistic sensitivity analysis	Source
(Continued from previous page)			
Secondary endpoints (not used in model)§§			
Placental malaria ACR per 1000 women (all gravidae; range)	63·00 (00·00–256·00)	Point estimate**	Kayentao et al (2013)[10]
Placental malaria relative risk (all gravidae; 95% CI)	0·51 (0·38–0·68)	Lognormal	Kayentao et al (2013)[10]
Secondary endpoints (not statistically significant, only relative risk shown; for information only, not used in model)¶¶			
Preterm delivery relative risk (G1/G2; 95% CI)	0·95 (0·81–1·11)	··	Kayentao et al (2013)[10]
Preterm delivery relative risk (G3+; 95% CI)	0·85 (0·56–1·27)	··	Kayentao et al (2013)[10]
Miscarriage relative risk (G1/G2; 95% CI)	1·75 (0·97–3·13)	··	Kayentao et al (2013)[10]
Miscarriage relative risk (G3+; 95% CI)	0·90 (0·37–2·19)	··	Kayentao et al (2013)[10]
Stillbirth relative risk (G1/G2; 95% CI)	1·14 (0·79–1·65)	··	Kayentao et al (2013)[10]
Stillbirth relative risk (G3+; 95% CI)	1·24 (0·61–2·50)	··	Kayentao et al (2013)[10]
Neonatal death relative risk (G1/G2; 95% CI)	0·74 (0·45–1·24)	··	Kayentao et al (2013)[10]
Neonatal death relative risk (G3+; 95% CI)	1·31 (0·59–2·93)	··	Kayentao et al (2013)[10]

Parameters are shown for all countries included in the meta-analysis by Kayentao and colleagues' meta-analysis:[10] Burkina Faso, Malawi, Mali, Kenya, Tanzania, Zambia. ACR=assumed control group risk. DALY=disability-adjusted life-years. DHS=Demographic and Health Survey. G1/G2=women in first or second pregnancy. G3+=women in third or more pregnancy. IPTp-SP=intermittent preventive treatment with sulfadoxine-pyrimethamine. SP2=two doses of IPTp-SP during pregnancy. SP3+=three or more doses of IPTp-SP during pregnancy. *Data for time needed to give one dose of IPTp-SP were obtained in observational studies in Ghana (n=18), Kenya (n=40) and Malawi (n=18); data from Ghana were the only data representative of a west African setting. †Salary scale and an average allowance package for nurses from Ministry of Health in Burkina Faso, Malawi, Mali, Kenya, Tanzania, and Zambia for 2012. ‡Cost per dose of IPTp-SP was calculated for three doses accounting for 5% wastage, 10% insurance and freight, and 10% transport. §The most recent Demographic and Health Survey datasets were: Burkina Faso (2010), Kenya (2008–09), Malawi (2010), Mali (2006), Tanzania (2009–10), Zambia (2007). ¶Average age was calculated from all trials included in the meta-analysis by Kayentao and colleagues,[10] except for the trial done in Tanzania because age data were not available to investigators. ||The life expectancy was analysed from the Global Burden of Disease 2010 database for the subgroups of interest (ie, women only, aged 20–24 years, meta-analysis countries and at birth, both sexes and meta-analysis countries, respectively). **The range shows the risk in low-risk and high-risk populations and will only be used in deterministic sensitivity analysis. ††We capped relative risk values in the deterministic sensitivity analysis at 1 because there is no evidence that suggests giving more doses of IPTp-SP could result in higher numbers of low birthweight, severe anaemia, or clinical malaria; in the probabilistic sensitivity analysis, distributions were assigned to the 95% CIs as reported by Kayentao and colleagues[10] irrespective of them including 1·0). ‡‡Passive case detection in the control of malaria in pregnancy in low transmission areas in Africa; a meta-analysis of observational studies of the association between fever and malaria infection; unpublished data that were presented at conference. §§No data available to be able to use placental malaria as a proxy for clinical malaria, it was therefore not used in the model. ¶¶Endpoints that were not statistically significant in any of the subgroups (G1/G2 or G3+) were excluded from the model and are listed here.

Table 2: **Input variables for the base case and probabilistic cost-effectiveness analysis**

data and the model as well as accuracy of all analyses. SF had final responsibility for the decision to submit for publication.

Results

We estimated a total of 555·7 DALYs per 1000 women in the SP2 group and 442·3 DALYs per 1000 women in the SP3+ group. The total number of DALYs averted per 1000 women amounted to 113·4, of which 112·4 (99·1%) can be attributed to low birthweight, 0·9 (0·8%) to severe anaemia, and 0·1 (0·1%) to clinical malaria in the mother.

Table 2 shows the average time to give one dose of IPTp-SP and the average monthly nurses' labour. We estimated the total health provider cost of giving one dose of IPTp-SP as US$0·63, of which $0·43 (68·3%) was the cost of nurses' time and $0·20 (31·7%) the cost of the drug.

Table 2 shows the direct cost of transport and indirect cost of time to the household, giving a total household cost of $1·64 per antenatal care visit of which $0·41 (25%) was attributed to IPTp-SP. The antenatal care attendance of women in the six countries was high, with 74·9% attending three or more times, 12·8% twice, 3·9% once, and 8·4% never (table 2).

The total economic cost of providing treatment to 1000 women was $1948·64 for IPTp-SP3+ and $1122·97 for IPTp-SP2, giving an incremental cost of $825·67 per 1000 women. $102·99 (12·5%) of the total incremental cost in the base case was the household cost of IPTp-SP, and the remaining $722·68 (87·5%) was the health provider cost. Total incremental financial cost was $752·38 per 1000 women.

The cost of delivering IPTp-SP3+ to 1000 pregnant women in the base case scenario (table 2) gives an incremental cost-effectiveness ratio of $7·28 per DALY averted. For the deterministic sensitivity analysis, figure 2 and table 1 show the results and percentage change for changes in parameter inputs, changes to methodological assumptions, or subgroup analysis in which the variation resulted in at least 5% change in the incremental cost-effectiveness ratio. The base case incremental cost-effectiveness ratio was substantially below the low willingness-to-pay threshold of $39·72 per DALY averted. Although some variations in the deterministic sensitivity analysis resulted in substantial percentage changes in the incremental cost-effectiveness ratio, only two relatively radical changes (in which relative risks for all outcomes and subgroups were varied to the upper limit of the 95% CI reported) increased the ratio beyond the low willingness-to-pay threshold of $39·72 and none of them resulted in a change beyond the middle willingness-to-pay threshold of $238·33.

The probabilistic sensitivity analyses for settings with a moderate risk of low birthweight (figure 3A) resulted in an incremental cost of $825·18 (95% CI 299·74–2541·85)

and 106·56 incremental DALYs averted (95% CI–17·23 to 201·71) per 1000 women. We estimated the average incremental cost-effectiveness ratio at $7·74 per DALY averted (median 5·96).

The probabilistic sensitivity analyses results for settings with low and high low-birthweight risk are shown in figures 3B and 3C. The average incremental cost-effectiveness ratio was $19·41 per DALY (median 13·87) averted for low-risk settings (incremental cost $819·00 [301·61–2482·48] and 42·20 incremental DALYs averted [–17·57 to 88·68]) and $3·99 per DALY averted (median 2·82) for high-risk settings (incremental cost $814·06 [299·01–2468·15] and 204·11 incremental DALYs averted [95% CI –107·29 to 425·63]). The simulations for setting with a low risk of low-birthweight were more densely concentrated around the median, with a higher proportion of points in the northwest quadrant of the cost-effectiveness plane. For settings with a high risk of low birthweight the estimates were more widely distributed around the median in both directions, but the overall proportion of simulations falling into the northeast quadrant was higher than in moderate-risk and low-risk settings.

Figure 3D shows the results of probabilistic sensitivity analyses for HIV-negative women. We calculated the incremental cost at $821·28 (299·50–2549·81) and the incremental DALYs averted at 132·53 (15·87 to 231·89). The incremental cost-effectiveness ratio was $6·20 per DALY averted (median 5·02). The simulations for HIV-negative women are more densely concentrated around the median in the northeast quadrant than in the probabilistic sensitivity analyses that included all women.

In figure 4, the probability of IPTp-SP3+ being cost-effective is shown in a cost-effectiveness acceptability curve for willingness-to-pay values up to $800 per DALY averted. The probability of IPTp-SP3+ falling below the highly attractive threshold of $39·72 and hence being highly cost-effective was 92·4% for moderate risk of low birthweight, 78·1% for low risk of low birthweight, and 90·4% for high risk of low birthweight, and 96·6% for HIV-negative women.

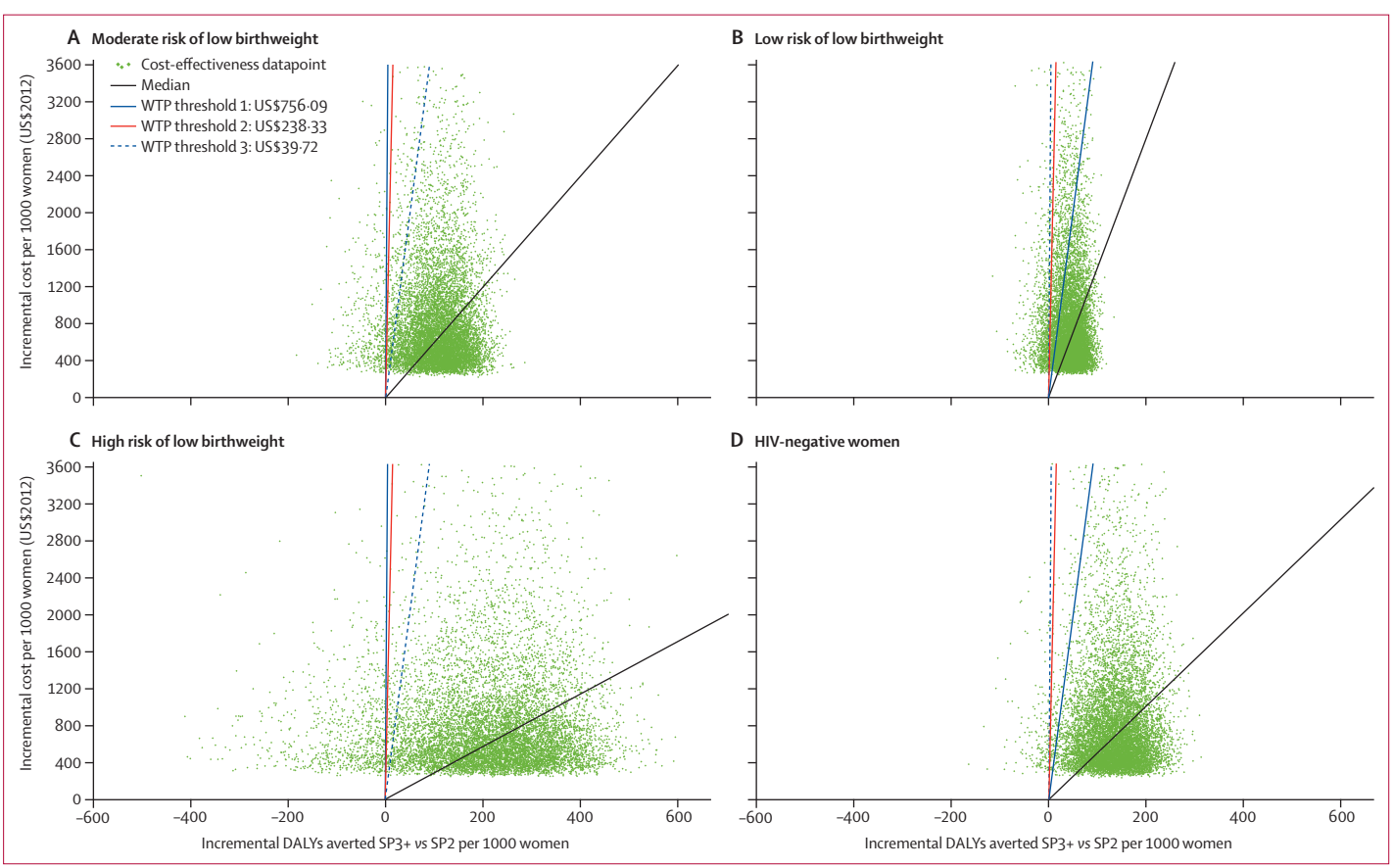

Figure 3: **Cost-effectiveness planes**

The graphs show the results of four different Monte Carlo Simulations with 10 000 iterations each using the value ranges and distributions specified in table 2. The assumed control group risk point estimates for low birthweight in both gravidae subgroups were varied in the three scenarios, representing cost-effectiveness in moderate risk (A), low risk (B), and high risk (C) of low birthweight settings. Panel D shows the results for the simulation using input parameters reported for HIV-negative women by Kayentao and colleagues.[10] For the moderate risk of low birthweight setting, we used the base case parameter values of the assumed control group risk reported by Kayentao and colleagues; for low-risk and high-risk groups we used the minimum and maximum value of the parameter range. All other values, ranges, and distributions were kept the same. WTP=willingness to pay. DALYs=disability-adjusted life-years. SP2=two doses of IPTp-SP. SP3+=three or more doses of IPTp-SP.

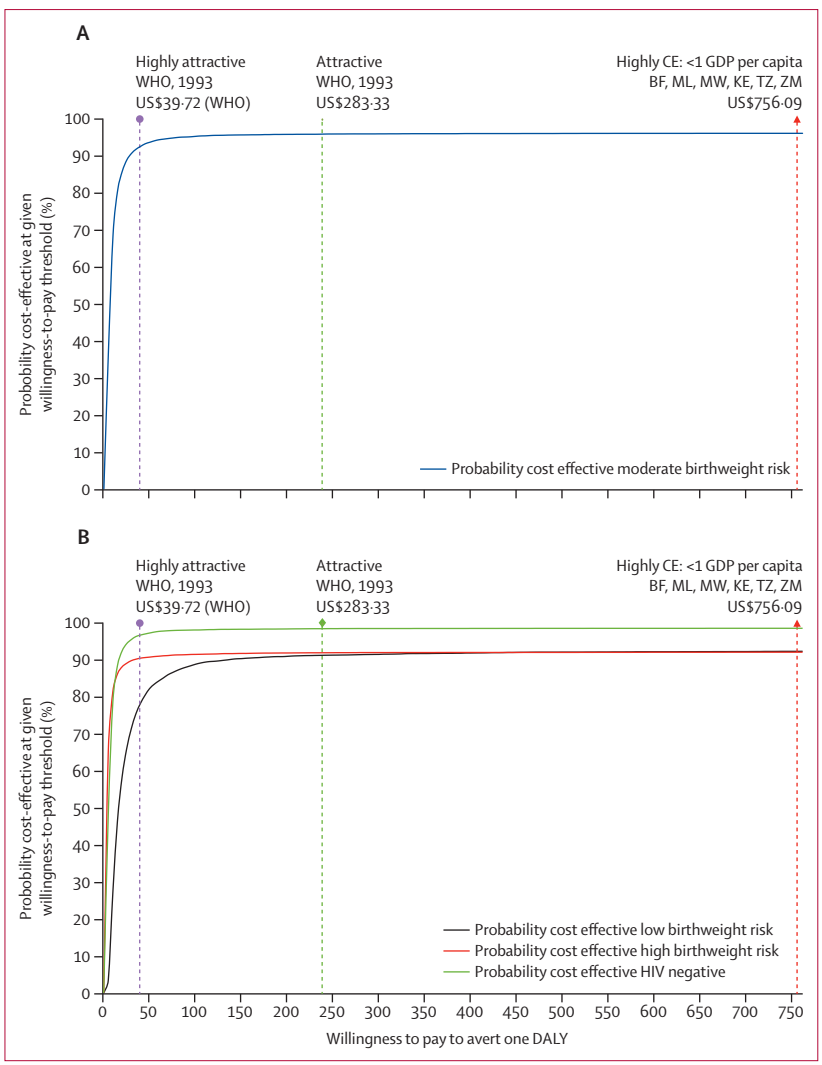

***Figure 4*: Cost-effectiveness acceptability curves**
The curves show the probability of three doses of intermittent preventive treatment with sulfadoxine-pyrimethamine being cost effective at any given willingness-to-pay (WTP) value for moderate (A), and low and high (B) low birthweight risk settings as well as for HIV-negative women only. The vertical lines indicate three WTP thresholds. BF=Burkina Faso. DALY=disability adjusted life year. GDP=gross domestic product. ML=Mali. MW=Malawi. KE=Kenya. TZ=Tanzania. WHO=World Health Organization. ZM=Zambia. CE=cost effective.

Discussion

Our findings suggest that, at just $7·28 per DALY averted, IPTp-SP3+ can be a highly cost-effective intervention when incorporated into an existing antenatal care package. In settings with moderate malaria transmission, IPTp-SP3+ has a 92·4% probability of being highly cost-effective using a threshold of $39·7 per DALY averted. It is substantially more cost-effective than many health interventions recommended for implementation in sub-Saharan Africa (ie, rotavirus vaccination recommended at $43 per DALY averted or PMTCT at $37–69 per DALY averted).[27] Furthermore, our deterministic sensitivity analysis indicates that IPTp-SP3+ remains highly cost-effective under a wide range of assumptions about key parameter values as well as structural assumptions. The incremental cost-effectiveness ratio was more than the willingness-to-pay threshold of $39·7 in only two extreme cases. Finally, our modelling results in figures 3 and 4 suggest that three or more doses of IPTp-SP would be highly cost effective for settings with low to high baseline risk of low birthweight. IPTp-SP3+ for HIV-negative women has an even higher probability of being cost effective (96·6%). Therefore, our findings not only lend support to the new WHO guidelines for IPTp-SP, with monthly dosing at each scheduled antenatal-care visit, but also show the cost-effectiveness of IPTp-SP3+ irrespective of whether all women or only HIV-negative women are considered (panel).

In estimating costs, we deliberately used a conservative approach by including both incremental staff time needed to give the intervention and the incremental costs to women of additional antenatal-care visits. This means that the costs shown here are likely to overestimate the actual cost and therefore underestimate the cost-effectiveness. Policy makers might take a more limited perspective on costs and therefore be interested in the results in the sensitivity analysis, which showed that, when only the costs to the health provider are considered, IPTp-SP3+ was even more cost effective (table 1 and figure 2). Furthermore, the incremental cost would be substantially reduced if it included cost savings due to a reduction in the number of babies born with low birthweight in particular, but also due to the number of cases of severe anaemia and clinical malaria averted. The probabilistic sensitivity analyses included the full range of the 95% CI reported for relative risks, even when these were not statistically significant and the range included one, implying that IPTp-SP2 could possibly be more efficacious than IPTp-SP3+ in a particular gravidity subgroup. Provision of more doses of IPTp-SP is highly unlikely to result in more cases of low birthweight, severe anaemia, or clinical malaria. We nevertheless chose to include the full 95% CI range in the probabilistic sensitivity analyses so the analysis could reflect the results presented by Kayentao and colleagues.[10] This choice explains the simulation points on the northwestern quadrant of the cost-effectiveness plane (positive incremental costs and negative incremental DALYs) and the inclusion of zero in the 95% CI of the incremental DALYs averted.

Our model had several limitations. In their meta-analysis,[10] Kayentao and colleagues pointed out some potential sources of bias, which could have led to the overestimation of the effectiveness of IPTp-SP3+, including the fact that only one of the seven trials was placebo-controlled; and the meta-analysis results could not be stratified by bednet use. Because of the unavailability of information about concurrence of outcomes, we were unable to construct one decision tree model for all three outcomes, but had to sum up our results from three independent decision tree models. Although not ideal, this is unlikely to have had an effect on our results because the largest proportion

(99·4%) of the DALYs averted originated from the low-birthweight cases averted and therefore the likelihood of double counting affecting the final results is minimal. Data for the number of episodes of clinical malaria during pregnancy were not available from the meta-analysis because these were rarely reported in the source trials; therefore we approximated this parameter by multiplying the risk of maternal parasitaemia by the average proportion of pregnant women with parasitaemia who had documented fever (6·8%) obtained from another meta-analysis.[17] Although not ideal, this approximation is unlikely to have affected the cost-effectiveness substantially because our surrogate measure of clinical malaria contributed less than 0·5% to the total DALYs averted.

A further limitation is that we calculated the hypothetical cost to the household of 100% coverage of antenatal care with at least two visits for the IPTp-SP2 arm and of at least three visits for the IPTp-SP3+ arm, translating into one incremental visit for all women attending care up to two times. However, we are aware that the potential cost of attending antenatal care might be much higher for women who never attend antenatal care, and the cost to the health provider of encouraging those women is unknown. Our model is based on the assumption that, on average, 2·8 doses were given in the IPTp-SP3+ groups and 1·6 doses were given in the IPTp-SP2 group. We acknowledge that monthly IPTp as recommended by WHO (if the average number of visits per woman exceed 2·8 visits) would result in higher costs, and the incremental efficacy of adding more doses of IPTp is unknown. However, we showed in the sensitivity analysis that increasing the costs based on an average of four antenatal care visits in the IPTp-SP3+ group increased the incremental cost-effectiveness ratio to $13·98 per DALY averted and IPTp-SP3+ remained highly cost effective.

Although IPTp-SP3+ is very likely to be highly cost effective, implementation of this new policy will present challenges. The proportion of women who received at least two doses of IPTp-SP is well below 60%[32] in most countries, which is in contrast with high antenatal care attendance in many countries (average number of visits in the six countries was 3·3). The reasons for low IPTp coverage seem to be diverse and include drug stockouts and unclear messages given to health providers about IPTp, especially about timing of the dose.[32] The introduction of IPTp-SP3+ could simplify the message to health professionals because it has to be given monthly at each scheduled visit, except during the first trimester. WHO has also recorded a "declining effort to scale-up IPTp in a number of countries".[8] To reverse this trend and ensure access and uptake of IPTp-SP in these settings, substantial efforts are needed for the benefits of monthly IPTp-SP to be realised. In other settings, such as Mali, average attendance is much lower, with 2·6 visits per woman and 30·2% never attending antenatal care.[12] In such settings, additional efforts are needed to encourage women to attend care earlier and more frequently. The household and provider costs of this attendance would need to be added to those of simply providing an additional intervention within an existing visit, and would reduce the cost-effectiveness of the intervention.

The diminishing effort in implementing IPTp-SP could partly be driven by health providers' awareness of the increase in sulfadoxine-pyrimethamine resistance, particularly in eastern and southern Africa, the decrease in malaria transmission,[33] and the hope for a new intervention to replace IPTp-SP soon. Although sulfadoxine-pyrimethamine resistance and malaria transmission intensity are heterogeneous across Africa, the results of the meta-analysis are consistent and do not show evidence for heterogeneity by resistance or endemicity level despite being done in areas with both low and high sulfadoxine-pyrimethamine resistance and intense perennial and highly seasonal transmission. However, all seven trials included in the meta-analysis were done in areas with either holoendemic malaria, where transmission is intense and occurs all year long, or in hyperendemic areas, with intense but highly seasonal transmission and periods of no malaria transmission during the dry season.[10] Therefore, our findings may not be representative of other parts of Africa with less intense transmission and where the relative contribution of malaria to low birthweight might be smaller. Nevertheless, we hypothesise that women living in low transmission areas who might have lower levels of acquired immunity could benefit from the more frequent regimen as infections are more likely to result in symptomatic malaria and potentially preterm low birthweight.[34,35]

Panel: **Research in context**

Systematic Review

We did no systematic review for this cost-effectiveness analysis. The baseline risks and measures of effect used in our analysis were taken from a meta-analysis based on a systematic review published by Kayentao and colleagues in 2013.[1] Other observational studies were either conducted by our own team, other people from the MiP consortium, or the literature was searched.

Interpretation

When provided as part of the existing antenatal care package, IPTp-SP3+ in combination with insecticide-treated bednets provides highly cost-effective protection from malaria for pregnant women in most of sub-Saharan Africa. Care should be taken when extrapolating these findings to areas with low or unstable malaria transmission or areas with so-called super resistance (super resistant areas include three hot spots of resistance in northern Tanzania, western Kenya, and southern Uganda), which were not accounted for in our analysis.

Alternatively, in terms of sulfadoxine-pyrimethamine resistance levels, the consistency of the effect estimates across the trials suggests that the results are generalisable within the limits of the resistance levels seen in the settings included in the studies, which are at present representative of more than 90% of sub-Saharan Africa.[7] The notable exceptions are super-resistant areas, which are restricted to three hot-spots of resistance in northern Tanzania, western Kenya and southern Uganda, where data suggest that resistance undermines malaria control efforts in pregnant women. For a detailed discussion of the implications of sulfadoxine-pyrimethamine resistance for our results, see the appendix.

Despite the fear that sulfadoxine-pyrimethamine resistance can render IPTp-SP ineffective and the need for alternative drugs to replace sulfadoxine-pyrimethamine or alternative strategies that use a more diagnostic-based test-and-treat intervention to replace IPTp with sulfadoxine-pyrimethamine in these areas, our findings show that IPTp-SP3+ in combination with insecticide-treated bednets provides highly cost-effective protection from malaria for pregnant women in most of sub-Saharan Africa. This finding stands irrespective of whether the intervention is given to all women, to women who have given birth once or twice, or to HIV-negative women only. The incremental cost-effectiveness ratio was robust to changes in low-birthweight risk. Our findings therefore lend strong support to WHO guidelines that recommend a monthly dose of IPTp-SP from the second trimester onwards. Caution is needed, however, when extrapolating the findings to areas with low or unstable malaria transmission or areas with high drug resistance (such as the three hotspots listed above). Policy makers in a wide range of settings should therefore be confident that changing to monthly sulfadoxine-pyrimethamine for IPTp will be a good use of their health budgets.

Contributors

SF, FOtK, KH, and ES had the idea for and designed the model. SF, FOtK, KK, AMvE, JW, JH, VW, JA, and MM acquired the data. SF, KH, and ES analysed and interpreted the data. SF and KH wrote the first draft of the paper. ES, FOtK, KK, AMvE, JW, JH, VW, JA, and MM critically revised subsequent drafts of the paper. SF and ES did the statistical analyses. FOtK and KH obtained funding. KH supervised the study.

Declaration of interests

We declare no competing interests.

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