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Cost-effectiveness analysis of three health interventions to prevent malaria in pregnancy in an area of low transmission in Uganda

Kristian Schultz Hansen[a,*], **Richard Ndyomugyenyi**[b], **Pascal Magnussen**[c], and **Siân E Clarke**[d]

[a]Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom [b]Ministry of Health, Kampala, Uganda [c]DBL-Centre for Health Research and Development, Faculty of Life Sciences, University of Copenhagen, Denmark [d]Department of Disease Control, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

Abstract

Pregnant women and their unborn children are vulnerable to malaria increasing the risk of maternal anaemia, low birth weight (LBW) and intrauterine growth retardation. There is little evidence on the cost-effectiveness of intermittent preventive treatment in pregnancy (IPTp) and insecticide-treated bed nets (ITNs) in areas of low transmission.

A randomised controlled trial with three arms was conducted in antenatal clinics in Kabale District, Uganda, an epidemic-prone highland area of low malaria transmission. The interventions were (i) IPTp with sulphadoxine/pyrimethamine (SP) given twice during pregnancy (IPTp-SP); (ii) ITNs alone; and (iii) a combined intervention with both ITNs and IPTp-SP. Primary health outcomes were LBW and maternal anaemia. The costs of providing IPTp-SP and ITNs as well as treatment of malaria episodes were captured from all health centres in the study area.

There were no significant differences in health outcomes among the three interventions. The cost-effectiveness analysis and sensitivity analyses performed did not provide convincing support for replacing IPTp-SP (current policy) by ITNs alone or by a combined intervention in this low transmission setting on economic grounds. The cost per pregnant woman of providing the services was lowest for the IPTp-SP intervention (US$0.79 per woman) followed by ITNs (US$1.71) and the combined intervention of IPTp-SP + ITNs (US$2.48). The relative cost-effectiveness of antenatal distribution of ITNs might improve if the cost savings accruing from continued use of a

[*]Corresponding author: Kristian.Hansen@lshtm.ac.uk. Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, United Kingdom. Tel. + 44 207 958 8329.

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long-lasting insecticidal net after pregnancy as well as positive externalities were also taken into account, and this warrants further study.

Keywords

malaria prevention; pregnancy; intermittent preventive treatment; insecticide-treated nets; cost-effectiveness analysis; low transmission; highlands

Introduction

According to recent estimates, more than 8 million people in Africa and 985 million people globally were living in areas with unstable *P. falciparum* malaria transmission in 2007.[1] Further, an estimated number of 0.4 million pregnancies in Africa and 30.6 million pregnancies globally were at risk of *P. falciparum* malaria in areas of unstable transmission in 2007.[1] Pregnant women are particularly vulnerable to malaria with adverse consequences to the mother and unborn child such as maternal anaemia, low birth weight (LBW) and intrauterine growth retardation.[2] Fortunately, a number of efficacious and cost-effective interventions exist to prevent malaria in pregnancy, however evidence of their cost-effectiveness in areas of low transmission areas is lacking.

Intermittent preventive treatment in pregnancy (IPTp) using a full dose of sulphadoxine/pyrimethamine (SP) two or more times during pregnancy has been shown to be effective in increasing mean birthweight and reducing the frequency of LBW babies.[3] Studies have shown IPTp with SP (IPTp-SP) to be a very cost-effective health intervention. Goodman et al[4] estimated the cost per disability-adjusted life year (DALY) averted to the public healthcare sector of this intervention to be US$12 if provided for primigravidae only and US $32 if provided for all pregnancies in a low income country. Furthermore, Wolfe et al[5] estimated the health sector cost per DALY averted in the range of US$11-14 depending on the number of doses of SP and HIV prevalence. Mbonye et al[6] found that the incremental cost per DALY averted for community-based delivery of IPTp-SP provided by traditional birth attendants, drug vendors, community health workers and adolescent peer mobilisers was just above US$1 compared with facility-based IPTp-SP in Uganda. Current World Health Organization (WHO) guidelines recommend IPTp with at least two doses of treatment in areas of medium or high transmission, whilst there is insufficient evidence to recommend IPTp in low and unstable transmission areas.[7]

Insecticide-treated nets (ITNs) may reduce the number of malaria infections and LBW babies as compared to not sleeping under a net during pregnancy.[8] Whilst ITNs have been found to be a very cost-effective health intervention for children below 5 years,[9,10] the benefits and cost-effectiveness among pregnant women are less well documented,[11] especially in areas of low malaria transmission.[12] The current WHO policy guidance for sub-Saharan Africa recommends the use of both IPTp and ITNs for the prevention of malaria during pregnancy in areas of stable transmission,[7] but there are no specific recommendations for areas of low and unstable transmission.

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There is little evidence on the impact and cost-effectiveness of the combined utilisation of IPTp and ITNs for the prevention of malaria in pregnancy in Africa, particularly in areas of low transmission.[13] Njagi et al[14] demonstrated a significant protective effect of combined ITNs and IPTp on anaemia in primigravidae, as well as a protective effect of ITNs alone, in an area of intense perennial transmission in western Kenya. Menendez et al[15,16] found no additional effect of IPTp on LBW but significant reductions in clinical malaria during pregnancy and in neonatal mortality in a placebo-controlled trial in Mozambique where all women also received an ITN. The cost-effectiveness component of the same study estimated that the incremental cost of IPTp per DALY averted was US$1 when reductions in both maternal malaria and neonatal malaria were included in the analysis.[17] The incremental cost per DALY averted was estimated to be US$17 when adding a bed net distribution programme to IPTp-SP in the Democratic Republic of Congo.[18]

We therefore conducted a randomised controlled trial and cost-effectiveness analysis in a low and unstable transmission area of Uganda with the objective of comparing current national policy of IPTp-SP with either ITNs alone, or with IPTp-SP given in combination with ITNs. The design of the trial and impact of the interventions on maternal and birth outcomes are reported elsewhere.[19] Here, we present the results of the cost-effectiveness analysis.

Methodology

Study site and population

The study was conducted in Kabale district in south-western Uganda, situated at an altitude between 1219m and 2347m above sea level. The majority of the district lies within the malaria epidemic-prone zone, between 1440m and 2200m above sea level and the temperature is fairly constant throughout the year, with maximum daily temperatures of 23.2-24.4 °C. Rainfall is seasonally bimodal, averaging between 1000 and 1480 mm per annum. Malaria transmission is low and unstable but occurs most years, and usually peaks during April-June and September-November following rainfall. The intensity and extent of transmission varies from year to year, resulting in periodic epidemics which are associated with high morbidity and mortality rates, and an increase in stillbirths.[20] The study area was limited to the lowest lying sub-counties of the district at greatest risk of malaria transmission.

Interventions

The current national policy in Uganda for prevention of malaria in pregnancy is IPTp-SP given twice during pregnancy [first dose in the second trimester, after quickening, and the second dose in the third trimester (gestational weeks 28-34)]. IPTp-SP is delivered as part of the standard antenatal care (ANC) services offered at health centres and hospitals. During ANC visits nurses will explain the benefits of IPTp to pregnant women and administer SP under direct observation.

The second intervention was ITNs without IPTp. Whilst this service was not routinely offered in the Ugandan public healthcare sector, the clinics participating in the trial

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delivered bed nets treated with KO-tab® deltametrin as part of standard ANC services. Pregnant women received a bed net at first ANC visit where proper use of the net was explained by nurses/midwives. Impregnation was done by health facility personnel prior to distribution.

The third intervention was a combination of both ITNs and IPTp-SP.

Study design

Pregnant women presenting at <27 weeks gestation at first ANC visit to rural health facilities, staffed with at least one midwife offering ANC services, were recruited into the study (see Ndyomugyenyi et al[19] for more details). Exclusion criteria included: severe anaemia at time of antenatal booking; current or past severe disease; and residence outside the study area. After written informed consent was obtained, women were randomised to one of the above-described interventions. Women were followed until 1 month after delivery (abortion or birth of child) resulting in a follow-up period of 5 months on average. The sample size for this superiority trial was determined to detect a 50% reduction in the prevalence of LBW (<2500 g) among babies born under current practice compared to the two new interventions. The birth of a LBW baby was the least common health outcome and assuming a significance level of 0.05 and power of 0.80, this resulted in a sample size of 1604 women per arm. Pregnant women were recruited over a period of three years from 2004 to 2007 whilst the required unit cost data were collected for the financial year 2004/05.

Measurement of health outcomes by study arm

Main health outcomes were the number og LBW babies and the prevalence of maternal anaemia at 36-40 weeks gestation among enrolled women. As part of the efficacy trial component of this study, a total of 1798, 1778 and 1752 pregnant women in each study arm respectively were followed over an average of 5 months until delivery to capture health outcomes (see Ndyomugyenyi et al[19] for details). Health outcomes were transformed into DALYs lost.[21] The (untreated) disability weight for LBW and the associated disabilities was 0.291,[21] whilst the life expectancies of a male and female newborn baby in Uganda in 2002 were 48.8 and 52.0 years, respectively.[22] Using an average life expectancy of 50.4 years for both sexes and the remaining value choices of the DALY including the age weighting function and a discount rate of 3% for future life years,[21] this resulted in 8.61 DALYs lost per LBW baby. Similarly, it was calculated that an episode of maternal anaemia meant a loss of 0.0015 DALYs based on an assumption that each episode lasted on average 1 month with a disability weight of 0.012.[21] Total DALYs lost were calculated for a reference population of 1000 women in each study arm by multiplying DALYs lost per LBW baby and per maternal anaemia episode by the number of adverse health outcomes for the reference populations using the prevalences found in the efficacy component of this study.[19]

Collection and measurement of costs by study arm

Costs were collected from a provider’s perspective meaning that only costs borne by the public healthcare sector were included. Economic rather than financial costs were collected. IPTp delivered as part of public sector ANC is free. It was also assumed that the distribution

of ITNs at ANC would be free so the full costs of these interventions were therefore assumed to be borne by the public healthcare sector.

Intervention costs consisted of the costs of administering SP during ANC visits at health centres and the costs of impregnating nets and distributing these from health centres. Cost savings might arise if an intervention reduces the number of malaria episodes during pregnancy leading to fewer outpatient visits for malaria treatment. The unit costs per service for administering SP during ANC, impregnation and distribution of ITNs and outpatient treatment for malaria were estimated based on cost data collected from all health centres situated in the study area. There were seven health centres within the study area of which five were recruiting women into the trial when the cost data were collected in 2005. Collection of cost data at health centres was guided by a combination of the standard step-down costing methodology[23,24] and micro-costing,[25] as described in more detail below.

Information on overall level of recurrent expenditure by category (drugs, stationery, utilities, etc) for the 2004/05 financial year for the study health centres was obtained from the accountant at the District Director of Health Services' Office in Kabale. A list of staff, job title and grade was compiled during field visits and the annual salary including allowances by type of personnel was calculated using the government salary scale. Capital inputs at health centres were buildings, equipment and furniture. The size (in m^2) of health centres was approximated using plans of standard health centres available from Ministry of Health and information on construction cost per m^2 for such buildings was captured from a public sector quantity surveyor. An inventory of equipment and furniture was developed during the field visit at each health centre and these items were subsequently valued using a relevant price list[26] and a price survey conducted in Kampala. Annual equivalents[23] of these capital costs were calculated using a discount rate of 3% and expected life spans of buildings, equipment and furniture of 30, 7 and 10 years, respectively.

The total recurrent and capital costs at health centre level were in the first step of the standard step-down costing[23,24] distributed to the relevant cost centres including overhead activities (administration), support activities (pharmacy, laboratory) and final services (ANC visits, vaccinations, outpatient visits, etc) using relevant allocation criteria expected to reflect actual resource utilisation. The second and third steps of the step-down costing consisted of allocating the costs of overhead and support activities respectively to individual final services including ANC visits with SP, impregnation and distribution of ITNs, and outpatient visits for malaria treatment. Allocation criteria for the three steps were developed during the data collection visits. For instance, salary costs were allocated to main activities following interviews with staff who estimated how much time was spent on each type of service e.g. 15 minutes per outpatient visit, 15 minutes to distribute and explain the proper usage of an ITN, 20 minutes for impregnating a net and 15 minutes per ANC visit of which 20% or 3 minutes were dedicated to administering SP. As another example of an allocation criterion, building costs of different rooms were allocated according to the purpose of the room i.e. the pharmacy was allocated to pharmacy services. With respect to SP tablets, bed nets, insecticide used per bed net, malaria drugs given during an outpatient visit and medical disposables used for these services, interviews with relevant staff and official guidelines[27] provided information on utilisation per visit and prices of these commodities were taken

from a relevant price list.[26] At the end of this process, the health centre level costs had been allocated to final services, and dividing by the number of final services performed in the financial year 2004/05, the unit cost per individual service at the seven study health centres was arrived at.

Since administration of SP for IPTp was only one out of several standard activities performed as part of ANC, only 20% of salary costs and all other non-drug costs of an ANC visit were allocated to IPTp whilst all costs of SP tablets were included in the IPTp interventions. The expected lifespan of the bednets was 30 months but only 5/30 (16.7%) of the costs of these were allocated to the interventions since women typically first attended ANC during the fourth month of pregnancy and the measurement of health effects was confined to the 5 month observation period of the pregnancy. Likewise, only 5/30 (16.7%) of the salary and other health centre costs related to distribution of bednets were allocated to the interventions. A bednet was interpreted as a capital good and an annual equivalent was calculated, allocating 5/12 (41.7%) of the annual equivalent to the intervention. The period over which the impregnation was effective was 12 months so only 5/12 (41.7%) of the impregnation chemical costs were allocated to the study interventions.

The average of unit costs per service for administering SP during ANC, impregnation and distribution of ITNs and outpatient treatment for malaria was calculated from the seven study health centres and used for all subsequent cost calculations. Nurses at the study health centres captured the numbers of ANC visits with SP, ITNs distributed and outpatient visits for malaria treatment among all enrolled women, which were used to estimate the number of services for a reference population of 1000 women in each study arm. Total cost by study arm was calculated by multiplying these numbers by the average of unit costs.

Incremental cost-effectiveness ratios (ICER)

The total costs and effects measured in DALYs lost for each of the three intervention arms were used to calculate the incremental costs and incremental effects from replacing the current practice by each of the new interventions. The ICER of replacing current practice of IPTp-SP by ITNs only was calculated by subtracting the total cost of the IPTp-SP arm from the total cost of the ITNs only arm for the numerator and subtracting the total DALYs lost in the IPTp-SP arm from the total DALYs lost in the ITNs only arm for the denominator (intervention 2 versus intervention 1). This ratio could then be interpreted as the incremental cost per DALY averted (incremental effects) if IPTp-SP was replaced by ITNs only. The incremental cost-effectiveness ratio of adding ITNs to current practice of IPTp-SP (intervention 3 versus intervention 1) was calculated in the same fashion.

The trial component of this study showed that there were no significant differences in maternal anaemia and number of LBW babies born in the three intervention arms.[19] Since the trial was not designed as an equivalence trial,[28] the evaluation did not proceed as a cost-minimisation analysis.[29] Instead ICERs for the two new interventions were calculated and sensitivity analyses were used to quantify the uncertainty in incremental cost per incremental effect as recommended by several authors.[30,31]

Sensitivity analyses

Several parameters described above were uncertain so the robustness of the baseline ICERs was assessed with a range of sensitivity analyses. Probabilistic sensitivity analysis (PSA)[32] was used to assess the influence of multivariate uncertainty in health outcomes and cost per service on the ICER. Health outcome data for individual women in the different study arms were binomial and the uncertainty was therefore described by beta distributions[32] with the necessary parameters estimated from the trial component of this study[19] (Table 1). Calculation of the cost per service in seven health centres revealed that these varied considerably, mainly due to differences in volumes of patient attendance (Table 2). Uncertainty of average cost per service was represented by gamma distributions which are defined for non-negative values only and skewed to the right. Gamma distributions are therefore be particularly relevant for cost data.[32] Parameters for the gamma distributions were estimated based on cost per service from the study health centres (Table 2) and shown in Table 1. The PSA was designed as a Monte Carlo simulation with 10000 iterations using the @Risk software (Palisade Corporation, New York, USA). Each iteration used randomly drawn values from the distributions displayed in Table 1 to calculate costs and effects for a reference population of 1000 individuals in each study arm as well as ICERs of the two new interventions. The results of the sensitivity analyses were summarised by scatter plots of joint incremental costs and incremental effects (DALYs averted) and cost-effectiveness acceptability curves.[33]

Additional PSAs were repeated with new values for specific variables. First, time utilised per service was determined by asking health personnel themselves. Separate PSAs were run assuming that the time utilised by nurses for administering SP could range between 1 minute and 6 minutes and assuming that time taken to explain the use of bednets ranged between 5 minutes and 30 minutes. Second, the cost implications of distributing a long-lasting insecticidal net (LLIN) instead of a conventional ITN were investigated as a LLIN would have no pre-treatment costs to be borne by the public health service. The cost of using LLINs was explored under a range of assumptions, including a purchase price equal to a conventional ITN as well as a 30% higher or lower price. The efficacy of a LLIN was assumed equal to a conventional ITN.[19] Third, the cost per service for administration of SP, distribution of bednets, and outpatient visit for treatment of malaria was recalculated under the assumptions that attendance to all services offered was up to 10% higher and lower than the observed level in the seven study health centres.

Ethical approval

The study protocol was approved by the Uganda National Council of Science and Technology, the Ethical Committee of the London School of Hygiene and Tropical Medicine, and the Danish National Committee on Biomedical Research Ethics, and registered on a clinical trials database (www.clinicaltrials.gov: NCT00142207).

Results

Cost per service was captured from all seven health centres in the study area (Table 2). Average cost per service was used for producing the main results of the cost-effectiveness

component of the trial in Kabale District (Table 3). The level of maternal anaemia and the number of LBW babies born in the three intervention arm were not significantly different[19] and the number of DALYs lost were therefore also similar. The cost per pregnant woman covered by IPTp-SP was lowest (US$0.79) compared with ITN alone and the combined intervention (US$1.71 and US$2.48 per woman respectively). IPTp-SP was therefore the option with the lowest cost and at the same time having health benefits that were not significantly different from the other two interventions. The ICERs expressed as the cost per DALY averted of replacing IPTp-SP by a new intervention were found to be US$54 for ITNs alone and -US$53 for the combined intervention (Table 3).

The result of the PSA comparing ITNs only with IPTp-SP is presented in Figure 1, showing pairs of incremental costs and incremental effects following each individual iteration of the Monte-Carlo simulation. The current practice of offering IPTp-SP only is by definition represented by the origin so that points above the x-axis represent situations where the ITN intervention had higher cost than the IPTp-SP intervention and the opposite for points below the x-axis. Similarly, points to the right of the y-axis represented iterations where the ITN intervention had a better impact on health than the IPTp-SP intervention leading to a positive number of DALYs averted, while the opposite was the case for points to the left of y-axis. As shown in Figure 1, the swarm of joint pairs of incremental costs and effects extends across the y-axis but is situated completely above the x-axis reflecting the findings that there was no significant difference in health outcomes between the two interventions and that the ITN intervention had higher cost. The iterations indicated a relatively large variation in incremental costs and effects of changing policy from IPTp-SP to ITNs and therefore also a wide range of ICERs. A substantial proportion of the iterations led to a negative number of DALYs averted (Figure 1, left of the y-axis) meaning that IPTp-SP was more effective than ITNs and had lower cost so that IPTp-SP was the best option in those iterations. Figure 2 shows the results of the PSA of comparing the combined intervention of ITNs + IPTp-SP with IPTp-SP alone. Similar observations can be made from this sensitivity analysis as is above, except that the swarm of joint pairs of incremental costs and effects lies further up reflecting the fact that the combined intervention was the most expensive of the three interventions tested.

The ICER for each pair of incremental costs and effects is given by the slope of a line connecting a point and the origin in Figures 1 and 2. This characteristic can be used for the development of cost-effectiveness acceptability curves which measure the share of ICERs below a given ceiling ratio. If this ceiling ratio is interpreted as the willingness-to-pay (WTP) for a health improvement of a relevant health policy maker, then a cost-effectiveness acceptability curve will represent the probability of an intervention being cost-effective at different levels of WTP.[33] ICERs of Figures 1 and 2 may be represented by the cost-effectiveness acceptability curves shown in Figure 3. There was a 25% probability that replacing IPTp-SP by ITNs would be a cost-effective use of resources if the WTP for averting a DALY was US$25 and a probability of 64% of ITNs being cost-effective if the WTP for averting a DALY was US$150. These two thresholds have often been used to classify health interventions as being very cost-effective and cost-effective, respectively.[34] At a very high WTP of US$500 per DALY averted, the probability of ITNs being cost-effective was 69%. The probability of the combined intervention being a cost-effective use

of resources was much lower. For instance, the probability of the combined intervention being a cost-effective intervention in place of IPTp-SP was only 12% at a high WTP of US $500.

The additional PSAs to investigate the impact of different time utilisation by health centre personnel, use of LLINs instead of conventional ITNs and different levels of attendance in health centres did not give reason to alter the conclusions above, as the cost-effectiveness acceptability curves did not change markedly (results not shown). The largest impact was found in the situation where a LLIN was used at a price 30% lower than the price of a conventional ITN. The probability that this would be a cost-effective use of resources was 68%, 71% and 72% at WTPs of US$25, US$150 and US$500 respectively.

Generally, the PSAs did not provide strong support for spending the extra resources needed for replacing IPTp-SP by ITNs and in particular not for replacing IPTp-SP by the combined intervention.

Discussion

The present randomised intervention trial on the impact of ITNs alone and the combined package of IPTp-SP + ITNs delivered through ANC services found neither intervention to be superior to IPTp-SP alone (current policy) in preventing adverse maternal and birth outcomes in an area of low and unstable malaria transmission.[19] The cost-effectiveness analysis and associated sensitivity analyses did not offer strong support for replacing current policy of IPTp-SP by ITNs alone or a combination of IPTp-SP + ITNs on economic grounds. The best alternative to current policy was found to be ITNs alone where the sensitivity analyses suggested that there could be a probability of approximately 64% that replacing IPTp-SP by ITNs alone would be cost-effective if the WTP of relevant policy-makers was US$150 (Figure 3). However, even if the WTP of relevant policy-makers was $500 or above, the probability of ITNs being more cost-effective than IPTp-SP would not exceed 72%. These findings may help inform the development of guidelines for prevention of malaria in pregnancy in areas of low and unstable transmission in Uganda as well as in other African countries.

These conclusions were based on the trial design, measured outcomes and length of the period of follow-up in this study. These factors present specific limitations for interpretation of the cost-effectiveness analysis. In particular, the impact of the interventions on women and newborns over a longer follow-up period beyond the end of pregnancy was not evaluated, nor was the size of the costs and effects of individuals not directly protected by interventions investigated. The relevance of these considerations and influence for the conclusions on the relative cost-effectiveness of the interventions is discussed below. We discuss the potential influence of compliance and other factors on study findings elsewhere[19] and are confident that these factors did not affect our conclusions. Compliance to the interventions was high for both IPTp and ITN use, and there was no evidence of reduced efficacy of IPTp-SP.[19] Nonetheless, should coverage, compliance or efficacy of any of the interventions be reduced under operational conditions, this may affect the relative cost-effectiveness of the interventions. Similarly, should SP in the future be replaced by a

more expensive drug, this would also change the relative cost-effectiveness of the interventions.

The health outcomes available for analysis include only the immediate and direct impacts of malaria infection during pregnancy, measured at term, principally LBW and maternal anaemia. Pregnant women were followed for an average period of 5 months so costs and effects were measured for this period. However, interventions with ITNs in particular would be expected to have positive health effects in the future over the full lifespan of a bednet. Though the cost of a net was discounted over the 30 month lifespan during which a conventional treated net would remain fully efficacious, the possible additional health effects of sleeping under an ITN after the 5-month follow-up (averted malaria episodes and maternal deaths) were not captured. Also, the continuing positive health effects to the newborn child sleeping with the mother under the ITN were not captured as well as averted malaria episodes in children sleeping with the mother while she was pregnant. Averted adverse health events would also lead to cost saving both in the healthcare sector and for the households.

Furthermore, it has been demonstrated that with high coverage, ITNs may offer protection to individuals not sleeping under a bednet in a household and even people residing in households without bednets.[35-37] These additional benefits are often termed a positive externality or community effects.[9] The extent of a positive externality among individuals not sleeping under a net may become a relevant issue to explore .[37] If distribution of ITNs contributes to reduced transmission through increasing community coverage of ITNs, this intervention could have a positive externality. Estimating the size of the costs and effects of individuals indirectly protected by interventions presents a challenge for calculating the cost-effectiveness of ITNs. Including possible positive externalities and cost savings accruing from continued use of a LLIN after pregnancy would likely improve the relative cost-effectiveness of interventions with ITNs as compared to IPTp-SP.

Finally, there might be additional costs and effects of having a LBW baby in the longer term not captured in this study. While future adverse health events among LBW babies were in principle captured through the disability weight developed for the DALY methodology, this was not the case for the future additional costs. LBW babies would typically suffer more frequently from adverse medical conditions and disabilities over time thus possibly resulting in more frequent admissions to hospital. There might also be additional household costs for families with a LBW baby in terms of purchasing extra medicines, extra health care seeking and time lost when caring for the baby. Determining such morbidity and associated costs requires a longer follow-up period of 2-3 years with repeated household visits to record events such as illness episodes and deaths. Whilst repeated visits to households over an extended period of time have been applied for measuring malaria morbidity and treatment,[38] similar longitudinal studies focusing on household costs in preventive malaria interventions in pregnancy have not been done. As an alternative to repeated visits by interviewers, families may instead be trained in keeping diaries of relevant events.[39] Finally, future health benefits and averted costs for a longer period could be included using modelling techniques, which would require reliable estimates from other studies on the effectiveness of health interventions. Unfortunately, this was not possible in the context of this study, since there

have only been few studies on the effectiveness of ITNs in low transmission areas in Africa.[12] Designing preventive trials with a longer follow-up of mothers and their newborns may capture household costs which are not typically measured in cost-effectiveness studies thus potentially concluding that preventive interventions in pregnancy are more cost-effective when comprehensive household costs are collected. Nonetheless, including the long-term costs and effects of malaria on birthweight would probably not change the conclusions of the cost-effectiveness analysis presented here since there was no significant difference in the prevalence of LBW babies in the three interventions.

In conclusion, in the absence of any demonstrable difference in efficacy between three interventions on maternal and foetal outcomes[19], our economic evaluation did not provide any additional evidence on economic grounds for replacing IPTp-SP by ITNs alone or by a combined intervention in a setting of low and unstable transmission. However, the relative cost-effectiveness of antenatal distribution of ITNs might improve if the cost savings accruing from continued use of a LLIN after pregnancy and positive externalities were also taken into account and warrants further study.

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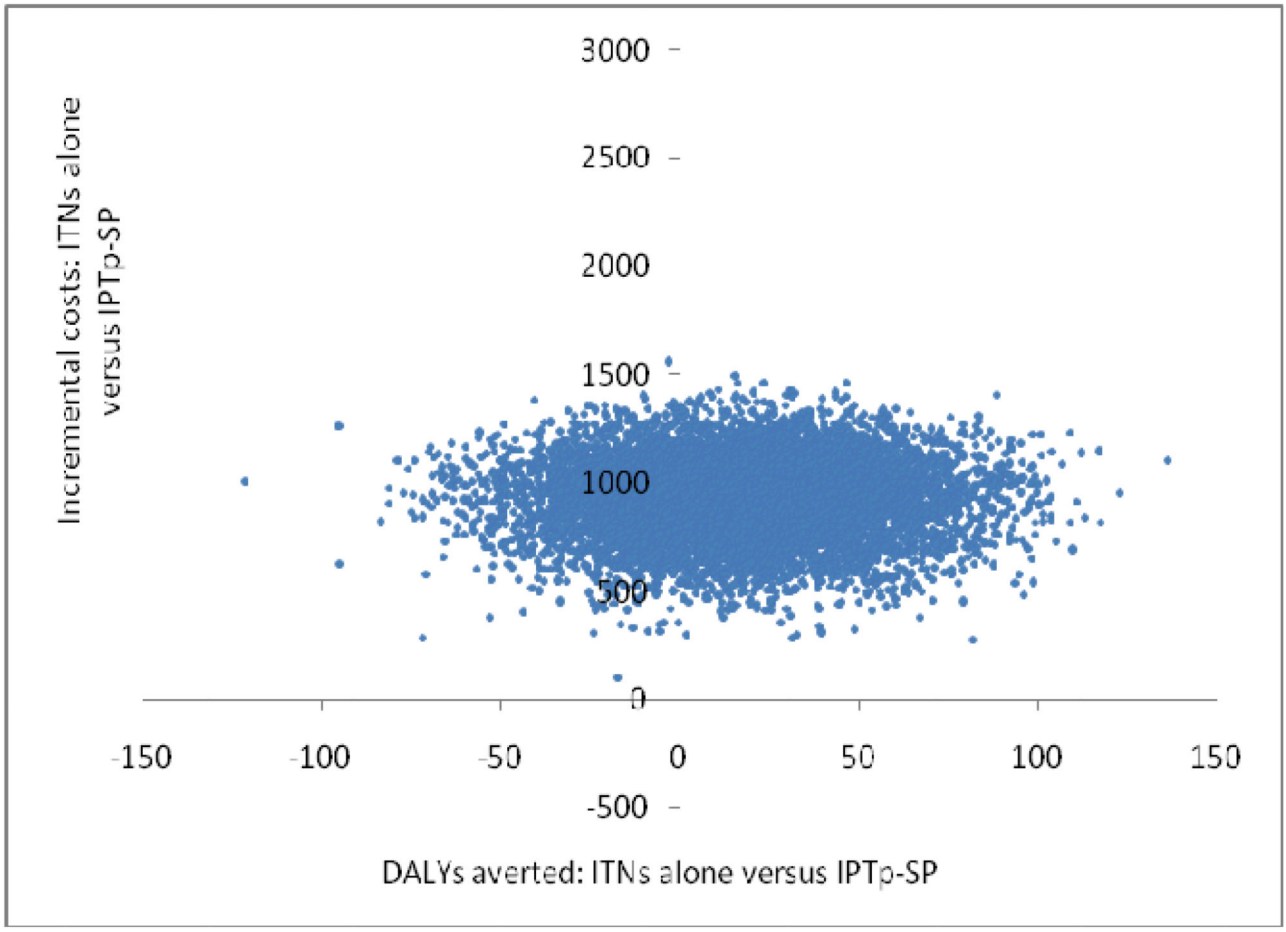

Figure 1. Scatter plot of incremental costs (US$) and incremental effects [disability-adjusted life years (DALY) averted] resulting from replacing the intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine (ITPp-SP) intervention by the intervention with insecticide-treated bednets (ITN) alone in an area of low and unstable malaria transmission, Kabale District, Uganda (US$1 = UGX1760).

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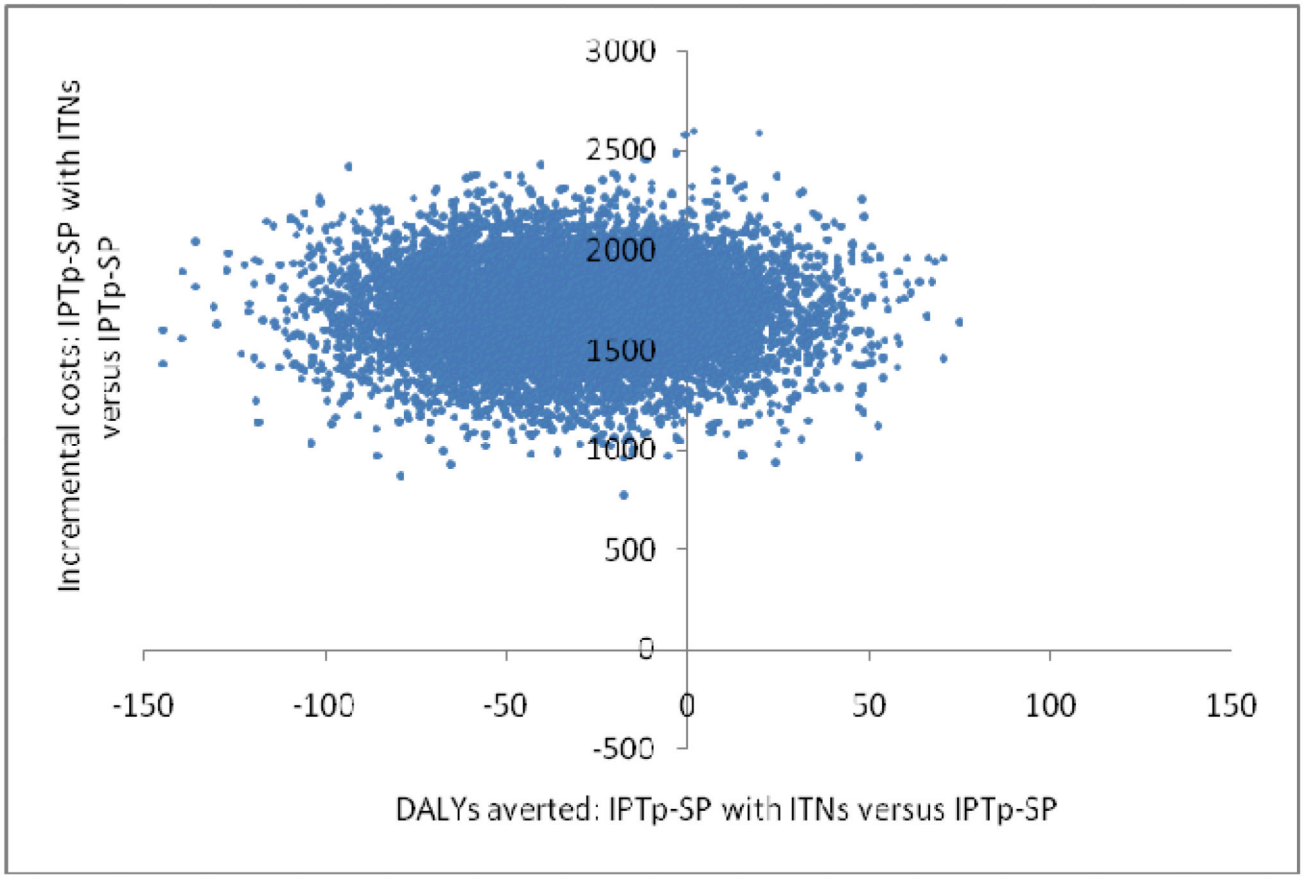

Figure 2. Scatter plot of incremental costs (US$) and incremental effects [disability-adjusted life years (DALY) averted] resulting from replacing the intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine (ITPp-SP) intervention by the combined intervention of IPTp-SP plus insecticide-treated bednets (ITN) in an area of low and unstable malaria transmission, Kabale District, Uganda (US$1 = UGX1760).

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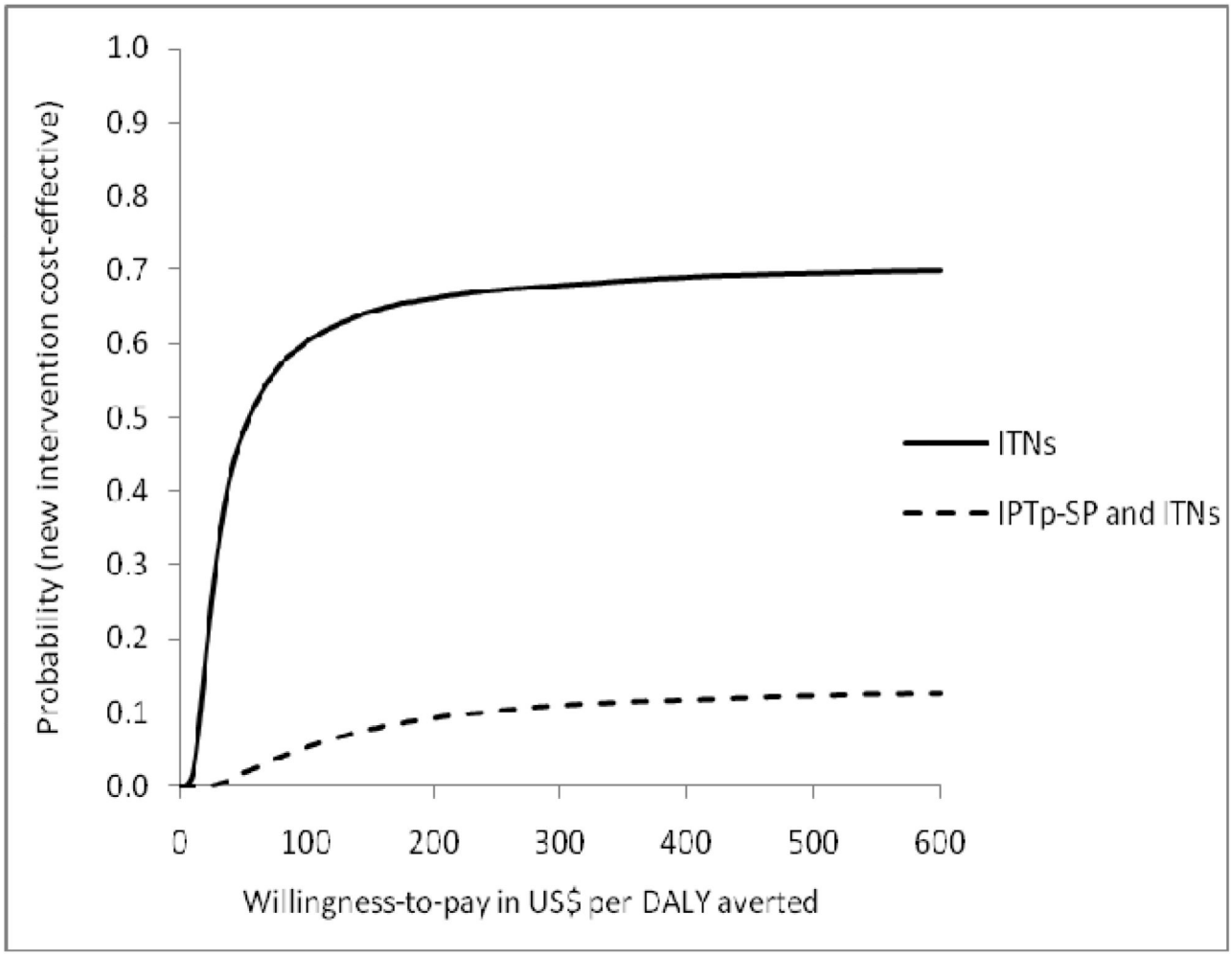

Figure 3. Cost-effectiveness acceptability curves for replacing intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine (ITPp-SP) (current practice) with (i) insecticide-treated bednets (ITN) only or (ii) a combined intervention of IPTp-SP plus ITNs, in an area of low and unstable malaria transmission, Kabale District, Uganda (US$1 = UGX1760). DALY: disability-adjusted life years.

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Table 1

Input variables and distributions used for the sensitivity analyses of three interventions to prevent malaria in pregnancy, Kabale District, Uganda (US$1 = UGX1760).

	Distribution			
Input variable	**IPTp-SP**	**ITN only**	**IPTp-SP + ITN**	**Source**
Health outcomes				
Maternal anaemia	Beta	Beta	Beta	[19]
Episodes	α=142	α=163	α=136	
	β=858	β=837	β=864	
Low birth weight	Beta	Beta	Beta	[19]
Babies	α=65	α=63	α=69	
	β=935	β=937	β=931	
Health centre cost per service in US$				
Administration of SP during ANC	Gamma		Gamma	Cost data from present study
	α=29		α=29	
	β=0.010		β=0.010	
Distribution of ITNs		Gamma	Gamma	Cost data from present study
		α=327	α=327	
		β=0.005	β=0.005	
Malaria treatment	Gamma	Gamma	Gamma	Cost data from present study
	α=42	α=42	α=42	
	β=0.017	β=0.017	β=0.017	

IPTp-SP: intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine; ITN: insecticide-treated bednet; ANC: antenatal care

Table 2

Cost per service in seven health centres in Kabale District, Uganda, for the financial year 2004/05 (US$1 = UGX1760).

	Health centre						
	1	**2**	**3**	**4**	**5**	**6**	**7**
SP administration during ANC							
Cost per service (US$)	0.33	0.19	0.34	0.30	0.30	0.26	NA
Distributed across (%):							
Salaries	30	28	26	31	27	17	-
Drugs	27	42	26	31	28	38	-
Bednets and insecticides	0	0	0	0	0	0	-
Other recurrent costs	2	1	2	4	3	1	-
Admin, other overhead	10	9	12	12	9	16	-
Capital costs	31	19	35	22	33	26	-
Total	100	100	100	100	100	100	-
Bed net impregnation and distribution							
Cost per service (US$)	1.73	1.56	1.72	1.81	1.66	NA	NA
Distributed across (%):							
Salaries	8	6	7	8	6	-	-
Drugs	0	0	0	0	0	-	-
Bednets and insecticides	84	90	85	83	86	-	-
Other recurrent costs	0	0	0	0	0	-	-
Admin, other overhead	4	2	4	4	3	-	-
Capital costs	4	2	4	4	4	-	-
Total	100	100	100	100	100	-	-
Outpatient visit for malaria treatment							
Cost per service (US$)	0.69	0.60	0.87	0.87	0.70	0.65	0.62
Distributed across (%):							
Salaries	36	45	38	39	42	23	22
Drugs	32	28	25	29	26	33	33
Bednets and insecticides	0	0	0	0	0	0	0
Other recurrent costs	2	1	1	3	2	1	2
Admin, other overhead	8	10	15	13	13	21	17
Capital costs	23	15	20	17	18	21	26
Total	100	100	100	100	100	100	100

SP: sulfadoxine/pyrimethamine; ANC: antenatal care; NA: not available

Table 3

Costs and effects of three interventions to prevent malaria in pregnancy and incremental cost-effectiveness ratios (ICER) of new interventions, Kabale District, Uganda (US$1 = UGX1760).

	Intervention		
	IPTp-SP	**ITN only**	**IPTp-SP + ITN**
Number of pregnant women	1000	1000	1000
Health outcomes			
Number of women with maternal anaemia	142	163	136
Number of low birthweight babies	65	63	69
Number of DALYs lost	558	541	590
Number of services			
Administration of SP	2680	0	2679
ITN distribution	0	999	1000
Treatment of clinical malaria at health centre	28	26	20
Cost per unit of service (US$) [a]			
Administration of SP	0.3	0.3	0.3
ITN distribution	1.7	1.7	1.7
Treatment of clinical malaria at health centre	0.7	0.7	0.7
Total costs by component (US$)			
IPTp component	766	0	766
ITN component	0	1696	1697
Treatment of clinical malaria	20	19	14
Total costs (US$)	786	1715	2477
Cost per pregnant woman (US$)	0.79	1.71	2.48
Incremental costs		929	1691
Incremental effects (DALYs averted)		17	−32
Incremental cost per DALY averted (ICER in US$)		54	−53

IPTp-SP: intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine; ITN: insecticide-treated bednet; DALY: disability-adjusted life year

[a] Mean costs among seven health centres in Kabale District, Uganda