Antimalarials during pregnancy: a cost-effectiveness analysis

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Antenatal clinics (ANC) provide an avenue for interventions that promote maternal and infant health. In areas hyperendemic for Plasmodium falciparum, malaria infection during pregnancy contributes to low birth weight (LBW), which is the greatest risk factor for neonatal mortality. Using current data and costs from studies in Malawi, a decision-analysis model was constructed to predict the number of LBW cases prevented by three antimalarial regimens, in an area with a high prevalence of chloroquine (CQ)-resistant malaria. Factors considered included local costs of antimalarials, number of ANC visits, compliance with dispensed antimalarials, prevalence of placental malaria, and LBW incidence.

For a hypothetical cohort of 10,000 women in their first or second pregnancy, a regimen consisting of one dose of sulfadoxine–pyrimethamine (SP) in the second trimester followed by a second dose at the beginning of the third trimester would prevent 205 cases of LBW at a cost of US$9.66 per case of LBW prevented. A regimen using a treatment dose of SP followed by CQ 300 mg (base) weekly would prevent 59 cases of LBW at a cost of $62 per case prevented, compared with only 30 cases of LBW prevented at a cost of $113 per case when the regimen involves initial treatment with CQ (25 mg/kg) followed by CQ 300 mg (base) weekly. In areas hyperendemic for CQ-resistant P. falciparum, a two-dose SP regimen is a cost-effective intervention to reduce LBW incidence and it should be included as part of the antenatal care package.

Introduction

In rural sub-Saharan Africa, antenatal clinics provide one of the few opportunities for interventions to promote maternal and infant health. A minimum set of services should be provided in the antenatal clinic (ANC), such as assessment and management of maternal or fetal risk factors; completion of relevant history on an antenatal card; immunization with tetanus toxoid for neonatal tetanus prevention; administration or dispensing of iron and folate to combat anaemia; testing for syphilis and treatment; and routine administration of antimalarials for prevention of malaria infection (1, 2). Antimalarials are important because, where Plasmodium falciparum transmission is high, women infected with malaria during pregnancy may develop placental parasitaemia leading to decreased fetal nutrition and low-birth-weight (LBW) infants (3–6), and consequent risk of neonatal and early infant deaths (7, 8). Prevention of malaria during pregnancy represents one of the few interventions that can be incorporated into the antenatal care package to reduce the incidence of low-birth-weight infants and the risk of premature death.

When resources are limited, women at greatest risk should be identified and interventions should be delivered selectively to this group. Women in their first pregnancy, and to a lesser extent their second, are more likely to become parasitaemic during the pregnancy (9–11), to have placental infection (3, 5), and to have low-birth-weight babies (8, 12) than women in later pregnancies. Therefore, women in their first or second pregnancies constitute the target group for antimalarial intervention.

The factors which must be considered in identifying a practical antimalarial regimen for pregnant women in Africa include the efficacy, safety and ease of delivery of the antimalarial to the target population, and their compliance with the dosage regimen. Clearly, the regimen must be efficacious to prevent placental parasitaemia. Clinic attendance is essential for the delivery of antimalarials to pregnant women through antenatal clinics. The antimalarial regimen should be acceptable to the pregnant women and the dose schedule simplified to minimize the risk of poor compliance. Finally, the regimen must be

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Reprint No. 5588
affordable, whether paid for by the women themselves or by the government (where ANC services are provided free).

In Malawi, ANC attendance is high and the national malaria policy has recommended that women be given weekly chloroquine (CQ) (300 mg base) throughout pregnancy. Two major problems existed with this regimen. First, there are high levels of CQ resistance throughout Malawi, and CQ has been documented to be of little benefit in clearing placental malaria in this setting (13). Second, a weekly CQ regimen relies on women remembering and self-administering the drug at home each week during the pregnancy. For reasons varying from minor side-effects to sociocultural beliefs, compliance with weekly CQ prophylaxis has been extremely poor in many settings (14, 15). Less frequent dosing, particularly on-site administration at antenatal clinic visits with a more efficacious drug, would alleviate compliance problems and increase the regimen’s effectiveness. The cost factor must also be considered. In Malawi, the cost of antimalarials delivered through antenatal clinics is borne by the government, which attempts to direct the limited available resources to those interventions that will give maximum benefit to the health of Malawians.

The National Malaria Control Committee in Malawi identified the control of malaria during pregnancy as a health priority for which a practical intervention was required. To aid in the selection of an antimalarial intervention for use during pregnancy, a study was conducted to examine the efficacy of regimens containing sulfadoxine–pyrimethamine (SP) and/or CQ (16). This paper examines the cost-effectiveness of these regimens when administered to women in their first and second pregnancy.

Methods

Antimalarial regimens. Based on efficacy, availability, safety, cost, and dosage, three regimens were selected as candidates for implementation through the national malaria control programme (16). These regimens were compared on the basis of the number of LBW cases prevented and the cost per case of LBW prevented (cost-effectiveness):

1. SP/SP—an initial single treatment dose of SP (3 tablets, 1500 mg sulfadoxine and 75 mg pyrimethamine), given at the first antenatal clinic visit (typically, 16th to 22nd week of gestation) and again at the beginning of the third trimester.

2. SP/CQ—an initial treatment dose of SP at the first antenatal clinic visit, followed by CQ chemoprophylaxis (300 mg base) weekly until delivery.

3. CQ/CQ—an initial treatment dose of CQ (25 mg/kg, administered as a divided dose over 3 days) at the first antenatal clinic visit, followed by chloroquine chemoprophylaxis (300 mg base) weekly until delivery.

Description of the model. A decision-analysis model was constructed to estimate the number of low-birth-weight cases prevented by each of the regimens for a hypothetical cohort of 10,000 women in their first or second pregnancy. Critical decision nodes in the model were the percentage of women attending the antenatal clinic, the expected compliance with weekly CQ, the expected placental malaria infection rates, and the incidence of LBW deliveries. The 1992 cost of antimalarials to the government of Malawi was used to calculate the projected cost of each regimen per case of LBW prevented.

At the first visit, which was assumed to occur at 20 weeks’ gestation, women would be placed on one of the antimalarial regimens (Fig. 1). Women on SP/SP would be given the first dose of SP, women on SP/CQ would be given an initial treatment dose of SP and a 1-month supply of CQ prophylaxis to self-administer each week at home. Women on CQ/CQ would receive the initial treatment dose of CQ and a 1-month supply of CQ prophylaxis. Women who return for a second clinic visit would then receive the second dose of SP administered on site, if the SP/SP regimen was being used. For women on SP/CQ or CQ/CQ, CQ would be dispensed for weekly use at home until delivery. Because compliance can be a major limitation to the regimen’s effectiveness, the model included expected compliance for women receiving CQ weekly.

The probability of placental malaria infection among women on the candidate regimens was estimated and the probability of women delivering a LBW newborn was predicted based on the woman’s malaria infection status.

Probability estimates. Probability estimates used in the model were derived from several recent studies conducted in Malawi (Table 1). Results from a national survey showed that 93% of pregnant women attend the antenatal clinic at least once and that among those who attend once, 94% return for one or more subsequent visits (17). According to national policy at the time of the study, women who continued attending the clinic were given CQ to be taken weekly at home until delivery. However, only 35% of these women complied with these recommendations (18).

Hospital surveillance data indicate that among women not attending the ANC and not receiving antimalarials during pregnancy, 38% would have placental malaria infection at delivery (19). In a
Cost-effectiveness of antimalarials during pregnancy

Fig. 1. Decision-analysis model to estimate, for each of three antimalarial regimens, the number of low-birth-weight cases expected for a hypothetical cohort of 10,000 women in their first or second pregnancy. Critical decision nodes include the number of women attending the antenatal clinic (ANC) for the first and second visits; expected compliance with weekly CQ; placental malaria infection rates at delivery; and the incidence of LBW. Assumptions include: the first visit occurs at 20 weeks’ gestation and the second at 24 weeks, at which time the second dose of SP is administered.

Table 1: Probability estimates and data sources for specific variables used in the model for the cost-effectiveness of antimalarials used during pregnancy

<table>
<thead>
<tr>
<th>Probability estimate</th>
<th>Data source</th>
</tr>
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<tbody>
<tr>
<td>First ANC visit</td>
<td>93%</td>
</tr>
<tr>
<td>Return rate for ANC attenders</td>
<td>94%</td>
</tr>
<tr>
<td>Compliance to CQ</td>
<td>35%</td>
</tr>
<tr>
<td>Placental malaria infection rate:</td>
<td></td>
</tr>
<tr>
<td>CQ/CQ</td>
<td>32%</td>
</tr>
<tr>
<td>SP/CQ</td>
<td>26%</td>
</tr>
<tr>
<td>SP/SP</td>
<td>9%</td>
</tr>
<tr>
<td>No antimalarials</td>
<td>38%</td>
</tr>
<tr>
<td>LBW rate:</td>
<td></td>
</tr>
<tr>
<td>With placental malaria</td>
<td>28%</td>
</tr>
<tr>
<td>No placental malaria</td>
<td>20%</td>
</tr>
</tbody>
</table>

recent antimalarial efficacy study in which compliance was ensured by observed administration of all antimalarials, 9% of the women who received SP/SP, 26% of the women who received SP/CQ, and 32% of the women who received CQ/CQ had placental malaria infection at delivery (16). Among women scheduled to receive the SP/CQ regimen who were non-compliant with weekly CQ, the incidence of placental malaria infection was predicted to be less than among women who received the full course of SP/CQ. Therefore, we used an intermediate estimate that 32% had placental malaria infection at delivery. Women who received one dose of SP but failed to return to the antenatal clinic were analogous to
women returning to the clinic, but failing to comply with weekly CQ, so the incidence of placental malaria among those women was also estimated to be 32%. Among women who received CQ/CQ, non-compliance or failure to attend the antenatal clinic was estimated to increase the placental malaria infection rate to 35%. Among women who received SP/SP but failed to return for the second dose, placental malaria infection rates were estimated at 32%. Since SP/SP was administered on site, compliance was not included as a determinant of the effectiveness for this regimen.

Data from a large cohort study (19) and ongoing hospital surveillance documented a LBW rate of 28% among women in their first or second pregnancy who had placental malaria infection at delivery. Among women in their first or second pregnancy who did not have placental malaria infection, a LBW rate of 20% was observed.

Cost estimates. Antimalarial cost was based on the cost to the government in the spring of 1992; the cost of a treatment dose was US$ 0.11 for SP and 7.5 cents for CQ. The cost incurred at the first visit was for the initial treatment dose plus any antimalarials that would be dispensed. On the return visit, the costs included antimalarials given on site for the two-dose SP group, or the cost of CQ dispensed for use at home. The cost-effectiveness (cost per case of LBW prevented) was then calculated for each regimen. Finally, univariate and multivariate sensitivity analysis was performed to test the robustness of the cost-effectiveness analysis.

Results

Effectiveness and cost-effectiveness. Using the decision analysis model, we estimated that 2304 cases of LBW would occur per 10 000 women in their first or second pregnancy if no antimalarials were administered. For the SP/SP, SP/CQ and CQ/CQ regimens, the number of LBW cases expected would be 2098, 2245 and 2274, respectively. Therefore, the number of cases of LBW prevented by the SP/SP, SP/CQ and CQ/CQ regimens were 205, 59 and 30, respectively. The total cost for the cohort of 10 000 women in their first or second pregnancy was calculated at US$ 1984 for the SP/SP regimen, $3679 for the SP/CQ regimen, and $3353 for the CQ/CQ regimen. The cost-effectiveness of the regimens (cost per case of LBW prevented) for SP/SP, SP/CQ and CQ/CQ was estimated to be $9.66, $59 and $113, respectively (Table 2).

Sensitivity analysis. In the univariate analysis, the critical variables affecting the regimen’s effectiveness were ANC attendance and drug efficacy. Compliance was a limiting factor for regimens containing CQ but not for SP/SP. An example of how these factors influence the number of cases of LBW prevented by each of the regimens is shown in Table 3. If ANC attendance decreased to 50% for either the first or the follow-up visit, or if compliance with weekly CQ increased to 80%, the relative cost-effectiveness of the three regimens remained similar. The variables most affecting costs were the price of the antimalarials, the duration of CQ prophylaxis, drug efficacy, and compliance. However, regardless of changes in each of these factors, the relative cost-effectiveness of the regimens did not change substantially (Table 4, see page 212).

Multivariate sensitivity analysis was performed to test further the robustness of the results. The relative cost-effectiveness did not vary significantly with simultaneous alteration of multiple variables. The cost-effectiveness of the SP/SP regimen remained constant at $10 to $14 per case of LBW prevented, except when the price of SP was changed. With the CQ/CQ regimen, the cost per case of LBW prevented decreased from $113 to $59 when compliance was increased to 80% and the duration of CQ prophylaxis was shortened to 12 weeks. Under the same circumstances, the cost of SP/SP was only $10 per case of LBW prevented. SP/SP remained most cost-effective, even when the cost of SP/SP was increased threefold and the efficacy was reduced such that 18% of women receiving SP/SP had placental malaria at delivery (Table 4).

Table 2: Overall cost (US$) and the cost per low-birth-weight case prevented using three antimalarial regimens administered to a hypothetical cohort of 10 000 women in their first or second pregnancy

<table>
<thead>
<tr>
<th>Regimen*</th>
<th>Cost of first visits (93%)</th>
<th>Cost of return visits (94%)</th>
<th>Total cost</th>
<th>No. of LBW cases prevented</th>
<th>Cost/ LBW case prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP/SP</td>
<td>$1023</td>
<td>$962</td>
<td>$1985</td>
<td>205</td>
<td>$9.66</td>
</tr>
<tr>
<td>SP/CQ</td>
<td>$1581</td>
<td>$2098</td>
<td>$3679</td>
<td>59</td>
<td>$62.01</td>
</tr>
<tr>
<td>CQ/CQ</td>
<td>$1256</td>
<td>$2098</td>
<td>$3354</td>
<td>30</td>
<td>$113.05</td>
</tr>
</tbody>
</table>

* SP (sulfadoxine–pyrimethamine) cost: $0.11/treatment dose (3 tabs). CQ (chloroquine) cost: $0.075/treatment dose (25 mg/kg); $0.015/week prophylaxis dose (300 mg base).
Table 3: Univariate sensitivity analysis: number of LBW cases prevented for a hypothetical cohort of 10 000 women in their first or second pregnancy who followed one of three antimalarial regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of LBW cases prevented with:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First visit decreased to 50%</td>
<td>Return visit decreased to 50%</td>
</tr>
<tr>
<td></td>
<td>SP/SP 110</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>SP/CQ 32</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>CQ/CQ 16</td>
<td>26</td>
</tr>
</tbody>
</table>

* Results illustrated in this Table were calculated using the figures for the original model and varying only the factor as shown in the column heading. Factors used in the original model were: first visit, 93%; return visit, 94%; compliance, 35%; CQ prophylaxis duration, 20 weeks; CQ/CQ placental infection rate, 32%.

The model was applied to settings where the rates of placental malaria infection or LBW were different from those in rural Malawi. Table 5 illustrates the cost-effectiveness of the regimens in a setting where placental malaria infection rate in untreated women was 25%, and LBW incidence was 20% among women with infected placentas and 15% among women with uninfected placentas. The cost per case prevented increased substantially, but SP/SP remained more cost-effective (Table 5). Again, this relative cost-effectiveness remained unchanged in both univariate and multivariate sensitivity analysis.

Discussion

When identifying interventions to prevent malaria during pregnancy, the efficacy of the antimalarial is necessary but not sufficient by itself for success. We constructed a decision-analysis model that incorporated socio-behavioural and biological factors to assess the relative effectiveness of antimalarial regimens for use in a national malaria prevention programme in pregnant women. The model identifies drug efficacy, compliance, and antenatal clinic attendance as major factors limiting the regimen’s effectiveness. The cost-effectiveness was most influenced by the drug’s efficacy and cost, the total number of weeks CQ was administered, and, to a lesser extent, compliance. By utilizing a regimen that allows single-dose intermittent treatment with a highly efficacious antimalarial, administered on-site in an antenatal clinic, only the clinic attendance remains a potential limiting factor to the regimen’s effectiveness.

The costs presented in this analysis are described from the perspective of the Ministry of Health, which provides free antenatal services at government health facilities. Programme costs, including fixed costs, were not included in the model on the assumption that delivery of antimalarials would be incorporated as one part of the package of services delivered to women attending the antenatal clinic. Furthermore, the costs of administering any of the three regimens through this system should be similar and would not alter the relative cost-effectiveness of the regimens. In Malawi, the cost of SP/SP would be significantly higher if purchased by women outside the health care system. Many
potential costs were not addressed, including those associated with adverse drug reactions or delivery of a LBW infant (e.g., prolonged hospitalization and follow-up clinic visits), or with the value of years of life lost for LBW infants who die.

An important consideration with any drug to be used during pregnancy is its safety for both the fetus and the mother. The major concern with SP during pregnancy is a theoretical increase in the risk of kernicterus in the newborn due to competition between bilirubin and sulfadoxine for binding sites on albumin. Although an increase in kernicterus was reported in one early study in which sulfonamides were administered to newborns (20), subsequent studies have not found any increased risk of kernicterus after administration of a sulfonamide to the pregnant woman (21-23). Therefore, the risk of serious maternal or fetal side-effects after a two-dose regimen administered during the second trimester and early in the third trimester was thought to be insignificant when compared with the increased risk of neonatal mortality due to malaria-associated LBW.

Further analysis comparing the relative cost of antimalarials delivered through antenatal clinics with that of other health interventions (nutritional supplementation, focusing on reduction of low birth weight or neonatal mortality) is required to ascertain the relative economic efficiency of interventions. Within the context of antimalarial interventions, this analysis demonstrates that CQ/CQ, at present used in many countries with CQ-resistant *P. falciparum*, is neither an effective nor inexpensive intervention to prevent LBW. A regimen consisting of two-dose SP was less costly and prevented significantly more cases of LBW, resulting in a relative cost-effectiveness that remained unchanged even when critical factors were varied. These results provide further argument for replacing the widely recommended CQ/CQ regimen with a more efficacious antimalarial which can be delivered intermittently under controlled circumstances (e.g., in an antenatal clinic) to reduce malaria-associated LBW. Currently, the Malawi Ministry of Health has changed the national policy for malaria control to recommend SP/SP administration to pregnant women and this recommendation is widely implemented through government antenatal care programmes.

### Acknowledgements

The authors are grateful to Deborah McFarland for reviewing the model construction and cost analysis and Laurence Slutsker for reviewing the manuscript.
Résumen

Antipaludiques pendant la grossesse: analyse coût/efficacité

En Afrique subsaharienne rurale, les dispensaires anténatals offrent l'une des rares occasions d'intervention en faveur de la santé maternelle et infantile. Le traitement par des antipaludiques doit figurer parmi les interventions, car là où la transmission de *Plasmadium falciparum* est intense, l'infection de la mère au cours de la grossesse peut entraîner une parasitémie placentaire, associée à un faible poids de naissance chez l'enfant et à un risque de décès néonatal ou au cours de la première enfance. De plus, la prévention du paludisme par administration d'antipaludiques représente l'une des rares interventions qui puisse être intégrée dans les soins anténatals et qui soit capable de réduire efficacement l'incidence du faible poids à la naissance.

Cet article examine le rapport coût/efficacité de trois schémas de traitement antipaludique contenant de la sulfadoxine-pyriméthamine (SP) et/ou de la chloroquine (CQ), administrés lors de la première et de la deuxième grossesses. Les schémas retenus ont été sélectionnés par le programme national de lutte contre le paludisme au Malawi d'après les résultats d'évaluations portant sur l'efficacité, la disponibilité, l'innocuité, le coût et la facilité d'administration des médicaments.

1) SP/SP — une dose unique initiale de SP (3 comprimés, soit 1500 mg de sulfadoxine et 75 mg de pyriméthamine) lors de la première visite au dispensaire anténatal (habituellement entre la seizième et la vingt-deuxième semaine de la grossesse), et de nouveau au début du troisième trimestre.

2) SP/CQ — une dose initiale de SP lors de la première visite au dispensaire anténatal, puis une chimiothérapie par CQ (300 mg de chloroquine base), une fois par semaine jusqu'à l'accouchement.

3) CQ/CQ — une dose initiale de CQ (25 mg/kg, répartition sur 3 jours) lors de la première visite au dispensaire anténatal, puis une chimiothérapie par CQ (300 mg de chloroquine base) une fois par semaine jusqu'à l'accouchement.

D'après les données et coûts résultant d'études réalisées au Malawi, un modèle d'analyse décisionnelle a été établi pour prédire le nombre de cas de faible poids à la naissance qui peuvent être évités grâce aux trois types de traitement antipaludique, et le rapport coût/efficacité relatif de ces derniers dans une région à forte prévalence de paludisme chloroquinorésistant. Les déterminants de l'efficacité étaient la fréquence des visites au dispensaire anténatal, l'observance du traitement antipaludique, la prévalence du paludisme placentaire, et l'incidence du faible poids à la naissance. Dans une cohorte hypothétique de 10 000 femmes pendant leur première ou leur deuxième grossesse, recevant chacun des schémas étudiés, il serait ainsi possible d'éviter 205 cas de faible poids à la naissance avec le schéma SP/SP, 59 cas avec le schéma SP/CQ et 30 cas avec le schéma CQ/CQ. Le coût total pour cette cohorte a été évalué à US$ 1984 pour le schéma SP/SP, US$ 3679 pour le schéma SP/CQ, et US$ 3353 pour le schéma CQ/CQ. Le rapport coût/efficacité des schémas (coût par cas de faible poids à la naissance évité) pour les schémas SP/SP, SP/CQ et CQ/CQ a été évalué, respectivement, à US$ 9,66, US$ 59 et US$ 113.

Ces résultats démontrent à nouveau l'intérêt du remplacement du schéma CQ/CQ, actuellement largement recommandé, par un antipaludique plus efficace, qui puisse être administré périodiquement sous surveillance (par exemple dans un dispensaire anténatal) pour réduire l'incidence du faible poids à la naissance associé au paludisme. Ils montrent que le schéma SP/SP est une intervention rentable pour réduire l'incidence du faible poids à la naissance dans les régions où *P. falciparum* chloroquinorésistant est hyperendémique, et qu'elle doit figurer dans le programme de soins anténatals. Le Ministère de la Santé du Malawi a modifié la politique nationale de lutte antipaludique et recommande maintenant l'administration de SP/SP aux femmes enceintes.

Références


