Malaria in Pregnancy Before and After the Implementation of a National IPTp Program in Gabon

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Abstract. Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine has recently been adopted by many African countries to reduce maternal and neonatal morbidity and mortality associated with malaria in pregnancy. We assessed the impact of a newly established national IPTp program on maternal and neonatal health in Gabon. Data on prevalence of maternal Plasmodium falciparum infection, anemia, premature birth, and birth weight were collected in cross-sectional surveys in urban and rural regions of Gabon before and after the implementation of IPTp in a total of 1403 women and their offspring. After introduction of IPTp, the prevalence of maternal Plasmodium falciparum infection decreased dramatically (risk ratio 0.16, \( P < 0.001 \)). Whereas only a modest effect on the rate of anemia in pregnant women was observed, there was a marked benefit on the prevalence of low birth weight and premature birth for women adhering to national recommendations. These effects were most pronounced in primi- and secundigravid women.

INTRODUCTION

Malaria in pregnancy causes considerable morbidity and mortality in pregnant women and newborns in sub-Saharan Africa.1 The World Health Organization recommends a three-pronged approach to tackle malaria in pregnancy based on the implementation of impregnated bed nets, effective case management of clinical disease, and intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine.2,3 The recommendation of IPTp was initially based on several studies conducted in East and South-East Africa demonstrating beneficial effects on the prevalence of maternal anemia and low birth weight.4–7 This benefit was most pronounced for nulli- and primiparous women living in high-transmission regions. Epidemiologic variations and parity of pregnant women may therefore significantly influence the overall risk/benefit analysis for regional IPTp programs.8,9 Since the World Health Organization has recommended the use of IPTp in sub-Saharan Africa, several countries have adopted this strategy for the prevention of malaria in pregnancy.3 Whereas several clinical trials evaluating IPTp regimens in Africa have been conducted recently, there is a lack of data on the impact of national IPTp programs under real-world conditions in Central Africa.

The central African country Gabon implemented a nationwide IPTp program in 2005. This program aims at providing two doses of sulfadoxine–pyrimethamine as presumptive treatment of all pregnant women free of charge.10 Based on data from a cross-sectional survey of pregnancy-associated malaria in the period before the implementation of IPTp in Gabon (2003/2004), we conducted a re-assessment after the full implementation of IPTp in 2005/2006. The aim of this work was to provide epidemiologic evidence of whether implementation of the IPTp in Gabon led to a favorable risk/benefit analysis for maternal and neonatal health in Gabon.

MATERIALS AND METHODS

This study consists of two cross-sectional surveys conducted from May 2003 to February 2004 and from May 2005 to September 2006 (subsequently referred to as survey 2004 and survey 2006). Both surveys took place in obstetrics departments of local hospitals in the cities of Libreville (Center Hospitalier de Libreville) and Lambaréné (Hôpital Régional de Lambaréné and Albert Schweitzer Hospital) in the central African country Gabon. Libreville, the capital of Gabon, is a typical urban region, with the surrounding region home to approximately half of the country’s total population, currently estimated at 1.2 million. Lambaréné is a small city of 250 km southeast of Libreville located in the province Moyen-Ogooué. Lambaréné is characterized by a rural setting. Both regions are characterized by stable perennial malaria transmission and Plasmodium falciparum highly resistant to chloroquine.11 HIV prevalence in adults (of age 15–49 years) was estimated at 7.9% in 2005.12

Women attending the hospital for delivery were invited to participate in this survey. Informed consent was sought from the mother and the guardian accompanying the patient to the hospital. The study protocol was approved by the Ethics Committee of the International Foundation for the Albert Schweitzer Hospital in Lambaréné. An investigator obtained necessary information from the mother–child health booklet and performed a structured interview. A thick blood smear was performed according to the Lambaréné method,13 and hemoglobin measurements of capillary blood were performed in a subgroup of participants.13

Definitions. Gestational age was calculated based on information on last date of menses. Birth weight of the newborn was recorded (± 5 g) immediately after delivery. Deliveries before week 37 of gestation were classified as premature.
Anemia was stratified as moderate (≤ 11 g/dL) and severe
(≤ 8 g/dL). Threshold levels for low birth weight and very low
birth weight were defined as < 2500 and < 1500 g, respectively.
Participants were stratified in two groups depending on
adherence to IPTp recommendations for respective analysis
(no IPTp administration during pregnancy, “No IPTp” group;
and at least two doses of IPTp, “IPTp” group).

Data were captured on paper forms and reviewed manually
before analysis (JMP 5.0, SAS Institute, Inc., Cary, NC). Only
women with singleton births were considered eligible for
analysis. Risk ratios were computed for primary outcome
measures and differences of continuous data were analyzed
(t-test). Threshold of statistical significance was set at a two-
sided level of \( P < 0.05 \).

The primary outcome measure of this study was the assess-
ment of the impact of IPTp on maternal and neonatal health.
For this purpose, \( P. falciparum \) prevalence and prevalence of
anemia were analyzed as surrogate markers for maternal
health. Prematurity and prevalence of low birth weight were
defined as indicators for neonatal health. Secondary outcome
measures included the comparison of maternal hemoglobin,
gestational age, and birth weight as continuous variables.
Sample size calculation was based on prevalence data of sur-
vey 2004 and on the assumption of a 15% reduction of re-
spective primary outcome measures to reach statistical signifi-
cance at \( \alpha = 0.05 \) and \( \beta = 0.80 \). A sample size of 1000 was
necessary to allow for 10% of incomplete data sampling. Sta-
tistical analysis was performed employing a commercial soft-
ware package (JMP 5.0, SAS Institute, Inc.). Multivariate re-
gression analysis was performed for the association of number
of IPTp administrations during pregnancy and outcome vari-
ables controlling for study site, study period, gravidity, age,
number of consultations, and use of bed nets. Standard least-
square modeling was used for continuous endpoints (birth
weight, hemoglobin, gestational age), and nominal logistic re-
gression analysis was used for \( P. falciparum \) infection status.
Forward selection of variables was used for regression anal-
ysis (\( P < 0.25 \)).

RESULTS

Two hundred three and 186 participants were included in
survey 2004 in Libreville and Lambaréné, respectively. In the
second cross-sectional survey, 787 and 227 women were in-
cluded at the two respective study sites. Demographic char-
acteristics were similar and are depicted in Table 1.

Half of the pregnant women (189 of 366 [51.5%] and 400 of
797 [50.2%] in 2004 and 2006, respectively) reported use of
bed nets during pregnancy. However, bed nets are rarely im-
pregnated with insecticides in Gabon.19 One hundred thirty-
one of 389 (33.7%) women reported regular chemoprophyl-
laxis with chloroquine during pregnancy in survey 2004. After
the implementation of the national IPTp program, 83.2%
(726 of 873) and 57.1% (489 of 856) of participants had re-
ceived at least one dose or at least two doses of sulfadoxine–
pyrimethamine as presumptive treatment, respectively.
Among those women participating in the national program,
83.7% (548 of 655) received the first dose correctly during
the second trimester, whereas 7 (1.1%) received the amnialarial
before week 12 of gestation. The remaining 100 participants
started IPTp only during the third trimester (15.2%). There
was no significant difference in IPTp adherence between the
health-care centers of Lambaréné and Libreville.

Comparison of surveys 2004 and 2006. In 2004, the overall
prevalence of peripheral \( P. falciparum \) infection at delivery
was 10.5%. This prevalence dropped to 1.7% in 2006 after
implementation of the IPTp in Gabon. This decrease of \( P.
falciparum \) infection in pregnant women was similar for Li-
reville (21 of 203 [10.3%] in 2004 to 13 of 787 [1.7%] in 2006)
and Lambaréné (20 of 186 [10.8%] in 2004 to 4 of 224 [1.8%]
in 2006). The risk ratio of \( P. falciparum \) prevalence was there-
fore 0.16 (95% confidence intervals: 0.09–0.28; \( P < 0.001 \);
Table 2). A trend toward reduced rates of premature births
and low or very low birth weight was observed without reach-
ing the level of statistical significance (Table 2). In concor-
dance with these findings, gestational age and birth weight
were significantly lower in survey 2004 (38.2 versus 38.6
weeks and 3018 versus 3074 g, respectively). No difference
was observed for maternal hemoglobin levels.

In multivariate analysis, the total number of IPTp admin-
istrations during pregnancy was associated with birth weight
(\( P = 0.006 \), gestational age (\( P = 0.09 \)), and maternal hemo-
globin levels (\( P = 0.07 \)). No association was observed for
prevalence of maternal \( P. falciparum \) infection. Use of bed
nets was not associated with the respective endpoints in mul-
tivariate analysis.

Comparison of IPTp versus non-IPTp in survey 2006. Preg-
nant women participating in the 2006 survey were stratified in
two groups: those with at least two doses of sulfadoxine–
pyrimethamine during pregnancy (“IPTp”) in concordance
with national recommendations and those not having partici-
pated in the IPTp program (“No IPTp”).

No difference in prevalence of maternal \( P. falciparum \) in-
fecction was observed between groups (Table 3). However, the
rate of premature births was significantly reduced in the IPTp
group (22.2% versus 17.3%). This was similarly reflected in
an increase in mean gestational age at delivery (38.4 versus 39.0
weeks; \( P = 0.005 \)). Maternal hemoglobin levels and birth weight
differed significantly between groups (10.4 versus 10.9 g/dL,
\( P = 0.004 \); and 3029 versus 3112 g, \( P = 0.029 \), respectively).

Comparison of IPTp versus non-IPTp in survey 2006
among primi- and secundigravid women. Primi- and secundig-
gravid women are known to be at highest risk for adverse

| Table 1 |

<table>
<thead>
<tr>
<th>Demographic characteristics of participants in 2004 and 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age* (years)</td>
</tr>
<tr>
<td>Parity**</td>
</tr>
<tr>
<td>Parity stratified (PG, SG, MG; N)</td>
</tr>
<tr>
<td>Parity stratified (NP, PP, SP, MP; N)</td>
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<tr>
<td>Parity stratified (NP, PP, SP, MP; N)</td>
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<tr>
<td>Parity stratified (NP, PP, SP, MP; N)</td>
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<tr>
<td>Parity stratified (NP, PP, SP, MP; N)</td>
</tr>
<tr>
<td>Abortion*</td>
</tr>
<tr>
<td>Use of bed net</td>
</tr>
<tr>
<td>Minimum 1 dose of IPTp</td>
</tr>
<tr>
<td>Minimum 2 doses of IPTp</td>
</tr>
</tbody>
</table>

Differences between the total number of included participants and denominators in indi-
vidual analyses are due to missing data or discrepant information for respective variables.
\* Median (10–90% quantiles, N).
\+ PG, primigravidae; SG, secundigravidae; MG, multigravidae.
| NP, nullipara; PP, primipara; SP, secundipara; MP, multipara.
outcome due to malaria in pregnancy. Therefore, subgroup analysis restricted to this risk group was performed.

Use of IPTp was associated with a decreased risk of pre-mature births and lower-than-normal birth weight (risk ratios 0.65 and 0.45, respectively). These findings were similarly reflected by a prolongation of gestational age by 1 week and an increase of 172 g in birth weight. Although a trend for a reduction of severe maternal anemia was observed in stratified analysis (risk ratio 0.52), no significant difference was observed for mean hemoglobin levels. Similar results were obtained in multivariate regression analysis. The total number of IPTp administrations during pregnancy was associated with birth weight ($P = 0.03$), gestational age ($P = 0.09$), and maternal hemoglobin levels ($P = 0.02$).

### DISCUSSION

IPTp has recently been adopted in many African regions because of current recommendations by the World Health Organization.\(^3\)\(^,\)\(^7\) Evaluation of regional IPTp programs is a research priority given the scarcity of epidemiologic data and considerable differences in malaria transmission rates and potential shifts in its risk/benefit analysis within sub-Saharan Africa. In this study, we assessed the impact of a newly established IPTp program on maternal and neonatal health in urban and rural regions of Gabon.

Our data show a dramatic reduction of the prevalence of *P. falciparum* parasitemia at delivery after the implementation of the national IPTp program in 2005 (risk ratio 0.16). Ad-

### Table 2
Comparison of outcome measures of surveys from 2004 and 2006

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2006</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome measures, stratified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em> prevalence</td>
<td>10.5% (41/389)</td>
<td>1.7% (17/1014)</td>
<td>0.16 (0.09–0.28)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>50.3% (153/304)</td>
<td>49.8% (206/414)</td>
<td>0.99 (0.85–1.15)</td>
</tr>
<tr>
<td>Severe</td>
<td>4.6% (14/304)</td>
<td>5.3% (22/414)</td>
<td>1.15 (0.60–2.22)</td>
</tr>
<tr>
<td>Rate of prematurity</td>
<td>23.9% (85/355)</td>
<td>20.1% (167/828)</td>
<td>0.84 (0.67–1.06)</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>11.7% (45/385)</td>
<td>10.3% (81/788)</td>
<td>0.88 (0.62–1.24)</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>0.8% (3/385)</td>
<td>0.3% (2/788)</td>
<td>0.33 (0.05–1.94)</td>
</tr>
<tr>
<td><strong>Outcome measures, continuous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.7 (10.5–10.9; 304)</td>
<td>10.7 (10.5–10.8; 414)</td>
<td>$P = 0.862$</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38.2 (37.9–38.5; 355)</td>
<td>38.6 (38.4–38.8; 828)</td>
<td>$P = 0.040$</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3018 (2968–3069; 385)</td>
<td>3074 (3038–3109; 788)</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>

### Table 3
Comparison of outcome measures of participants adhering to IPTp recommendations (“IPTp”) or not (“No IPTp”)

<table>
<thead>
<tr>
<th></th>
<th>No IPTp</th>
<th>IPTp</th>
<th>Risk ratio/rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome measures, stratified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em> prevalence</td>
<td>1.9% (7/367)</td>
<td>1.8% (9/489)</td>
<td>0.96 (0.36–2.57)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>54.2 (90/166)</td>
<td>47.1 (96/204)</td>
<td>0.87 (0.71–1.06)</td>
</tr>
<tr>
<td>Severe</td>
<td>6.6 (11/166)</td>
<td>2.9 (6/204)</td>
<td>0.44 (0.17–1.17)</td>
</tr>
<tr>
<td>Rate of prematurity</td>
<td>22.2 (66/297)</td>
<td>17.3 (77/446)</td>
<td>0.78 (0.58–1.04)</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>12.6 (35/278)</td>
<td>8.7 (36/415)</td>
<td>0.69 (0.44–1.07)</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>0.4 (1/278)</td>
<td>0 (0/415)</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome measures, continuous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.4 (10.1–10.7; 166)</td>
<td>10.7 (10.5–10.8; 414)</td>
<td>$P = 0.004$</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38.4 (38.0–38.7; 297)</td>
<td>39.0 (38.7–39.3; 446)</td>
<td>$P = 0.005$</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3029 (2971–3087; 278)</td>
<td>3112 (3065–3160; 415)</td>
<td>$P = 0.029$</td>
</tr>
</tbody>
</table>

### Primi- and secundigravid women: 2006

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2006</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome measures, stratified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em> prevalence</td>
<td>2.7 (5/183)</td>
<td>2.7 (7/254)</td>
<td>1.01 (0.33–3.13)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>42.7 (32/75)</td>
<td>39.5 (43/109)</td>
<td>0.92 (0.65–1.32)</td>
</tr>
<tr>
<td>Severe</td>
<td>10.7 (8/75)</td>
<td>5.5 (6/109)</td>
<td>0.52 (0.19–1.43)</td>
</tr>
<tr>
<td>Rate of prematurity</td>
<td>26.7 (39/146)</td>
<td>17.3 (41/237)</td>
<td><strong>0.65 (0.44–0.95)</strong></td>
</tr>
<tr>
<td>Birth weight stratified</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>18.4 (25/136)</td>
<td>8.3 (18/217)</td>
<td><strong>0.45 (0.26–0.80)</strong></td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>0.7 (1/136)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome measures, continuous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.5 (10.1–10.9; 75)</td>
<td>10.9 (10.5–11.2; 109)</td>
<td>$P = 0.144$</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>37.9 (37.5–38.4; 146)</td>
<td>39.0 (38.7–39.4; 237)</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2881 (2802–2959; 136)</td>
<td>3053 (2991–3115; 217)</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>
mittenly, comparison of data with historical controls may be affected by bias and confounding. However, there is evidence to believe in a causal relation between the implementation of IPTp and the decrease in \( P. falciparum \) prevalence in pregnant women. Firstly, a similar decrease in \( P. falciparum \) prevalence was observed in all three obstetric departments independently. However, IPTp was not associated with a change in prevalence of \( P. falciparum \) infection at delivery in analysis of survey 2006 data, despite significant associations with other outcome variables. We speculate that this discrepancy was due to the fact that assessment of \( P. falciparum \) infection exclusively at delivery underestimated effectiveness of IPTp against \( P. falciparum \) infection during pregnancy. In general, results are in concordance with previous studies showing comparable risk ratios of maternal \( P. falciparum \) prevalence in Kenya and Mozambique (0.15 and 0.45, respectively).

Maternal anemia was the second marker for maternal health in this study. Although a trend for a reduced prevalence of moderate and severe anemia was observed, this reduction did not reach the level of statistical significance. This finding is in contrast to a previous report from a controlled setting in Kenya where IPTp had a protective efficacy of 39% against severe anemia. However, the higher baseline rate of severe maternal anemia in the Kenyan study population (23% versus ≈5% in our population) might be the main reason for this discrepancy. Additionally, a significant increase in mean hemoglobin concentrations was observed in the IPTp group of our study population, indicating a similar but more modest effect. Interestingly, no beneficial effects on prevalence of maternal anemia have been reported for multigravid women in The Gambia.

The prevalence of premature birth and low birth weight were the main outcome measures for neonatal health in this study. A significant reduction of the prevalence of premature birth was observed in all analyses, most pronounced in the subgroup analysis for primi- and secundigravid women. IPTp was associated with a mean increase of gestational age at delivery of 1 week. Given that the number needed to treat to prevent premature birth of one newborn is 8 for this high-risk population, IPTp is a highly efficacious intervention in this setting.

Similarly, IPTp was associated with an increase of 56–172 g in mean birth weight in our study population. This effect led to a reduction of the prevalence of low birth weight, which was again most pronounced—and statistically significant—in primi- and secundigravid women. The number needed to treat for the prevention of low birth weight was 10 in this group. These findings are comparable to previous studies under well-controlled conditions reporting an increase of birth weight between 162 and 151 g in pauciparous women, whereas no effect was seen for multigravid women.

Previous studies in West and East Africa supported the implementation of IPTp in these regions. In our study, implementation of an IPTp as a national program to prevent malaria in pregnancy in Gabon was paralleled by a dramatic reduction of maternal \( P. falciparum \) prevalence. Markers of neonatal health were affected beneficially, particularly in primi- and secundigravid women. The impact on maternal health was more modest in our epidemiologic context. Based on these data, the implementation of IPTp is successful and justified in our study regions. Implementation of a national IPTp program paralleled by operational advances in the distribution of impregnated bed nets may therefore be sufficient for the prevention of malaria in pregnancy.

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Contributors: M. Ramharter developed the study protocol, oversaw the implementation of the trial, and contributed to data analysis and drafting of the manuscript. K. Schuster, M. Bouyou-Akotet, A. A. Adegnika, K. Schmits, S. Nzenze Afène, I. Ndombi Onnas, G. Mombò-Ngoma, S. T. Agnadji, and J. Nemeth assisted in the implementation of the study, in data management and data analysis, and critical review of the manuscript. S. Issifou, M. Kombila, and P. G. Kremsner contributed to study design, monitoring of the study, data analysis, and drafting of the manuscript.

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