Problem New WHO strategies for control of malaria in pregnancy (MiP) recommend intermittent preventive treatment (IPTp), bednet use and improved care management.

Approach A pilot MiP programme in Mozambique was designed to determine requirements for scale-up.

Local setting The Ministry of Health worked with a nongovernmental organization and an academic institution to establish and monitor a pilot programme in two impoverished malaria-endemic districts.

Relevant changes Implementing the pilot programme required provision of additional sulfadoxine-pyrimethamine (SP), materials for directly observed SP administration, bednets and a modified antenatal card. National-level formulary restrictions on SP needed to be waived. The original protocol required modification because imprecision in estimation of gestational age led to missed SP doses. Multiple incompatibilities with other health initiatives (including programmes for control of syphilis, anaemia and HIV) were discovered and overcome. Key outputs and impacts were measured; 92.5% of 7911 women received at least 1 dose of SP, with the mean number of SP doses received being 2.2. At the second antenatal visit, 13.5% of women used bednets. In subgroups (1167 for laboratory analyses; 2600 births), SP use was significantly associated with higher haemoglobin levels (10.9 g/dL if 3 doses, 10.3 if none), less malaria parasitaemia (prevalence 7.5% if 3 doses, 39.3% if none), and fewer low-birth-weight infants (7.3% if 3 doses, 12.5% if none).

Lessons learned National-level scale-up will require attention to staffing, supplies, bednet availability, drug policy, gestational-age estimation and harmonization of vertical initiatives.

Background The magnitude and burden of malaria infection during pregnancy (MiP) have been well documented.\(^1\),\(^2\)

The need for action has been recognized by WHO, which now recommends that sub-Saharan African countries with stable malaria transmission address MiP through intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) during pregnancy (IPTp), maternal use of insecticide-treated bednets (ITNs) and good case management of maternal malaria and anaemia.\(^3\),\(^4\)

Context In 2003, the Mozambican health ministry piloted an MiP programme containing all principal elements of the new WHO strategy to determine the best mechanisms for national-level scale-up.

The ministry designed and implemented the pilot programme with technical, logistical and financial assistance from two partner institutions: a nongovernmental organization (NGO) and an academic institution.

The ministry selected Nhamatanda and Gondola districts from 10 districts in Manica Province and 13 in Sofala Province, based on high malaria burdens (31–41 cases/100 persons/year, according to ministry estimates), low socioeconomic status (72–93% of population living in poverty)\(^5\) and accessibility. Within each district, the five health units (out of eight in Gondola, six in Nhamatanda) with the largest antenatal caseloads (30–400 new patients/month) were chosen. Between 80% and 90% of local pregnant women are thought to attend antenatal care.\(^6\) All women presenting for initial antenatal visits between October 2003 and June 2004 were invited to enrol in an observational study. Women who declined could still

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\(^3\) Ministry of Health, Maputo, Mozambique.
\(^4\) Health Alliance International, Chimoio, Mozambique.
\(^5\) Health Alliance International, Seattle, Washington, USA.
\(^6\) National Malaria Control Programme, Ministry of Health, Maputo, Mozambique.

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receive IPTp. Follow-up continued until July 2004.

The protocol for collection of patient and programme data was approved by the Mozambican National Bioethics Committee and the University of Washington; informed consent was procured from all participants.

Pilot protocol
Antenatal nurses explained IPTp and demonstrated bednet use at each clinic session. Because of high HIV prevalence, 3 preventive SP doses (directly observed by nurses) were recommended. Dose 1 could be given at 16 weeks or after quickening (contraindications: adverse reaction to SP or co-trimoxazole [CTX], last SP dose within 1 month, current CTX use). Subsequent doses were indicated at intervals of 1 month or more. SP was not co-administered with CTX due to concerns about toxicity and cross-resistance.

Nurse supervisors visited each site weekly to collect data, answer questions and solicit suggestions. The authors and nurse supervisors (who did not engage in direct patient care) also conducted quarterly semi-structured interviews with clinic staff at each site. Subsequent adjustments to the pilot programme were made after discussion with ministry officials.

Observed problems and solutions
The set-up process, regular supervisory visits and quarterly site meetings yielded information on pertinent operational issues.

SP availability
SP was Mozambique’s second-line antimalarial; first-level health units were not authorized to stock it. The national formulary declared SP to be contraindicated in pregnancy. Provincial stocks of SP were inadequate for IPTp. We obtained additional SP and formulary restrictions were waived.

Directly observed SP
Only two sites had water consistently. Most had few or no drinking cups. We provided reusable plastic cups, spoons, jugs, buckets, trays, basins and hand towels (mean cost US $144.30 per health unit).

Gestational age estimation
There were marked differences among clinics in the proportion of women given SP at the first visit (range 47.7–88.5%).

We redefined SP eligibility to include audible fetal heart tones, quickening or estimated gestational age of 16 weeks or more barring contraindications, and the proportion of women given SP during the first antenatal visit rose significantly; for example, from 47.7% to 71.6% (P = 0.005). Using our new criteria, 85.9% of women were eligible for SP at the first visit, versus 74.7% when using quickening as the only criterion.

Uncertainty about gestational ages seemed well-founded due to poor maternal recall of menstrual periods and the absence of pregnancy tests and ultrasound. The eventual date of delivery was more than 28 days different than the estimated date in 31.8% of liveborn singleton deliveries.

Programmatic incompatibilities
We encountered multiple actual or potential incompatibilities (Table 1) between MiP interventions and other health initiatives. Frequent absences and staffing changes mandated on-the-job IPTp training for four new nurses in three sites. Because the standard antenatal card was created before the introduction of IPTp, we created an addendum for recording of preventive SP doses, ITN use and medication allergies. We were unable to devise a system for informing antenatal clinics of antimalarial treatment given elsewhere.

ITNs were only available for purchase at three sites. Elsewhere, we worked with local shopkeepers to establish sales posts. Highly subsidized nets were unavailable. Clinic nurses reported that the most common reason for not using ITNs was cost. We supplied ITNs for all antepartum and postpartum units, and for patient education. We recommended that symptomatic malaria occurring less than 1 month after preventive SP be treated with quinine. We maintained this policy when Mozambique changed its first and second-line drugs to SP + amodiaquine and artemether-lumefantrine.

Impact and outputs
Following WHO guidelines, we measured proportions of women with severe anaemia (haemoglobin 7 g/dL or less) or peripheral parasitaemia and the proportion of low-birth-weight infants, each stratified by SP exposure. We also measured the proportion of women who received one, 2 or 3 doses of SP, and the proportion reporting bednet use on the night preceding the first or second antenatal visit.

Antenatal nurses recorded SP administration and self-reported bednet use at each visit. Data were available for 7911 women; they comprised 90.2% of the 8767 new prenatal patients the ministry recorded during the pilot period.

Overall, 92.5% of women received 1 dose or more of SP. Of the 4988 women who had completed their pregnancies or reached term before July 2004, 22.1% received 1 dose, 30.4% received 2 doses, and 43.6% received 3 doses (mean: 2.2 doses). Of women with at least three antenatal visits, 78.6% received all 3 doses. However, 47.6% had less than three visits (Fig. 1). Of the 591 women who received no SP, 527 (89.2%) had only one visit, and 56.6% presented too early to be eligible.

Most SP administration errors were of omission. Only 45 women (0.6%) received SP in spite of having no fetal movements and a gestational age of 15 weeks or less. Rarely (0.5% of women), 4 doses were given.

At the first and second antenatal visits, 4.5% and 13.5% of women reported having used nets the night before. Women first reported using bednets at a mean estimated gestational age of 25.8 weeks (95% confidence interval, CI: 25.4–26.2).

For logistical and financial reasons, impact data were available only for subsets of women. In April and May 2004, a cross-sectional study of maternal haemoglobin (measured by HemoCue) and peripheral parasitaemia (Giemsa-stained peripheral blood smears, asexual P. falciparum parasites counted against 500 leukocytes, readings confirmed by two microscopists) was conducted in the two health facilities with laboratories. Study participants presenting for antenatal care at those facilities during this period were eligible, and we collected haemoglobin and/or parasitaemia data on 1167 women.

The prevalence of severe anaemia (haemoglobin 7.0 g/dL or less) was 3.4% in women who had not yet received SP and 0.8% in women who had received 2 doses or more of SP (P = 0.036). Maternal peripheral malaria parasitaemia was present in 39.3% of women who had not yet received SP and 7.5% in...
Table 1. Operational interactions between IPTp and other antenatal care initiatives

<table>
<thead>
<tr>
<th>Health initiative</th>
<th>Problem</th>
<th>Solution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provision of ferrous sulfate to prevent maternal anaemia</td>
<td>Some nurses asked patients to schedule follow-up visits at 35-day intervals (instead of the usual 28 days) to avoid giving second and third SP doses at intervals of less than a full calendar month. Ferrous sulfate was repackaged in 30-tablet lots; the nurses repackaged it in 35-tablet lots.</td>
<td>Redefine the minimum interval between SP doses as 28 days, rather than 1 month.</td>
<td>—</td>
</tr>
<tr>
<td>Treatment of syphilis</td>
<td>Some clinics used the genital ulcer arm of an algorithm for syndromic treatment of STIs to guide treatment for asymptomatic pregnant women with positive serologic tests for syphilis, because the syndromic algorithm contained no arm for treatment of asymptomatic persons. Patients were treated with a 3-day course of CTX and 3 injections of penicillin.</td>
<td>Advise nurses to give the first dose of SP at the time of the second dose of penicillin (usually one week after first dose) to avoid concurrent therapy with SP and CTX.</td>
<td>We brought this issue to the attention of WHO and the health ministry’s reproductive health division. The STI algorithm was in the process of revision during the study period.</td>
</tr>
<tr>
<td>Prophylaxis of AIDS-related opportunistic infections</td>
<td>Elevated risk of adverse reactions in HIV-infected persons treated with both CTX and SP. Concern about elevated risk of SP resistance in persons taking preventive CTX. Redundancy of giving preventive SP to persons on preventive CTX, which also prevents malaria infection.</td>
<td>Because AIDS treatment was not yet available in the pilot districts, this problem did not materialize during the study period.</td>
<td>We defined daily CTX treatment as a contraindication to SP prophylaxis. New Mozambican antenatal cards will include space for recording daily CTX use.</td>
</tr>
<tr>
<td>Highly active antiretroviral treatment (HAART)</td>
<td>Elevated risk of myelosuppression in women receiving both zidovudine and SP. Risk of diagnostic confusion should a patient develop severe cutaneous adverse reactions or hepatotoxicity after receiving both SP and daily nevirapine.</td>
<td>Because AIDS treatment was not yet available in the pilot districts, this problem did not materialize during the study period.</td>
<td>The health ministry has defined HIV-positive persons as a high-priority group for receipt of subsidized ITNs. New Mozambican antenatal cards will include space for recording antiretroviral treatment. Discussions are continuing regarding ideal IPTp regimen for women on HAART, and mechanisms of collaboration between antenatal and HIV clinics.</td>
</tr>
<tr>
<td>Treatment of symptomatic malaria in pregnancy</td>
<td>First-line malaria regimen at end of study was SP and amodiaquine. Pregnant women with symptomatic malaria were often treated outside the antenatal clinic by clinicians who did not ask when the most recent dose of SP had been given.</td>
<td>Provincial health officials circulated a letter advising local clinicians to check antenatal card for date of most recent SP dose, and to proceed to third-line treatment (quinine) in women who had recently been given preventive SP.</td>
<td>Revision of Mozambican prenatal card is in progress, and will allow easier charting of SP doses. Future IPTp trainings will include local physicians and health technicians as well as antenatal nurses.</td>
</tr>
<tr>
<td>Management of pregnant women with seizures and/or coma</td>
<td>Local written guidelines called for immediate treatment for eclampsia or pre-eclampsia, with antimalarial treatment to be considered only if symptoms failed to resolve in 24 hours.</td>
<td>Our discussions with local physicians revealed that their practice was to treat for both malaria and pregnancy-induced hypertension because of the clinical difficulty of distinguishing between the syndromes.</td>
<td>Future IPTp guidelines may recommend urgent treatment for both malaria and pregnancy-induced hypertension in case of seizures or coma.</td>
</tr>
<tr>
<td>Recording and reporting</td>
<td>Abbreviation “SP” used to denote sulfadoxine-pyrimethamine by malaria programme and to denote “seropositive for HIV” by HIV/AIDS programme.</td>
<td>Common local practice is to call sulfadoxine-pyrimethamine by its common trade name, Fansidar.</td>
<td>Future revisions of antenatal card may or may not use SP abbreviation to record HIV serostatus. Discussions in progress.</td>
</tr>
</tbody>
</table>

CTX, co-trimoxazole; HAART, highly active antiretroviral therapy; IPTp, intermittent preventive treatment of malaria in pregnancy; ITN, insecticide-treated bednet; SP, sulfadoxine-pyrimethamine; STI, sexually transmitted infection.
women who had received all 3 doses ($P < 0.001$). Haemoglobin levels and parasitaemia prevalence are described by gravidity and SP use in Table 2. SP use was associated with significantly higher haemoglobin levels and lower parasitaemia prevalence even when stratified by parity. We have reported elsewhere that ITNs and SP appeared to contribute independently to the reduction of maternal malaria parasitaemia, and that SP appeared to be effective even in HIV-infected study participants.\textsuperscript{10}

Birth weight data were only available for pregnancies terminating in an institutional delivery by July 2004. We acquired birth weight data on 2529 liveborn singleton infants and 71 pairs of liveborn twins. Low birth weight was noted in 12.5% of liveborn singleton infants delivered by women who had received no SP and 7.3% in women who had received 3 doses ($P = 0.019$ for trend; data not shown). A similar but non-significant pattern was observed in twins.

**Discussion**

In this pilot IPTp programme, antenatal nurses successfully administered at least 1 dose of preventive SP to over 90% of women. Although this level of performance is substantially higher than that reported elsewhere\textsuperscript{11–12} fewer than half (43.6%) received the full 3-dose course, largely because of infrequent antenatal attendance. Adjusting for antenatal care utilization patterns, the estimated population-level coverage of the full 3-dose regimen was 37.6%. Had we not revised our criteria for SP eligibility, our coverage would have been even lower.

Promotion of ITNs was far less successful than SP prophylaxis, apparently because local prices exceeded purchasing power. This, like our difficulties with drinking water and cups, is consistent with other reports.\textsuperscript{13–15}

Statistically significant associations between reported SP administration and three indicators of impact suggest that the pilot data accurately reflect actual clinical practice, that the reduction in adverse outcomes was unlikely to be caused by chance and that local *Plasmodium falciparum* resistance to SP had not yet rendered SP-based IPTp ineffective.\textsuperscript{16} Our maternal parasitaemia data also confirmed the health ministry’s indirect evidence that MiP was highly prevalent in the pilot region.

We believe that Mozambique’s approach was unique because of the attention given to real or potential conflicts between MiP-related interventions and other vertical initiatives affecting pregnant women, and because of its attention to the effect of imprecise gestational age estimation on SP uptake.

The difficulties encountered with SP supply, materials for directly observed SP administration, staff turnover, bednet availability and pricing, gestational age estimation and incompatibilities with other health initiatives are unlikely to be unique to Mozambique. However, details are likely to vary substantially by site, thus limiting generalizability of our findings.

The observed level of success would not have been possible without the intensive support of the study supervisors, funds with which to complement the core health ministry budget and the enthusiastic participation of health authorities at all levels. These conditions may not be replicable elsewhere. Measurement of output and impact indicators was particularly labour-intensive. However, lessons learned from the pilot should enable scale-up to occur with less intensive supervision and support than was required for the pilot programme.

**Lessons learned**

The pilot IPTp programme merits replication at the national level in Mozambique. Mozambique’s modifications of standard WHO protocols (e.g. definition of contraindications to SP, redefinition of eligibility criteria for first dose) should be preserved. Pilot programme procedures for estimating SP need, providing materials for directly observed SP and expanding the antenatal card should be adopted nationally. Increased communication and cooperation among stakeholders will be required to eliminate programmatic incompatibilities. Attention to the provision of ferrous sulfate, folic acid and/or multivitamins, with particular attention to HIV-infected women, should also be enhanced.\textsuperscript{17,18} Donor support may be required for population-level provision of ITNs. The support of the scientific community will be required for pharmacovigilance, monitoring of long-term effectiveness of SP, definition of safe and effective alternatives to SP (including acquisition of data on pharmacodynamics of antimalarials in pregnant women with and without HIV infection, including those on antiretroviral therapy), and malaria-related operations research.\textsuperscript{19–21} Frequent supportive supervision at the health-clinic level is indispensable in our experience.

With adequate political will, however, we believe that all of this is feasible, even in the resource-constrained setting we describe. Indeed, in the aftermath of this pilot programme, IPTp was successfully implemented throughout Sofala and Manica provinces based on the lessons we have learned and described.
Table 2. Maternal peripheral malaria parasitaemia and maternal haemoglobin levels in cross-sectional evaluation

<table>
<thead>
<tr>
<th></th>
<th>All women (n = 1167)</th>
<th>Primigravidae (n = 269)</th>
<th>Secundigravidae (n = 203)</th>
<th>Gravida ≥ 3 (n = 696)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All levels of SP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of SP doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n = 712)</td>
<td>10.5 (10.4–10.6)</td>
<td>10.1 (9.9–10.3)</td>
<td>10.7 (10.5–10.9)</td>
<td>10.6 (10.4–10.7)</td>
</tr>
<tr>
<td>1 (n = 214)</td>
<td>10.6 (10.4–10.8)</td>
<td>10.2 (9.7–10.2)</td>
<td>10.6 (10.3–10.9)</td>
<td>10.4 (10.2–10.6)</td>
</tr>
<tr>
<td>2 (n = 175)</td>
<td>10.8 (10.6–11.0)</td>
<td>10.5 (10.0–11.0)</td>
<td>10.7 (10.0–11.3)</td>
<td>10.8 (10.5–11.0)</td>
</tr>
<tr>
<td>3 (n = 66)</td>
<td>10.9 (10.5–11.2)</td>
<td>11.0 (9.9–12.1)</td>
<td>10.9 (10.2–11.6)</td>
<td>10.8 (10.4–11.3)</td>
</tr>
<tr>
<td>P-value (linear regression)</td>
<td>&lt; 0.001</td>
<td>0.009</td>
<td>0.173</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All women (n = 1078)</th>
<th>Primigravidae (n = 248)</th>
<th>Secundigravidae (n = 188)</th>
<th>Gravida ≥ 3 (n = 641)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All levels of SP exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of SP doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n = 649)</td>
<td>277 (25.7%)</td>
<td>106 (42.7%)</td>
<td>58 (30.9%)</td>
<td>113 (17.6%)</td>
</tr>
<tr>
<td>1 (n = 199)</td>
<td>255 (39.3%)</td>
<td>99 (63.1%)</td>
<td>52 (43.7%)</td>
<td>104 (28.0%)</td>
</tr>
<tr>
<td>2 (n = 163)</td>
<td>10 (5.0%)</td>
<td>4 (9.3%)</td>
<td>3 (9.4%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>3 (n = 67)</td>
<td>5 (7.5%)</td>
<td>1 (7.7%)</td>
<td>2 (12.5%)</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>P-value (χ²)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Cl, confidence interval; SP, sulfadoxine-pyrimethamine.

Acknowledgments
This project was supported under a cooperative agreement from the US Centers for Disease Control and Prevention through the Association of Schools of Public Health (Grant Number U36/CCU300430–20). We also received financial and/or technical support from Health Alliance International, Population Services International in Mozambique, WHO in Mozambique and the African Region, and the United Nations Children’s Fund in Mozambique. We are grateful to the study nurses and participants, the Provincial Health Directorates of Sofala and Manica provinces, and the District Health Directorates of Nhamatanda and Gondola for their enthusiastic participation. The contributions of study supervisors Fernanda Toulha and Maria Felicidade Faria and of bednet coordinator Fungai Chimbe Chinhacata were indispensable.

Competing interests: None declared.

Résumé
Traitement préventif intermittent contre le paludisme des femmes enceintes dans le centre du Mozambique

Problématique Les nouvelles stratégies de l’OMS pour la lutte contre le paludisme pendant la grossesse préconisent un traitement antipaludique préventif intermittent, l’utilisation de moustiquaires de lit et une amélioration de la prise en charge des cas.

Démarche Un programme pilote pour la Mozambique de lutte contre le paludisme pendant la grossesse a été conçu pour déterminer les besoins liés au passage à l’échelle supérieure.

Contexte local Le ministère de la santé a collaboré avec une organisation non gouvernementale et un établissement d’enseignement supérieur dans la mise au point et le suivi d’un programme pilote appliqué dans deux districts appauvris d’endémie du paludisme.

Modifications pertinentes Pour la mise en œuvre du programme pilote, il a fallu fournir une quantité supplémentaire de sulfadoxine-pyriméthamine (SP), du matériel pour l’administration sous surveillance directe de ce médicament et des moustiquaires. Il a également fallu modifier la fiche anténatale et obtenir une dérogation au guide national de prescription concernant la SP. Le protocole de départ a dû être modifié car l’imprécision dans l’évaluation de l’âge gestationnel conduisait à une prise incomplète des doses de SP. Plusieurs incompatibilités avec d’autres initiatives sanitaires (y compris les programmes de lutte contre la syphilis, l’anémie et le VIH) ont été découvertes et surmontées. Les principaux résultats et effets ont été mesurés : 92,5 % des 7911 femmes enceintes ont reçu au moins une dose de SP, le nombre moyen de doses de SP reçues étant de 2,2. Lors de la deuxième visite anténatale, 13,5 % des femmes utilisaient une moustiquaire de lit. Parmi les sous-groupes (1167 personnes pour les analyses en laboratoire, 2600 naissances), on a relevé une association significative entre l’utilisation de SP et une élévation du taux d’hémoglobine (10,9 g/dl pour la prise de 3 doses de SP contre 10,3 g/dl en l’absence de toute dose de SP), une baisse de la prévalence des parasites du paludisme (7,5 % pour la prise de 3 doses contre 39,3 % en l’absence de toute prise de SP) et une baisse de la proportion d’enfants de petit poids à la naissance (7,3 % pour la prise de 3 doses contre 12,5 % en cas l’absence de toute prise de SP).
Enseñanzas extraídas
Para extender masivamente las medidas de control a nivel nacional habrá que prestar atención al personal necesario, los suministros, la disponibilidad de mosquiteros, la política farmacéutica, la estimación de la edad gestacional y la armonización de las iniciativas verticales.

Enseñanzas extraídas
Para extender masivamente las medidas de control a nivel nacional habrá que prestar atención al personal necesario, los suministros, la disponibilidad de mosquiteros, la política farmacéutica, la estimación de la edad gestacional y la armonización de las iniciativas verticales.

References