Title:

Evaluation of the use of sulfadoxine-pyrimethamine (SP) intermittent treatment (IPT) to prevent malaria during pregnancy in Ndola, Zambia.

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own work and that I have not previously submitted it to any other university for degree purpose.

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ABSTRACT

Background: Malaria in pregnancy is associated with many negative outcomes on the pregnant woman, the fetus and the neonate. Intermittent Preventive Treatment during pregnancy (IPTp) using Sulfadoxine-Pyrimethamine (SP) is one of the main strategies used to prevent malaria in this vulnerable group in conjunction with use of Insecticide Treated mosquito Nets (ITN) and Indoor Residual Spray (IRS). The aim of this study was to evaluate the effectiveness of these strategies on the prevalence of the disease in pregnant women, five years after their implementation in Zambia. If possible to make recommendations on how prevention can be improved.

Methods: A questionnaire on socio-demographic information, history of malaria during the current pregnancy (any anti-malaria treatment) and malaria prevention strategy used (ITN and repellent use) was administered to 450 consecutive patients. Information was collected from the antenatal cards on the last menstrual period, date at which each dose of IPTp was taken, gravidity, and Human Immuno-deficiency Virus (HIV) status. A blood slide to assess parasitaemia was collected from each woman when they attended the labour ward.

Results: 2.4% of participants had a positive parasitemia. All the participants took at least one dose of SP/IPTp with 87.6% completing the stipulated three doses. The mean gestational age for each dose were 22.1 (SD 4.6), 29.1 (SD 4.4) and 34.4 (SD 3.9) weeks for the first, second and third doses respectively. The Insecticide Treated Nets (ITN) ownership percentage was 79.5% and the ITN regular utilization rate 74.1%.

Conclusion: We found that the prevalence of malaria in pregnancy in Ndola is remarkably low due to the implementation of different preventives strategies under the Roll Back Malaria (RBM) initiative.
A considerable proportion of pregnant women received the three recommended doses, though the timing of delivery of each dose needs to be improved. The study also showed that the ownership rate of ITNs was high, but that the utilization rate still needs to be increased. Ministry of Health should continue supporting and encouraging the implementation of these strategies as they are certainly impacting positively on the reduction of malaria burden on the pregnant women.

INTRODUCTION AND BACKGROUND

Malaria infection due to *Plasmodium falciparum* still causes significant morbidity and mortality in countries with limited resources situated in endemic zones. It is still a global health problem with most of the disease burden carried by children less than five years of age and pregnant women (1). Although there are four species causing malaria, most of the adverse effects are due to *Plasmodium falciparum* species (1-3). It is estimated that up to 90% of global cases of malaria occur in sub-Saharan Africa (1, 2).

In pregnancy, malaria poses a risk to the mother, the fetus and the neonate. In areas of stable malaria where adult women have considerable acquired immunity, *P. falciparum* infection during pregnancy does not typically develop into a symptomatic febrile disease, but rather leads to maternal anemia and placental malaria infection, particularly in the primigravidae and the secudigravidae (1,4). On the other hand, pregnant women who are HIV positive are particularly vulnerable to malaria (5-8).

Malaria due to *P. falciparum* is associated with an increased risk of prematurity, maternal anaemia and mortality; the placental malaria in turn leads to cord anemia, intrauterine growth retardation, low birth weight (LBW) and possibly intrauterine death. Neonatal malaria is also possible and leads to an increased risk of infant mortality (1, 9,10). In view of the above, measures are taken to prevent malaria in pregnancy to detect it early and provide efficacious treatment of the infection once it has occurred.

Zambia is a southern African country where malaria is endemic and still constitutes a major public health problem. The Zambian government has malaria control as one of its priorities, as demonstrated in the National Health Strategic Plan 2006-2010 (11). It is estimated that in Zambia 3.4 million cases of malaria occur every year, translating into 308 infections/1000 persons/year and that Sulfadoxine/Pyrimethamine(SP) total treatment failure has risen from 14.5% in 2003 to 37.0% in 2004 (5). The HIV infection prevalence in Zambia, is 16.0% among adults aged 15-49 years, while among pregnant women attending ANC settings, this prevalence is 19.0% (12).

Efforts to control malaria in Zambia are currently being scaled up and coordinated under the Roll Back Malaria (RBM) initiative. Under this initiative, the Zambian government, in collaboration with other partners, has come up with four strategies: use of Insecticide Treated mosquito Nets (ITN), Indoor Residual Spray (IRS) in all the houses, the use of Intermittent Preventive Treatment of malaria in pregnancy (IPTp), and prompt effective case management.

The IPTp was introduced in 2003 and requires three doses of Sulfadoxine/Pyrimethamine(SP) combination or ***Fansidar™*** that are given to the pregnant women at gestational ages of 16, 20 and 24 weeks, during their Ante Natal Care (ANC) visits (13). Though studies elsewhere advise monthly SP for HIV positive pregnant women (14, 15); a 2007 study, conducted in Zambia at the

Tropical Diseases Research Centre (TDRC), concluded that in zones of mesoendemic malaria transmission, monthly SP/ IPTp, was not more efficacious than the standard 2-dose regimen in HIV positive women for prevention of placental malaria or adverse birth outcomes; and that policy in other countries should take into consideration local malaria transmission patterns and local HIV prevalence (5).

On the other hand a review to evaluate toxicity of SP (including cutaneous reactions, teratogenicity, and alterations in the bilirubin metabolism) showed that, despite folate antagonist use in the first trimester being associated with neural tube defects, large case-control studies had demonstrated that, if SP is exclusively administered in the second and third trimesters of pregnancy (after organogenesis) as IPT, it does not result in an increased risk of teratogenesis (16). Nonetheless due to redundant mechanisms of action and synergistic worsening of side effects, it is not advised to use SP concomitantly with cotrimoxazole (16). The implication of this is crucial for HIV positive women who are on co-trimoxazole prophylaxis. Folic acid is also recommended in all pregnant women to reduce the rate of congenital abnormalities, but a high dose of it may compromise the preventive action of SP. Fortunately at the recommended standard dose of folic acid (5 mg/day) there is no effect on SP efficacy. The review also concluded that there was no clinical association between use of SP/IPT and kernicterus (16).

At the ANC visits, ITNs are also distributed at a very subsidized price and health talks about the effects of malaria on pregnancy are conducted. The IRS is provided through the District Health Management Teams (DHMT), and should ideally reach every home.

The Ministry of Health recommends that a pregnant woman, who has been diagnosed with malaria, be treated only with Quinine in the first trimester or if the malaria is severe. In the second and third trimesters, SP can be prescribed. The treatment should be commenced within 24 hours of the onset of symptoms (11, 13).

Rationale for the study:

Taking into consideration the fact that Zambia is an endemic zone of malaria, the ***Fansidar™*** (SP) resistance pattern in this area and the level of HIV prevalence amongst pregnant women; we set out in this study to evaluate the impact of different strategies employed under the RBM initiative. The information gathered will help to assess the effectiveness of the program in preventing malaria amongst pregnant women five years after its implementation.

AIM AND OBJECTIVES

The aim of this study was to evaluate the effectiveness of strategies employed to prevent malaria in pregnant women, under the RBM initiative on the prevalence of malaria in pregnancy (five

years after its introduction in Ndola, Zambia) and if possible to make recommendations on how prevention can be improved.

The objectives were:

- To determine the proportion of pregnant women who access and complete the recommended three dose course of SP/IPTp
- To determine the gestational age at which each dose of IPTp is taken
- To determine the prevalence of maternal parasitemia in pregnant women taking SP/IPTp
- To determine the proportion of pregnant women who regularly sleep under ITN and use other preventative measures
- To determine what type of medication is prescribed to pregnant women when they contract malaria.

METHODS

A cross sectional study aimed at evaluating the impact of the RBM prevention strategy on the prevalence of malaria in pregnancy within the labour ward.

Settings: The study was conducted in three health clinics in the suburb of Ndola (Masala clinic, Lubuto clinic and Chipokota-Mayamba clinic) between January 2009 and April 2009. Ndola is one of the urban centers in the copperbelt province of Zambia, in southern Africa. These three clinics provide health care to approximately 96,000 people. In all these clinics, the strategies of malaria prevention in pregnancy follow the national programme of sleeping under an ITN, receiving three doses of SP/IPT and yearly Indoor Residual Spraying (IRS) with pyrethroids and dichlorodiphenyltrichloroethane (DDT); which is done by the Ndola District Health Management Team.

Sample size: Taking into consideration that in the chosen three clinics, the average combined number of deliveries is 7,000 per annum and expecting a malaria prevalence at delivery of 13.6% without SP/IPT and 6.3% after SP/IPT as in *Challis et al.*'study,2004 (17), a minimum sample size of 350 was calculated using Cochrane's cross-section survey sample size calculation.

Enrollment: The participants were enrolled consecutively as they came to the labour ward- If they had given informed consent, were at least 28 weeks pregnant and 18 years or older. We excluded those with a history of splenectomy, sickle cell disease, allergy to Sulfadoxine and/or Pyrimethamine and those who came to the labour ward without the antenatal card. Enrollment was stopped once 450 patients had consented.

Questionnaire procedures: Enrolled women were administered a questionnaire by the local midwife to collect socio-demographic information, history of malaria during the current pregnancy, any anti-malaria treatment, and malaria prevention strategy used (commercial insecticide and repellent use). From the Ante Natal Cards (ANC), we collected information on the Last Menstrual Period (LMP), date at which each dose of IPTp was taken, gravidity, and HIV status.

Laboratory procedures: A drop of blood was collected using a finger prick sample, a blood slide was prepared and air dried. The slides were stained with Giemsa stain, then examined at the Tropical Disease Research Centre twice a week by one laboratory technician. The number of parasites per 200 white blood cells determined the parasite count; and a slide was only considered negative after 100 oil- immersion fields were examined and no parasite found.

Ethical considerations: The study was approved by the Committee of Human Research, Stellenbosch University in South Africa and the Ethics Committee, Tropical Disease Research Centre in Zambia. Individual written informed consent was obtained from every participating woman. The questionnaire was explained to the participants, either in English or in Bemba (local language). The purpose of the study and possible risks and benefits were explained. Participants' information was linked to a code number in order to maintain confidentiality and privacy.

RESULTS

We enrolled 450 women, divided into 150 from each of the three clinics, and their characteristics are shown in Table 1. Out of the 450 participants, 11 (2.4%) blood slides tested positive for malaria parasite and 439 (97.6%) negative.

Table 1: Characteristics of enrolled women

Characteristics	n	%
Marital status	**450**	
single	20	4.4
married	430	95.6
Gravidity	**445**	
primigravidae and secundigravidae	122	27.4
multigravidae (3 or more)	323	72.6
Education level	**443**	
primary school (grades 1-7)	153	34.5
secondary school (grades 8-12)	281	63.4
tertiary school (college or university)	9	2.0
HIV status	**445**	
positive	89	20.0
negative	356	80.0

IPT	**450**	
no	0	0.0
yes (any dose)	450	100.0
one dose	4	0.9
two doses	52	11.6
three doses	394	87.6
ITN use	**448**	
no	92	20.5
yes	356	79.5
regularly (4 or more times per week)	332	93.3
occasionally (2-3 times per week)	16	4.5
seldom (once or less per week)	8	2.2
Insecticide use	**448**	
no	343	76.6
yes	105	23.4
regularly (4 or more times per week)	35	33.3
occasionally (2-3 times per week)	33	31.4
seldom (once or less per week)	37	35.2
Repellents use	**448**	
no	443	98.9
yes	5	1.1
regularly (4 or more times per week)	0	0.0
occasionally (2-3 times per week)	3	60.0
seldom (once or less per week)	2	40.0
Blood slide results	**450**	
positive	11	2.4
negative	439	97.6

IPT= Intermittent Preventive Treatment , ITN = Insecticide Treated mosquito Net .

Out of 450 participants, 430 (95.6%) were married and 443 (98.4%) had some form of education with 281 (63.4%) of these having been in a secondary school, while 153 (34.5%) had only primary school level education and 9 (2.0%) had some form of tertiary education.

Information about the gravidity of five participants was missing, of the 445 for whom information was collected, 122 (27.4%) were either primigravidae or secundigravidae. This represents the group of pregnant women who are at a higher risk for adverse outcomes.

Out of the 445 participants who accepted to reveal their HIV status, 89 (20.0%) were HIV positive. And out of these 15 (16.9%) were either primigravidae or secundigravidae. This means that fifteen women out of the 445 were both, HIV positive and either primigravidae or secundigravidae, representing 3.4%.

All of the 450 participants had taken at least one dose of SP/IPTp (100.0%), and 394 (87.6%) had completed all three doses. Of the remaining 56 (12.4%), who did not complete, only four (0.9%) took a single dose. This means that 99.1% of participants took two or three doses of IPT.

The corresponding gestational ages at which sequential doses of IPTp were taken, are shown in Figure 1, 2 and 3. The mean gestational age for each dose were 22.1 (SD 4.6), 29.1 (SD 4.4) and 34.4 (SD 3.9) weeks for the first, second and third doses respectively.

We had only18 participants (4.1%) taking the first dose at 16 weeks, 3 (0.7%) taking the second dose at 20 weeks and 1(0.3%) taking the third dose at 24 weeks, as recommended in the national guidelines. In addition, 14.9% of the women who completed their three doses of IPT received their last dose after 38 weeks of gestation.

Figure 1: Gestational age at the time of taking first dose of IPTp

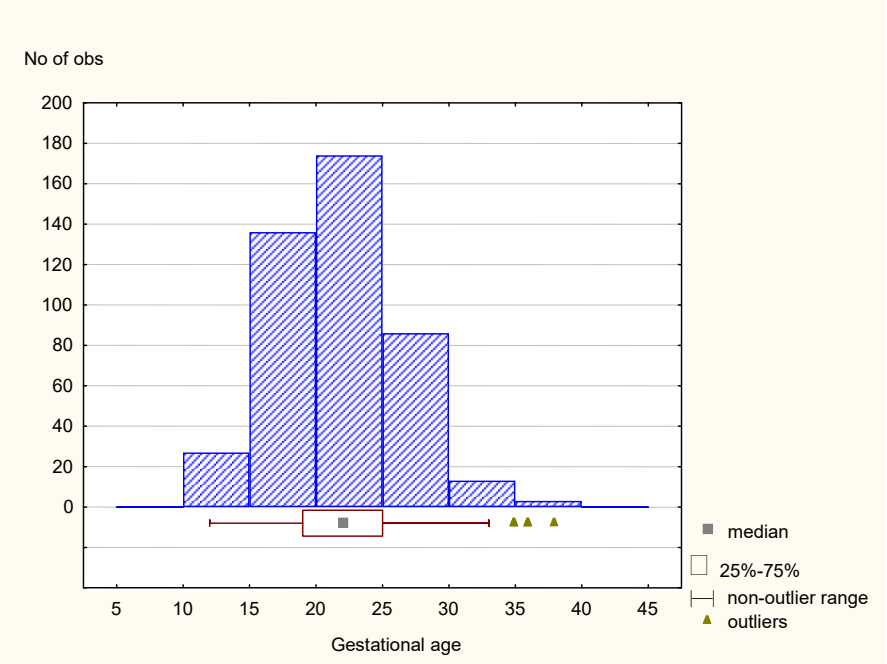


Figure 2: Gestational age at the time of taking second dose of IPTp

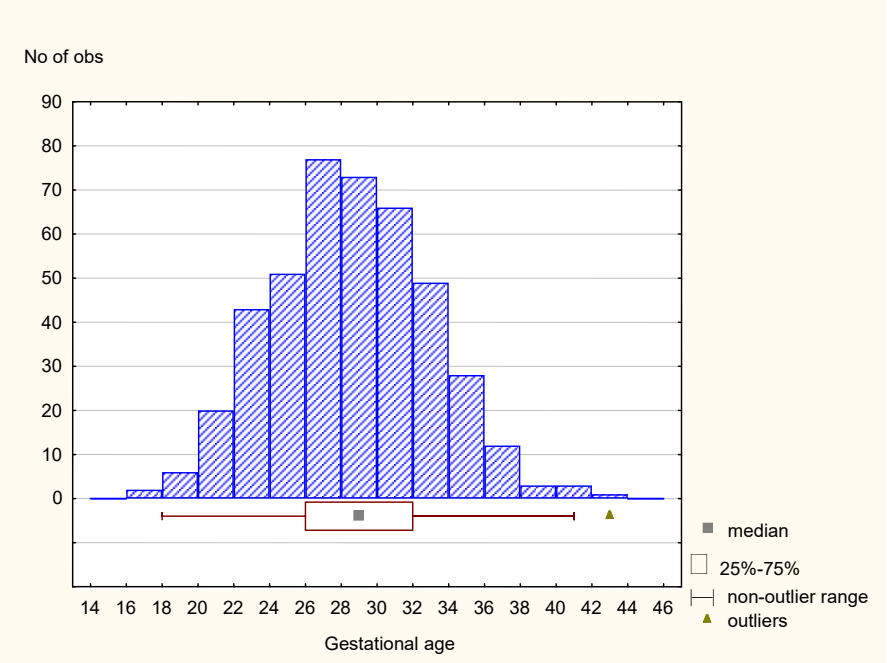
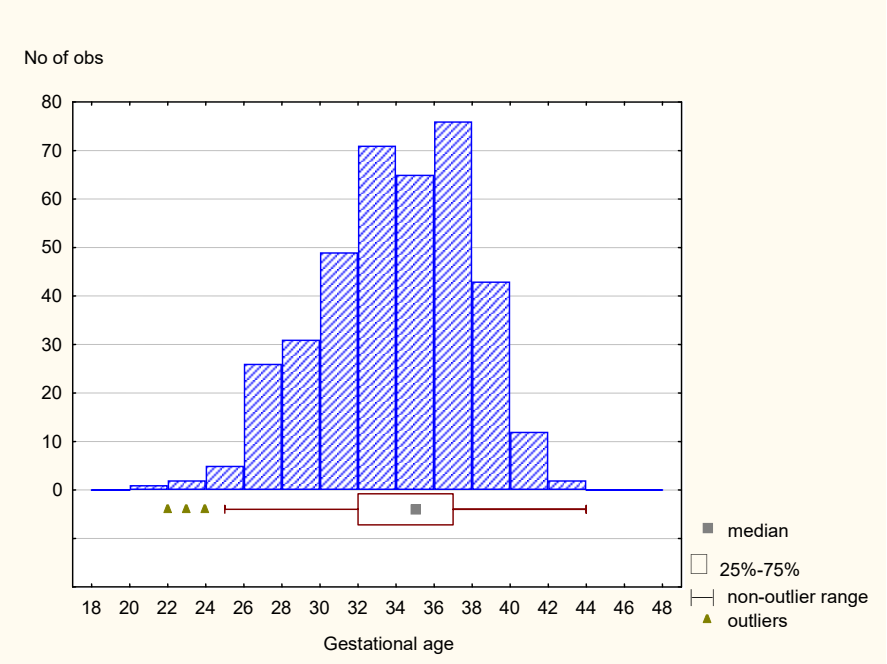


Figure 3: Gestational age at the time of taking third dose of IPTp



We had 448 participants who owned an Insecticide Treated Mosquito Net, but of these only 356 (79.5%) actually used it. This translates into 79.1% of all participants using ITN. The results also show that 332 women (73.8%) used their ITN regularly (4 times a week or more).

Collected information about use of commercial insecticide spray showed that 105 participants (23.4 %) had used it. Only 35 (7.8%) used it regularly, this means that the majority of our participants (92.3%), either use it occasionally or do not use it at all. More importantly, 76 (72.4%) women out of the 105 still used ITN regularly. Only five participants (1.1%) applied any mosquito repellents.

Although only 2.4% of women were positive for malaria when tested (Table 1), 15.8% reported that they had had malaria during their pregnancy and received treatment, as shown in Table 2.

Table 2: Self reported malaria and treatment received.

Variable	n	%
Malaria	**448**	
no	377	84.2
yes	71	15.8
Curative medication received	**71**	
Artemisinin	1	1.4
SP	44	62.0
Quinine	26	36.6

Almost two third (62.0%) of women who suffered from malaria, were treated with Sulfadoxine/Pyrimethamine (SP), while only a third (36.6%) received quinine.

DISCUSSION

The primary objective was to determine the proportion of pregnant women who accessed and completed the recommended three dose course of SP/IPT and those who regularly slept under an ITN and relate them to the prevalence of malaria during pregnancy. We found that the prevalence of malaria in pregnant women in the labour ward was 2.4%. This is significantly lower than the 6.3% that Challis et al found in Mozambique (17). The difference in the results of these two studies can be explained by the fact that in the Zambian situation, many other strategies are implemented under the Roll Back Malaria (RBM) initiative; such as Indoor Residual Spraying (IRS) and ITN, as part of the Integrated Vector Control Programme in conjunction with a prompt treatment of infected individuals. This results in a reduction of the number of infective bites.

Although we found 15.8% of participants reported having suffered from malaria during their current pregnancy, many people, suffering from any febrile illness in an endemic region like

Zambia, would call it malaria and a large number will self medicate. In addition, most pregnant women who present at their local clinic with fever are likely to be told that they are suffering from malaria and receive treatment with anti-malaria medication. Many healthcare workers still prescribe anti-malarial treatment even when the malaria test is negative (18). Nonetheless, this percentage is particularly close to the 15.7% malaria parasitemia found in Burkina Faso (4). In this case, the study was done in a more rural area, and the prevention strategy did not include regular Indoor Residual Spray and the IPTp progamme had only been running for one year. On the other hand, the fact that malaria in pregnancy is usually asymptomatic means that many pregnant women with no fever do not seek medical advice even if they may have malaria. The true prevalence of malaria in pregnancy therefore can only be better assessed through placental biopsy.

Although the levels of total treatment resistance to SP have increased over the past few years, it seems that its effectiveness as an intermittent preventive treatment is still high. This was also demonstrated in a systematic review (14). It is also possible that the use of SP/IPT as an integrated part of a larger strategy including other measures, such as ITN, increases the effectiveness.

The Ministry of Health and the World Health Organization (WHO) recommend Quinine as the drug of choice during the first trimester and in severe malaria in pregnancy, while *Fansidar™* (SP) can be prescribed in the second and third trimesters (1,13). We can only assume that the two-thirds (62.0%) of those who reported malaria and were treated with SP, had malaria after the first trimester and that the third (36.6 %) who received Quinine, developed malaria in the first trimester. However, with the current SP resistance level in Zambia (19), cost-effectiveness studies should be conducted with the view of prescribing Quinine throughout pregnancy as the drug of choice. WHO actually recommend that in areas of combined resistance to Chloroquine and SP, Quinine should be the first line drug even in second and third trimester (1). In addition, studies should be done locally, to assess the possible utilization of Artemisinin and Artemisinin Combination Therapies (ACT). Currently Zambia does not recommend prescription of ACT during pregnancy as there is no evidence base to show its safety in pregnancy. There is emerging data showing that Artesunate and ACT are safe and efficacious in pregnancy (20).

Out of the 11 women who had a positive slide, 5 were HIV positive, representing 45.5% of the positive slides. Of the 89 HIV positive participants, these 5 represent a 5.6% prevalence amongst this sub group. This is more than double the overall prevalence of 2.4%. Despite the fact that 11 positive slides is a small number, this supports earlier findings that HIV + pregnant women are more prone to malaria then HIV negative women.

We found that all the participants (100.0%) had at least one dose of IPTp and that 87.6% had the recommended three doses. This is a very encouraging finding, which falls within the goal of the

Ministry of Health (MoH) of Zambia to insure access to IPT for at least 80% of women by December 2008, as stated in the National Health Strategic Plan 2006-2010. This is also an improvement from the findings of the Zambia National Malaria Survey of 2006, which recorded 85.9% of women in urban Zambia accessing any IPTp and only 71.2% accessing the three recommended doses.

However, the timing at which the different doses of SP are delivered proved to be contrary to the recommended 16, 20 and 24 weeks of gestational age, for respectively first, second and third doses of IPTp. On average the first dose was received 6 weeks later than recommended, the second dose was 7 weeks after the first, and the third dose five weeks after the second; instead of the recommended four week interval. This late delivery certainly increases the time that pregnant women spend at risk. In addition, there are suggestions that the late delivery of the first dose of IPTp could be related to the subsequent late delivery of the other following doses, or lead to an incomplete IPTp schedule (21). Infection in early or late pregnancy has been associated with more negative effects on the pregnancy outcome (22) and this fact should advocate more in favor of giving the first dose of IPTp on time.

We found that 79.5% of participants owned an ITN and that 93.3% of these, representing 74.1% of participants used the ITN regularly. This achievement is not far below the target of 80% pregnant women accessing ITN by December 2008, as stated in the National Health Strategic Plan 2006-2010 (11). Though the document is silent about the target concerning the use of these nets, we would want to believe that the spirit of the document was to achieve a comparable target in terms of use of the ITN (80%). This will mean that the current utilization rate (74.1%) is well below the expected. Nonetheless, there has been tremendous improvement when compared to 18% of urban women who slept under an ITN in 2006 (23).

The fact that 72.4% of the participants who used commercial insecticide spray in their homes, still kept on sleeping under their ITN, shows that a good proportion of the population (23.4%), sees these commercial insecticides as complementary to ITN, and not as a substitute. We believe that studies should be conducted to determine the safety in pregnancy, for different compounds found in Zambia.

On the other hand, only five participants (1.1%) applied commercial repellents and none of them regularly. It implies that application of insect repellent ointments or lotion is not a practice that is commonly embraced by the population. However there is evidence to show that insect repellent in addition to ITN, provides greater protection, especially in areas were mosquitoes feed in early evening, between dusk and bedtime (24). In countries with restricted economic power, this might not be a very cost-effective programme, but one which is particularly advocated for tourists and those who can afford it. However, more studies are needed to clarify their safety profile in pregnancy.

There are some limitations in this study, mostly related to the fact that we only included women who came to deliver in the clinics. These women are likely to have frequented the same clinics for their ANC visits and are likely to have been educated about the risk factors related to pregnancy in general and malaria in particular. Therefore they are likely to have received the IPTp and ITN and are also more likely to report that they slept regularly under their ITN. The results therefore for the whole community of pregnant women, which includes those giving birth at home, those not attending the clinic and those in rural areas, are likely to be worse.
The other limitation is that the records in some participants did not specify the exact date at which the pregnant woman took the different doses of IPT.

RECOMMENDATIONS

- Though only 2.4% had positive blood slides in labor ward; the fact that 15.8% self reported malaria during pregnancy, should prevent any complacency and encourage us to step up efforts in the integration of all the available preventive measures. It is important that diagnostic equipment is readily available to allow healthcare workers to, promptly and effectively, treat patients within the prescribed 24 hours period of symptoms onset.

- There is a need to improve the gestational age at which the first dose of IPT is delivered, as well as the follow up doses, which are supposed to be every four weeks after the first dose has been administered. In addition, globally, the public health benefits of SP/ IPT are said to be reducing due to SP resistance and therefore alternative drugs may have to be found. Some approaches using Amodiaquine alone or in combination with SP, and Azithromicine combined with Chloroquine have been tested with encouraging results (25, 26). Further studies are required to evaluate these alternatives.

- Although the RBM initiative reached its goal of ensuring access to ITN, for at least 80% of women by December 2008; the utilization rate of these ITN still needs to be improved, ideally to 100% as objected in the National Malaria Control Plan 2009 (18). The overall goal of the Ministry of Health, to have a malaria free Zambia, dovetails with this strategy as well. Populations still need more education about the use of ITN and healthcare seeking behavior.

- The correct treatment of malaria in pregnancy as well as the risks of over prescription of anti-malaria drugs needs to be emphasized to healthcare workers, during continuing medical education sessions.

- More research needs to be conducted to evaluate the situation in rural areas and amongst those women who give birth at home with the help of traditional birth attendants.

CONCLUSION

The 2.4% positive parasitemia is certainly very encouraging, but should only be seen as an indicator of prevalence at the end of pregnancy during labour and does not represent the overall prevalence of malaria in pregnancy, which should be assessed by placental biopsy. The self reported malaria treatment during pregnancy of 15.8%, which shows that the prevalence is probably higher, and should serve as a call for a more improved and integrated strategy. There is a need for more educational messages to pregnant women about the dangers of malaria, the emphasis on taking IPT on time and always sleeping under ITN, especially if one is HIV positive.

The Ministry of Health should continue supporting, encouraging and reinforcing the implementation of these strategies as they are impacting positively on the reduction of malaria burden in pregnant women.

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