

## Review Article

Indian J Med Res 128, September 2008, pp 246-253

# Control measures for malaria in pregnancy in India

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Received September 7, 2007

**The purpose of this paper is to examine the current status of malaria in pregnancy (MiP) in India and review current control measures, programmes and interventions that work, and to suggest areas that need to be addressed. MiP can have serious health consequences for both the mother and infant, and thus presents a major public health challenge. Roll Back Malaria (RBM), a supporting agency of the World Health Organization (WHO), recommends reducing the burden of MiP through the following control measures: insecticide treated nets (ITNs), intermittent preventive therapy (IPTp), and effective case management. Even though India has a comprehensive national malaria programme, specific control measures aimed at decreasing the burden of MiP are limited in availability or are not adequately available. Components of the national malaria programme, which may serve to alleviate the MiP burden include the integration of malaria control with general health services and use of indoor residual spraying (IRS). These control strategies are beneficial because they reduce overall malaria exposure, both for pregnant women and the general population. However, there are several challenges and issues that India still faces regarding MiP. Major among them are the lack of ITNs, socio-cultural issues, growing resistance to antimalarials and insecticides, a new, yet to be fully implemented drug policy, and a highly centralized malaria control programme. A review of the current control measures for MiP in India indicates that these challenges and issues must be addressed in order to alleviate the MiP situation in India.**

**Key words** India - insecticide-treated bednets - intermittent preventive therapy - malaria - pregnancy

### Introduction

Malaria in pregnancy (MiP) can have serious health consequences for both the mother and infant. MiP increases the chances of foetal death, prematurity, intrauterine growth restriction, low birth weight (LBW) and maternal anaemia<sup>1-4</sup>. In India, limited

epidemiological data on MiP exist limiting the ability to develop effective policies to address this problem. MiP policies have mostly been derived from studies in sub-Saharan Africa where the burden of MiP and measures to reduce associated morbidity have been thoroughly investigated. Although the majority of

malaria cases are found in sub-Saharan Africa, malaria remains an area of public health concern in densely populated countries in Southeast Asia. With about a sixth of the world's population situated in a country with endemic malaria, it is important to address the issue of MiP in India. This article discusses the current status of MiP in India and reviews current control measures, programmes and interventions that work, and also suggests areas that need improvement.

### **Malaria burden in India**

Malaria is endemic in India and constitutes a major public health challenge. India's National Vector Borne Disease Control Programme (NVBDCP) reports 1.5-2.0 million malaria cases with approximately 1000 malarial deaths per year<sup>5</sup>. Due to India's large population, 1.1 billion in 2006<sup>6</sup>, the actual number of malaria cases and deaths are very low: 16 cases per 10,000 persons and 1 death per 1 million persons. The magnitude of the malaria problem in India is small when compared to Africa which experiences 12 million malaria episodes and up to 310,000 deaths per year<sup>7</sup>. With Africa's population at approximately 900 million in 2006<sup>6</sup>, this translates to 133 malaria cases per 10,000 persons and 344 deaths per 1 million persons; significantly greater than the rates of malaria in India. India's surveillance data indicate a decreasing trend in the number of cases and deaths attributable to malaria in recent years. The reported incidence of laboratory-confirmed cases has declined from 3.0 million cases (1996) to 2.1 million cases (2001) to 1.78 million cases (2003)<sup>8</sup> during a time when diagnostic testing for malaria, including rapid diagnostic testing (RDT), has been improving.

Although this is an encouraging trend, it is important to note that these numbers are thought to underestimate the true number of malaria cases by as much as a hundred-fold as surveillance mechanisms do not capture all cases. A recent model to map the global distribution of clinical episodes of *Plasmodium falciparum* malaria indicates that the number of clinical attacks due to *P. falciparum* might be 1.5-2 times higher than World Health Organization (WHO) estimates<sup>9</sup>. Globally, the model suggests that, in 2002, 2.2 billion people were exposed to the threat of *P. falciparum* malaria, resulting in a conservative estimate of 515 million clinical attacks. Southeast Asia contributed a quarter of the world's clinical attacks, a reminder that India, which accounts for two-third of the total population in Southeast Asia, remains vulnerable to the

threat of malaria. WHO estimates that India accounts for three-quarter of all malaria cases in South East Asia<sup>10</sup>. With approximately 120 million cases of *P. falciparum* malaria in South East Asia in 2002<sup>9</sup>, this implies that India may have as many as 90 million cases of *P. falciparum* malaria per year. With almost half of all malaria cases in India attributable to *P. falciparum*<sup>11</sup>, the total number of annual malaria cases in India can be estimated at 180 million. This is a substantially higher estimate than those derived from surveillance data which record only 1.5-2 million confirmed cases per year. With an estimated surveillance sensitivity of 1 per cent, it is clear that national surveillance that relies solely on passive data collection will not be able to capture all malaria cases.

India is predominantly characterized by unstable malaria transmission. Transmission is seasonal with increased intensity preceding the monsoon rains. Due to the low and unstable transmission dynamic, it is likely that much of the population has not developed adequate immunity toward malaria<sup>12</sup>. As a result, the majority of Indians living in malarious areas are at risk of infection with all age groups affected. This is in contrast to Africa's moderate to high malaria transmission which predominantly affects children.

### **MiP in India**

Limited epidemiological data exist for MiP in India. A prospective hospital-based study conducted in Chandigarh, northern India from 1984-1985 showed that severity of clinical illness was significantly higher in pregnant patients for both *P. vivax* and *P. falciparum*<sup>13</sup>. Although the prevalence of MiP in this study was very low (1.4%), pregnant woman affected by malaria experienced a greater proportion of maternal death, cerebral malaria, intrauterine foetal death, and preterm labour than pregnant women who did not have symptomatic malaria. A hospital-based study in Gujarat, West India, from 1987-1988 demonstrated that, compared to the general population, pregnant women were more susceptible to malaria<sup>14</sup>. The effects of MiP included maternal anaemia and severe peripartum complications like abortion, stillbirth, premature labour, and low birth weight (LBW). A community-based study in Orissa, East India, found that primigravidae were more likely to be parasitaemic than multigravidae and that newborn infants of infected mothers were more likely to be infected with malaria<sup>15</sup>.

Several MiP studies have been conducted by the National Institute of Malaria Research (NIMR) in

Jabalpur, Madhya Pradesh<sup>16-19</sup>. Pregnant women were more likely to be parasitaemic than non-pregnant women, and pregnant women with severe *P. falciparum* infection experienced complications such as cerebral malaria, abortion, and intrauterine foetal death<sup>16,17</sup>. Malaria infection was more prevalent in primigravidae than multigravidae<sup>16,17</sup> with the highest prevalence of infection seen in the second trimester, irrespective of parity<sup>16,18</sup>. Analysis of data from 1992-1995 shows that pregnant women with malaria were more anaemic than uninfected pregnant women or infected non-pregnant women<sup>16</sup>. In addition, LBW was observed in neonates from infected mothers compared to neonates from uninfected mothers.

Two community-based studies were conducted in tribal villages in central India looking at both symptomatic and asymptomatic pregnant women and infants<sup>18,19</sup>. During a malaria epidemic in 1997-1998, 55 per cent of pregnant women and 44 per cent of infants investigated had malaria at some time during the study<sup>18</sup>. *P. falciparum* was responsible for the majority of malaria episodes (88%). Of the women found infected with *P. falciparum*, 3 per cent had abortions, 4 per cent stillbirths, and 2 per cent had babies who died while neonates. In comparison, 1 per cent of uninfected pregnant women had abortions and there were no recorded stillbirths or neonatal deaths<sup>18</sup>.

In India, *P. falciparum* is responsible for the majority of malaria episodes in pregnant women (approx 2/3) with the remainder due to *P. vivax*<sup>13-15,17</sup>. The detrimental effects of *P. falciparum* in pregnancy for both mother and child are well known; however, little is known about MiP due to *P. vivax*. Studies from Thailand<sup>20</sup> and central India<sup>16</sup> have demonstrated that *P. vivax* malaria was more common in primigravidae than in multigravidae, and was associated with mild anaemia and an increased risk of LBW. *P. vivax* malaria was not associated with miscarriage, stillbirth, or with a shortened duration of pregnancy.

### Prevention and management of MiP

Roll Back Malaria (RBM), a supporting agency of WHO, recommends a three prong approach to reduce the burden of MiP: effective case management, insecticide treated nets (ITNs), and intermittent preventive therapy (IPTp)<sup>21</sup>. Episodes of MiP elicit various complications and symptoms which depend on the intensity of malaria transmission and acquired immunity within the population. As a result, RBM organizes MiP strategy based on different intensity levels: low (unstable) epidemic transmission vs moderate/high (stable) epidemic transmission<sup>21</sup>.

Prevention and management of MiP in a setting of unstable malaria transmission involve effective case management and ITNs. The latter intervention, ITNs, reduces overall mortality and morbidity in pregnant women and infants. In areas of unstable transmission, pregnant women are more susceptible to severe forms of malaria because acquired immunity is low (or non-existent). In this setting, the risk of maternal mortality in these patients is 2-10 fold higher to that of non pregnant women<sup>22</sup>. Pregnant women with symptomatic malaria must receive prompt treatment with effective anti-malarial medication accompanied by recommended supportive care. Close collaboration between malaria control and reproductive health programmes can facilitate development of systematic management protocols and drug supply strategies<sup>23</sup>. Populations with low malarial immunity have an increased risk of severe malaria; therefore, limiting malaria exposure is of great importance. This can primarily be achieved through widespread use of indoor residual spraying (IRS), vector habitat control, and ITNs.

MiP control measures in an area of stable transmission include all 3 approaches: effective case management, ITNs, and IPTp. In areas of stable transmission, most adult women have developed an adequate level of immunity which results in asymptomatic infection. In this setting, maternal morbidity is mainly due to malaria-related anaemia. The major effect on the foetus is LBW due to the presence of malaria parasite in the placenta. LBW is responsible for higher infant mortality and impaired child development. IPTp is an integral component of MiP control in areas with stable transmission and replaces weekly chloroquine (CQ) chemoprophylaxis in pregnancy. Several studies in Africa have shown that IPTp with at least 2 doses of sulphadoxine-pyrimethamine (SP) in the second and third trimesters of pregnancy significantly reduces the prevalence of maternal anaemia and placental parasitaemia, and the incidence of LBW<sup>24-26</sup>. SP is considered safe for pregnant women with very limited side effects. The long half life of SP allows for single dose regimens which can be closely monitored and administered by healthcare workers in antenatal clinics. The treatment and prophylactic effect of SP is important for the efficacy of IPTp and has shown to be effective in both clearing parasites from the placenta and preventing new infections of malaria<sup>27</sup>. SP is an excellent option for IPTp in areas of stable malaria transmission with limited SP resistance. However, faced with increasing SP

resistance, current drug policies must be re-evaluated and must include an updated arsenal of drug options, including artemisinin-based combination therapy (ACT) once safety has been established for pregnancy.

An effective toolkit comprised of evidence-based strategies exists to control MiP: effective case management, ITNs, and IPTp<sup>21</sup>. Although indoor residual spraying (IRS) is an important malaria control measure, the role of IRS on MiP is undetermined and therefore omitted from the list of evidence-based strategies to control MiP. The challenge is to implement these strategies within national programmes so that these are effective in reducing the mortality and morbidity associated with MiP.

### **What is needed for control of MiP in India**

In certain districts with stable malaria transmission, India has a comprehensive malaria strategy: early case detection, prompt treatment, vector control, community participation, environmental management, source reduction, and programme evaluation and monitoring. Although this comprehensive strategy is comprised of critical components, policies addressing MiP issues in India appear to have limited effectiveness, at least partially due to a limited epidemiological understanding of MiP in India.

*(A) Integration with general health services:* India's malaria control activity is tightly integrated with general health services. The structure of the rural Indian health system is hierarchal with various services found at different levels. The problem faced by this current system is that healthcare workers are overburdened by the number of patients. As a result, NVBDCP has established drug distribution centres (DDCs) and fever treatment depots (FTDs) within villages. By moving services towards the periphery, NVBDCP is able to better serve the health needs of the population. In terms of malaria control, DDCs will give any patient with fever a 3 day regimen of CQ. Furthermore, primary health care centres are equipped with basic microscopes so that blood smears are routinely conducted and analyzed. Patients confirmed with malaria will be given 'radical treatment', a 3 day regimen of CQ + PQ (primaquine). This active case detection is able to collect nearly 100 million blood smears annually. Early case detection and prompt treatment is one of the main strategies of malaria control in India.

*(B) Indoor residual spraying:* India has successfully limited malaria exposure through rigorous use of IRS.

The use of dichloro-diphenyl-trichloroethane (DDT) as a residual insecticide was an effective vector control that had an enormous impact on India's malaria situation<sup>28</sup>. Although DDT has potential limitations, its effectiveness as a tool to interrupt malaria transmission must not be discounted. A recent study in Orissa shows that DDT still remains a viable option to limit malaria exposure<sup>29</sup>. Although DDT has been relatively ineffective in controlling *A. culicifacies*, the species responsible for 60 per cent of total malaria transmission within the country<sup>30</sup>, its use cannot be discontinued because it remains an effective vector control for other species. Malaria is highly complex with the current epidemiological situation varying from one region to another. IRS can be successful in reducing MiP burden because it can limit malaria transmission not only in pregnant women, but also for the entire general population.

### **Challenges and issues regarding MiP**

There are several challenges and issues that India faces regarding MiP. These include lack of ITNs, socio-cultural issues, growing resistance to antimalarials and insecticides, a new antimalarial drug policy<sup>31</sup> that has not yet been fully implemented, and a highly centralized malaria control programme.

*(A) Insecticide treated nets:* In a setting of unstable malaria transmission, the current RBM recommendation to reduce the burden of MiP is through effective case management and ITNs. India's integration of malaria control with general health services has created an effective means to quickly detect and treat malaria cases. Although effective case management has had some success in India, ITN use is relatively poorly implemented. Several studies conducted in India have demonstrated the efficacy of ITNs against malaria<sup>32-36</sup>.

Although ITN efficacy is well proven, distribution and implementation still present challenges. ITNs can be used in various malaria situations, however for programme effectiveness, these should be used as selective vector control. ITNs are more effective in certain situations, in particular, situations involving vulnerable communities such as children under 5 and pregnant women living in moderate to high risk areas<sup>37</sup>. Unfortunately, the experience in India suggests that targeting ITN use towards pregnant women may be difficult as anecdotal evidence suggests that ITNs are primarily used by either heads of family, elder family members, or children. The current Indian government policy states that ITNs should be given free to people

living below the poverty line in endemic areas (Chatterjee A, personal communication, Sept. 15, 2006). With approximately one fifth of the Indian population living below the poverty line, it is obvious that a more realistic and defined distribution system must be developed. India should include a policy that protects vulnerable sub-populations such as pregnant women living in moderate to high risk areas. There are currently no strategies that specifically target ITNs for pregnant women living in moderate risk areas. Integration of malarial control with antenatal clinics would provide a suitable mechanism to deliver ITNs to pregnant women. Greater emphasis on providing ITNs to pregnant women is an important step towards alleviating MiP burden in India; however, additional studies must be conducted to monitor and evaluate ITN use by pregnant women before implementing it as an intervention package.

*(B) Socio-cultural issues:* Challenges regarding India's MiP burden are further compounded by socio-cultural issues. Low compliance by pregnant women will limit the efficacy of any antimalarial intervention, so it is important to determine the reasons behind such low acceptance rates. A study conducted in central India demonstrated that there are socio-cultural barriers to pregnant women accepting malaria chemoprophylaxis<sup>38</sup>. Of the 155 participants in the study, chemoprophylaxis was given to only 19 per cent of pregnant women. The study targeted pregnant women from low socio-economic groups and provided chemoprophylaxis within individual households. Reasons cited for refusing participation included: objections by family members (husbands) towards male health workers prescribing prophylaxis, fear of mixing medications, medication not prescribed by antenatal clinics, and infertility conspiracies. Some of the pregnant women in the study were suspicious of healthcare workers prescribing prophylaxis when they neither had malaria nor felt sick. In addition, when 16 women taking prophylaxis delivered only daughters, they believed that it was a result of the medication. Rumours broke out and all the remaining women stopped taking prophylaxis<sup>38</sup>.

The importance of understanding socio-cultural dynamics is integral in addressing the problems of MiP in India. A more socially appropriate means to increase proper acceptance and use of antimalarial chemoprophylaxis may involve administration by female health care workers at antenatal clinics. In addition, education campaigns must be conducted by these antenatal clinics to educate women about the

benefits and risk associated with taking chemoprophylaxis. By addressing these socio-cultural issues and finding appropriate solutions to these problems, the likelihood in increasing adherence and acceptability toward antimalarial chemoprophylaxis can be attainable.

*(C) Growing resistance:* Increased resistance to antimalarial drugs and insecticides limits the effectiveness of malarial prophylaxis and treatment, inhibits malaria control and results in high morbidity and mortality. Studies in India have indicated that development of vector resistance has contributed to the declining effectiveness of DDT<sup>39-41</sup>; however, in some instances DDT remains a viable IRS insecticide owing to its effectiveness in well supervised spray operations<sup>29,42</sup>. Furthermore, malaria parasites have grown resistant to common antimalarials. There is widespread resistance to CQ and other antimalarials in India which has resulted in the rise of *P. falciparum*<sup>43,44</sup>. The increase in resistance to antimalarial drugs has led to the recent government decision to drastically modify its antimalarial policy in favour of artemisinin-based combination therapy (ACT).

*(D) Current drug policy:* There are many challenges faced by the Indian government regarding MiP drug policy. In terms of specific strategies targeting MiP, the new NVBDCP policy recommends chemoprophylaxis for pregnant women in high risk areas<sup>31</sup>. In India, CQ is the drug of choice for MiP prevention and treatment in places that do not have resistance. Chemoprophylaxis for pregnant women starts during the second trimester and continues one month after delivery. In areas with CQ resistance a weekly regimen of CQ with supplementation by proguanil is recommended. As the percentage of *P. falciparum* cases continue to increase, CQ is becoming more ineffective. For example, a study in central India demonstrated that 8 per cent of pregnant women experienced CQ treatment failure<sup>19</sup>. This study shows that although the majority of malaria cases in endemic areas can still be treated with CQ, treatment failures are a cause for concern.

CQ chemoprophylaxis has several additional drawbacks; of most concern is poor programme effectiveness. Several studies from Africa and Papua New Guinea have demonstrated that despite high reported CQ chemoprophylaxis coverage, peripheral and placental malaria rates remain high and are associated with known adverse outcomes during pregnancy<sup>45-48</sup>. Further, it can be hard to deliver and

sustain an intervention when a pregnant woman must take CQ every week for as many as 20-25 wk. Side effects (especially itching) and long regimen course result in poor adherence. Although recommended by the national policy, actual implementation of this policy by government hospital is rare. In addition to these problems, the possibility of inducing drug resistance limits usefulness of this current drug policy.

An alternative strategy to weekly chemoprophylaxis is IPTp. In areas of stable malaria transmission, IPTp with SP is efficacious and recommended for pregnant women by the WHO. With only 2 curative courses, one course each during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester, this strategy is inexpensive and easily deliverable. It can be given under direct observation which can guarantee adherence and limit resistance. India does have SP in their current drug policy; however, SP is only used as a second line of treatment and is not readily available for pregnant women. Further, SP may not be effective in certain States like Assam that have reported SP resistance<sup>49</sup>. In this case, use of ACT may be considered once the safety profile for pregnancy is established. The Indian government has realized the importance of this issue and is currently in the process of expanding and updating their malaria drug policy.

*(E) Centralized control programme:* India's centralized malaria control programme limits the ability of states to address specific malaria issues such as MiP. With no State specific control measures, the Indian national malaria eradication programme in Delhi prescribes a single control strategy to all local state governments<sup>50</sup>. As a result of India's complex malaria epidemiology, one cannot categorize malaria transmission as distinct entities (unstable vs. stable, low vs. high, *etc.*). Instead, it should be viewed as a continuum with a range of different transmission dynamics. Control programmes must be designed to address all the complex issues related to the epidemiology of malaria. Each Indian State is unique with a variety of different ecosystems, disease transmissions, and resistances. Therefore, greater autonomy needs to be given to individual States that have a better understanding of the malaria epidemic and situation. With 25-30 per cent of the health budget going towards malaria control<sup>40</sup>, the Indian government is making a concerted effort to tackle the current malaria situation. In terms of dealing with MiP, the Indian government should integrate malaria control programme with local antenatal clinics, scale up ITN usage for pregnant women and update current drug policies to reflect current antimalarial knowledge.

## Conclusion

The burden of malaria in India continues to be a public health challenge. A review of the current control measures for MiP in India indicates that there are clearly areas for improvement. Epidemiological studies have shown that pregnant women are more susceptible to malaria and have higher risks of anaemia and birth complications. With approximately 3 per cent of the entire Indian population pregnant, the number of pregnant women in India is considerable (30 million in 2006)<sup>51</sup>. The Indian government must make a concerted effort to address the issues of MiP and include antimalarial interventions that are appropriate for pregnant women. Specific recommendations to address MiP in India include:

(i) Create a strategic framework for scaling up the use of ITNs for both pregnant women and the general population.

(ii) Address socio-cultural barriers by distributing antimalarial chemoprophylaxis through antenatal clinics and conducting awareness campaigns to educate women about the dangers of MiP and the benefits and risk associated with taking prophylaxis.

(iii) Tackle the issue of growing resistance by re-evaluating and updating current drug policy to include current drug options such as SP IPTp and potentially ACTs, once their safety and pharmacokinetic profile is better established, for pregnant women.

(iv) Provide autonomy for individual States and regions by integrating malaria control programme with local antenatal clinic to improve case management based on proactive screening for MiP and to create an effective system to distribute ITNs and administer IPTp.

Prevention and control of MiP is an important and achievable goal. These proposed strategies represent feasible solutions in reducing the burden of MiP in India, and, if effectively implemented, should serve to reduce the incidence of anaemia in pregnant women, placental malaria, and low birth weight babies.

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