Interventions, surveillance and monitoring of malaria in pregnancy in rural southern Malawi
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Chapter 1  General introduction and study objectives
INTERVENTIONS, SURVEILLANCE AND MONITORING OF MALARIA IN PREGNANCY IN RURAL SOUTHERN MALAWI

1.0: General Introduction

The term malaria is relatively new. Some believe the disease is older than man having been passed from our primate ancestors [1, 2]. Hippocrates’ description of symptoms and its relation to warm weather in approximately 500 B.C. stands as the first accurate observation. But it was in 1753 that the term malaria (bad air) was introduced by Italians. In 1880, Alphonse Laveran, a French Army Physician working in Algeria demonstrated malaria parasites on fresh unstained blood taken from a malaria patient. Alphonse made his observation in 180 out of 192 patients. About twenty years later, a British Physician, Ronald Ross working on the hypothesis that malaria parasites were transmitted by mosquitoes, actually found pigmented malaria parasites granules in stomach and salivary glands tissues of *Anopheles and Culex* mosquitoes that he fed on malaria patients and worked out the complete cycle in mosquitoes in 1897 [1]. It was therefore Alphonse Laveran who identified the parasites (*Plasmodium* spp) responsible for malaria and Sir Ronald Ross proved that it was the mosquito that spread the infection.

Symptomatic disease and malaria transmission

Human malaria is caused by one of the four protozoan parasites: *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax*. The disease is transmitted to humans by the bite of the infected female anopheline mosquito, which passes the malaria sporozoites from its salivary glands into the blood stream of the human host. In uncommon cases, malaria may be transmitted through exposure to infected blood products and congenitally. However, transplacentally transmitted maternal immunoglobulin G antibodies are usually protective to the fetus.

Although each type of infection causes debilitating febrile illness, only *P. falciparum* carries a substantial risk of death, causing the most morbidity and mortality. In areas where malaria is endemic, the population acquires some degree of immunity against the clinical manifestations of the infection. In unstable malaria transmission areas, acute febrile disease is the overwhelming clinical manifestation resulting in severe anaemia, cerebral malaria, and death in individuals of all ages. In areas of high and stable malaria transmission, the disease has different effects in children and adults. Children experience chronic or recurrent and often asymptomatic parasitaemias which may lead to severe anaemia and increasing risk of death. Some individuals acquire a level of immunity by the age of 5 years, which reduces the likelihood of severe disease and may subsequently experience asymptomatic infection.

In pregnant women, living in unstable transmission areas, it causes acute febrile disease which may be severe and can lead to pregnancy loss and maternal death. In areas with stable malaria transmission, pregnant women are usually asymptomatic although often parasitaemic and with a high density of placental parasites.
Burden of malaria

Malaria is endemic in over 90 countries in which 2400 million people live; this represents 40% of the world's population [3]. Globally, malaria causes 300-500 millions cases of illness each year and is a leading cause of morbidity and mortality, especially among the pregnant women and children under the age of five years. Of the estimated 1-3 million malaria deaths recorded globally each year, 90% occur in sub-Saharan Africa (SSA) and 75,000 to 200,000 infant deaths are attributable to malaria infection in pregnancy. The adverse impact of malaria is largely caused by *Plasmodium falciparum* [4-7].

Malaria in pregnancy

It is estimated that every year, approximately 25-30 million women become pregnant in sub-Saharan Africa and are at risk of *falciparum* malaria infection. In stable malaria transmission areas of SSA, at least 28% of pregnant women have evidence of peripheral or placental malaria at the time of delivery [4, 8-9] although high coverage with insecticide treated bednets (ITNs) and intermittent preventive treatment with antimalarials in pregnancy (IPTp) should reduce these prevalence estimates. In low, unstable or seasonal transmission African settings, the median prevalence of peripheral (at antenatal care clinics) and placental parasitaemia have been estimated at 13·7% and 6·7%, respectively. For low-transmission areas outside Africa, estimates may be as high as 6·2 and 9·6% respectively [10].

Risk factors for malaria during pregnancy

**Gravidity**

The relationship between *falciparum* peripheral or placental infection and gravidity is well established. Early and recent studies have consistently shown that prevalence is higher in primigravidae than in secundigravidae and higher in secundigravidae than in multigravidae [8-16]. It is estimated that primigravidae have a two- to four-fold increased risk of placental malaria compared to multigravidae [15-16]. In stable high transmission areas, almost all primigravidae, if unprotected, are likely to be infected in early pregnancy and approximately half of these would remain infected by the time of delivery if untreated. In multigravidae, especially for higher parities, prevalence is substantially low which in part relates to the acquisition of parity specific immunity. Antibodies that inhibit placental parasite adhesion are associated with protection from *P. falciparum*, and these antibodies are acquired over successive pregnancies, explaining in part the susceptibility of primigravidae [7, 13, 17-18]. In low, unstable or seasonal transmission areas women of all gravidae are at risk because gravida-specific immunity is not acquired.

**Maternal age**

A number of studies conducted in sub-Saharan Africa have reported an association between maternal age and malaria infection during pregnancy. Parasitaemia at first antenatal visit was more frequent in those aged 12–19 years than in older mothers (62·6% vs 38·2%). This effect remained independent of gravidity in a multivariate analysis (adjusted odds ratio
Parasitaemia at delivery was also more common in those aged less than 20 years (OR 2.1 [95% CI 1.4–3.0]) [16-17]. In a separate study also from Malawi, maternal age and season were found to be more important than gravidity in determining the presence of parasitaemia [20]. This suggests that under conditions of low-to-moderate transmission, pregnancy-specific immunity may develop more slowly and therefore age-related immunity may have a greater influence on malaria prevalence during childbearing years [20]. An increased risk of malaria in those under 20 years of age (after adjustment for gravidity) has also been shown in studies from Cameroon, Kenya and Mozambique [21]. The importance of adolescent age as a risk factor for malaria in pregnancy has also been reported [22].

Maternal HIV status
HIV infected pregnant women are at increased risk of malaria and of its adverse consequences than non-infected women. This was first shown in studies from Malawi [23-24]. HIV infected women experienced consistently more peripheral and placental malaria (summary relative risk 1.58 and 1.66, respectively), higher parasite densities, more febrile illnesses, severe anaemia, and adverse birth outcomes than HIV uninfected women, particularly in multigravidae [25]. HIV alters the characteristic gravidity-specific pattern of malaria risk by increasing parasitaemia risk in women of all parities. The proportional risk estimate for malaria during pregnancy attributable to HIV was 5.5% and 18.8% for populations with HIV prevalences of 10% and 40%, respectively [25]. Co-infection of HIV and malaria in pregnancy has been described as a collision of two Titans [26]. It is estimated that approximately one million pregnancies are complicated by both malaria and HIV infection in sub-Saharan Africa annually [27]. The relation between HIV and malaria also varies with malaria transmission intensity. HIV infected pregnant women in low or unstable malaria transmission areas have higher risk compared to those in high or stable transmission areas [26].

Gestational age
It has been well known for many years that malaria prevalence is higher in early gestation with probable peak prevalence at 13-16 weeks gestation [8]. Prevalence changes in early pregnancy can be explained by an early decrease and subsequent increase in recovered rate from infection. In this sense pregnancy may allow sub-patent infections to reach detectable threshold. The decrease in the recovery rate in early pregnancy is likely to be related to immunological changes during early pregnancy [20, 28].

Season
Prevalence of peripheral parasitaemia is significantly higher in the wet than dry season in a number of studies [20, 29]. In areas with highly seasonal transmission in Africa, placental malaria has been identified more frequently in the dry season than would be expected from the low incidence of infection during this low-transmission season, suggesting that infections acquired during the peak (wet) transmission season may persist in the placenta for several months [10, 30].
**Maternal ABO blood group phenotype**
Blood group O has been associated with increased placental malaria infection in primiparae and reduced risk of infection in multiparae [31-32].

**Maternal iron status**
Iron deficiency causes anemia, but for unknown reasons it has been associated with reduced risk of malaria [33-34]. However, a recent study in Kenya showed that iron supplementation does not put pregnant women at increased risk of placental malaria [35].

Table below shows a summary of factors associated with malaria during pregnancy.

**Table 1: Summary of factors associated with malaria during pregnancy in women living under stable malaria transmission**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gravidity</strong></td>
<td>Primigravidae have two- to four fold increased risk of malaria than multigravidae.</td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td>Adolescents (age &lt;20 years) have a higher risk of malaria during pregnancy than older women (age ≥20 years).</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td>HIV infected pregnant women of all gravidae have higher risk of malaria than non- HIV infected. HIV shifts the gravid-specific malaria risk from primigravidae to all gravidae.</td>
</tr>
<tr>
<td><strong>Gestation age</strong></td>
<td>Peripheral malaria parasitaemia prevalence is higher in the second trimester than in other trimesters.</td>
</tr>
<tr>
<td><strong>Season</strong></td>
<td>Malaria in pregnancy is more common in rain and post rain seasons than in dry season</td>
</tr>
<tr>
<td><strong>Maternal ABO blood group phenotype</strong></td>
<td>Maternal blood group O is associated with increased risk of placental malaria infection in primigravidae and reduced risk in multigravidae</td>
</tr>
<tr>
<td><strong>Maternal iron status</strong></td>
<td>Iron deficiency is associated with reduced risk of malaria.</td>
</tr>
</tbody>
</table>

**Effects of malaria during pregnancy**

**Effects on maternal health**

**Anaemia**
Malaria induced anaemia is caused by immune haemolysis of both parasitized and non-parasitized erythrocytes, suppression of haematopoiesis, splenic clearance of red cells and secondary folate deficiency. In sub-Saharan Africa, 5–10% of pregnant women develop
severe anaemia (haemoglobin <70 g/L or <80 g/L) [10]. The proportion of severely anaemic pregnant women of all gravidities that is attributable to malaria (population attributable fraction) is estimated to be 26%. Thus, depending on the relative contribution of other possible causes of anaemia and local epidemiological factors, approximately one in four cases of severe anaemia may be prevented with adequate prevention of malaria in pregnancy. Anaemia is a significant cause of maternal death [10]. As malaria is more frequent in the first than later pregnancies in women living under stable malaria conditions then it would be expected that malaria related anaemia prevalence would be higher in primigravidae than multigravidae.

**Maternal death**

Despite decades of work on the epidemiology of malaria in pregnancy, accurate estimates of its effect on maternal mortality in sub-Saharan Africa are difficult to determine. Percentage of direct and indirect malaria-related maternal deaths range from 0·5% to 23·0% in hospital studies and from 2·9% to 17·6% in community-based studies. One model estimated that in holoendemic malarious areas with a 5% prevalence of severe anaemia (haemoglobin <70 g/L), there would be nine maternal deaths related to severe malarial anaemia per 100 000 livebirths and 41 non-malarial anaemia related deaths [10, 36].

**Effects on infant outcomes**

**Low birthweight**

Low birthweight (birthweight <2500 g) is associated with increased infant mortality. In areas of high malaria transmission, the risk of low birthweight approximately doubles if women have placental malaria with the greatest effect in primigravidae. The odds ratio of low birthweight associated with malaria is two to seven times higher in primigravid than multigravid women. In sub-Saharan Africa, nearly 20% of low-birthweight deliveries are attributable to malaria in pregnancy, and this is 35% of preventable low birthweight in women of all parities. Malaria induced low birthweight is estimated to be responsible for between 62 000 and 363 000 infant deaths every year in Africa, which translates to 3 to 17 infant deaths per 1000 livebirths [10]. Another estimate reports that 11·4% of neonatal deaths and 5·7% of all infant deaths in malaria endemic areas of Africa may be caused by malaria in pregnancy-associated low birthweight, translating to approximately 100 000 infant deaths [37]. Not surprisingly, this effect is greatest in infants born to primigravidae with estimates of 17·6% of neonatal deaths, and 9·8% of infant deaths [38]. In low transmission areas, acute malaria episodes do not seem to be associated with low birth weight [39].

**Intrauterine growth retardation (IUGR)**

In areas of high malaria transmission, malaria in pregnancy may be responsible for up to 70% of intrauterine growth retardation (IUGR), whereas its contribution to preterm delivery, although still substantial, is relatively lower at up to 36% [10]. Accurate estimates for IUGR are difficult to determine as there are almost no studies which have used ultrasound for accurate gestational age determination [40].
Abortion and Stillbirths
In low or unstable malaria transmission areas, pregnant women with malaria often have fever which may lead to abortion. In high stable transmission areas, malaria in pregnancy is usually asymptomatic and therefore prevalence of malaria induced abortions or preterm deliveries are lower than in low transmission areas, although even in these areas this is a recognisable complication. A recent review of mainly hospital-based studies has reported that placental malaria was associated with twice the risk (odds ratio 2·19) for stillbirth [41]. This did not take into account the effect of gravidity; it is likely that this effect is greater in primigravidae [10]. Systematic reviews of randomised controlled trials have shown that successful prevention of malaria in pregnancy among primigravidae with intermittent preventive treatment, and/or insecticide-treated bednets, results in substantial reductions in perinatal mortality (27%) and spontaneous abortions and stillbirths (33%) [10]

Infant anaemia at birth
The prevalence of infant anaemia at birth is high in babies born in malaria-endemic areas. This has been associated with high-density placental parasitaemia [42]. Few studies reported the effect of malaria in pregnant women on anaemia or malaria in the infant [43]. The risk of all-cause anaemia is estimated to be three times higher among infants born to women with placental parasitaemia, even after adjusting for environmental and ecological confounders [10].

Congenital malaria
Congenital malaria in the indigenous populations of malaria-endemic areas has generally being reported as rare and more frequent in offspring of malaria non-immune women. However, more recent reports from both malaria-endemic and non-endemic areas show higher prevalences of congenital malaria ranging from 8% to 33%. The apparent increasing trend in the incidence of congenital malaria may be the result of increasing drug resistance, increasing virulence of the maternal parasite, HIV interaction, or increased reporting or detection of cases by the use of PCR [10]. A birth cohort study from Tanzania has reported a 41% increased risk of malaria infection in infants born to women with placental malaria, after adjusting for potential confounding environmental and ecological factors [44].

Long term consequences to the child
There is limited evidence on whether and how malaria in pregnancy affects developmental outcomes in infancy independent of low birthweight. Only one study from Malawi has implicated placental malaria as a risk factor for poor anthropometric status in infancy independent of low birthweight [45]. Low birthweight may also affect the second generation; it is associated with incomplete catch-up growth and subsequent short stature in adolescence and adulthood, which in turn may increase the risk of delivering low-birthweight babies when these women become pregnant.

Tables three and four below have been adapted from WHO guidelines [6, 46] summarising the effects of malaria in pregnancy on maternal and infant outcomes.
Table 3: Summary of the contribution of malaria in pregnancy to maternal complications and pregnancy outcomes

<table>
<thead>
<tr>
<th>Adverse health event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal anaemia</td>
<td>2-15</td>
</tr>
<tr>
<td>Maternal death (Direct and indirect)</td>
<td>3-18</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>8-14</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>8-36</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>13-70</td>
</tr>
<tr>
<td>Infant death</td>
<td>3-8</td>
</tr>
</tbody>
</table>

Adapted from WHO: A strategic framework for malaria prevention and control during pregnancy in the Africa Region. World Health Organization, Geneva; 2004. AFR/MAL/04/01
Table 4: Summary of effects of malaria in pregnancy on maternal and infant outcomes

<table>
<thead>
<tr>
<th>Malaria in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Maternal febrile illness</td>
</tr>
<tr>
<td>Placental infection</td>
</tr>
</tbody>
</table>

- **Maternal Risk**
  - Anaemia
  - Maternal febrile illness
  - Placental infection
    - Abortion
    - Preterm delivery
      - Infant anaemia
      - Congenital malaria
      - IUGR
      -Stillbirth
      - Low Birthweight
      - Increased risk to infection
      - Long term consequences to the child

Key: IUGR: Intrauterine growth retardation

Malaria prevention and control during pregnancy

The World Health Organization (WHO) recommends a package of interventions for controlling malaria during pregnancy in areas with stable (high) transmission of *P. falciparum*. The package includes the use of insecticide treated nets (ITNs), intermittent preventive treatment (IPTp) and effective case management of malaria and anaemia [6]. Table five summarises WHO recommended interventions for prevention and control of malaria during pregnancy.

Table 5: WHO recommended interventions for malaria prevention and control during pregnancy

<table>
<thead>
<tr>
<th>WHO recommends that policies for malaria prevention and control during pregnancy in areas of stable transmission should emphasize a package of intermittent preventive treatment and use of insecticide-treated nets and ensure effective case management of malaria and anaemia.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermittent preventive treatment</strong></td>
</tr>
<tr>
<td>All pregnant women in areas of stable (high) malaria transmission should receive at least two doses of intermittent preventive treatment after quickening, the first noted movement of the fetus. Currently, the recommended drug for intermittent preventive treatment in Africa is sulfadoxine–pyrimethamine (IPTP-SP), because it is safe for use during pregnancy, effective in women of reproductive age and can be delivered as a single dose under observation by a health worker. At least two doses are required to achieve optimal benefit in most women. WHO recommends a schedule of four antenatal clinic visits, with three visits after quickening. Intermittent preventive treatment at each scheduled visit after quickening will ensure that a high proportion of women receive at least two doses. Doses should not be given more frequently than monthly. In settings with HIV prevalence among pregnant women greater than 10%, it is more cost effective to treat all women with a 3-dose regimen than to screen for HIV and provide the regimen only to HIV-infected women.</td>
</tr>
<tr>
<td><strong>Insecticide-treated nets</strong></td>
</tr>
<tr>
<td>Insecticide-treated nets should be provided as early in pregnancy as possible to all pregnant women living in malarious areas, including epidemic and disaster situations, according to the perceived need in the locality. Their use should be encouraged for women throughout pregnancy and postpartum. Nets can be provided in the antenatal clinic or through other sources in the private and public sectors.</td>
</tr>
<tr>
<td><strong>Effective case management of malaria illness and anaemia</strong></td>
</tr>
<tr>
<td>Effective case management of malaria illness for all pregnant women in malarious areas must be ensured. Iron supplementation for the prevention and treatment of anaemia should be given to pregnant women as part of routine antenatal care. Pregnant women should also be screened for anaemia, and those with anaemia should be managed according to national guidelines.</td>
</tr>
</tbody>
</table>

Adapted from WHO: Malaria in pregnancy: Guidelines for measuring key monitoring and evaluation indicators. Health Organization, Geneva; 2007
Safety and Effectiveness of IPTp with SP for malaria prevention and control

Randomized controlled trials and meta-analyses have consistently shown that two or more doses of IPTp-SP reduces the risk of maternal anaemia and peripheral parasitaemia at delivery, placental malaria, low birth weight and infant death [47]. Schultz and colleagues first demonstrated that two doses of SP were highly effective in reducing placental malaria in a study in Malawi before the introduction of IPTp-SP Policy in 1993 [48]. This was later confirmed by a study by Rogerson et al. who showed that two or more doses of SP were associated with decreased placental malaria prevalence from 31.9% with no SP to 22.8%, and decreased low birthweight prevalence from 23% in women not receiving SP to 10.3% [49]. Verhoeff et al. also in Malawi observed that the incidence of low birth weight in primigravidae or multigravidae who had received two or more doses of SP was half that of those who had received none or a single dose [50]. Babies born to women who received two or more doses of SP had higher mean birth weight than those born to women who received a single dose [50]. In Kenya, a study undertaken between 1994-1996 (before the introduction of IPTp-SP Policy in 1997) showed that two doses of SP significantly reduced the risk of placental malaria and low birth weight [51]. Recent randomised controlled trials done in Mozambique and Mali confirm these findings [52-54]. Further more, of the two trials in Mozambique, one showed that two or more doses of SP reduced neonatal mortality by 61.3% (95% CI 7.4%- 83.8%; p = 0.024) [52]. Several reviews are in agreement with these findings [55-56]. Cochrane systematic review concluded that IPTp-SP reduced risk of antenatal malaria, antenatal anaemia, placental malaria, low birth weight and improved mean birth weight [47]. The protective effect of IPTp-SP is reduced in the presence of insecticide treated bednets [55-56] as malaria exposure and attack are reduced.

IPTp-SP may be effective even in areas where SP resistance for clinical malaria in children under five years of age is as high as 39%, and/or HIV prevalence is 10% or more [57]. In HIV positive pregnant women, at least three doses of SP are required for maximum benefit. The safety of IPTp-SP (2-4 doses), even in the presence of HIV and anti-retroviral therapy, has been highlighted [57-60].

Based on the above and other evidence, WHO therefore recommends that IPTp-SP is effective even in areas with high (up to 30%) SP resistance for the treatment of clinical malaria. IPTp-SP is also effective and safe in areas with HIV prevalence of 10% or more [6, 61-62].
Table 6: Summary of safety and effectiveness of IPTp-SP

- Two or more doses of IPTp-SP reduces the risk of maternal anaemia and peripheral parasitaemia at delivery, placental malaria, low birth weight, infant death and raises mean birth weight.
- IPTp-SP is effective even in areas where SP resistance for the treatment of clinical malaria is up to 30%
- In areas where HIV prevalence is 10% or more, at least three doses of SP are required for maximum benefit
- Protective efficacy of IPTp-SP is reduced in the presence of ITNs
- IPTp-SP is safe even in HIV positive pregnant women and can be combined with ITNs

IPTp-SP Policy and implementation strategies

WHO recommends an antenatal care clinic (ANC) based approach for the implementation of IPTp-SP policy. All pregnant women in areas of stable (high) malaria transmission should receive at least two doses of intermittent preventive treatment after quickening. Four ANC visits are recommended, with three visits after quickening. Intermittent preventive treatment at each scheduled visit after quickening will ensure that a high proportion of women receive at least two doses. Doses should not be given more frequently than monthly [6]. The figure shows the WHO recommended administration of IPTp-SP linked to the focused antenatal visits in relation to the gestational pattern of fetal growth.
WHO recommended administration of IPTp-SP doses given at antenatal clinics after quickening

IPTp-SP targets: Abuja Declaration and the revised targets

On 25 April 2000, 44 out of 50 Heads of State from malaria endemic countries in Africa committed their countries to ensuring that at least 60% of pregnant women have access to effective prevention and treatment of malaria by the end of 2005. This commitment was aimed at contributing to the realization of the Roll Back Malaria goal of halving the malaria burden by 2010.

To achieve this goal, the African heads of state set up the following targets to be achieved by 2005:

- At least 60% of those suffering from malaria have access to correct, affordable and appropriate treatment within 24 hours of onset of symptoms
- At least 60% of those at risk of malaria particularly children under the age of five years and pregnant women to have access to a suitable combination of personal and community protective measures such as ITNs
- At least 60% of pregnant women especially those in their first pregnancies to have access to IPTp-SP.

This commitment from African leaders and the goals that they set, facilitated the adoption and implementation of the WHO recommended three-pronged strategy for the prevention and control of malaria in pregnancy in areas of stable transmission [63-64].

In 2005, Roll Back Malaria Partnership revised the targets as follows:

By 2010, through targeting universal coverage:

- 80% of people at risk from malaria are using locally appropriate vector control methods such as long lasting insecticidal nets (LLINs) and indoor residual spraying (IRS).
- 80% of patients are diagnosed and treated with effective anti-malarial treatments within 24 hours of onset of symptoms
- 100% of pregnant women in high malaria transmission areas receive IPTp-SP

By 2015:
- Universal coverage. Thus:
  - 100% of people at risk of malaria are using effective vector control methods
  - 100% of malaria patients are diagnosed and treated with effective anti-malarial drugs
  - 100% of pregnant women in high malaria transmission areas receive IPTp-SP [65].

Table seven summarises the Abuja and the revised targets for WHO recommended interventions.

**Table 7: Summary of the Abuja and the revised targets for malaria interventions as set in 2000 and 2005**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>By 2005</th>
<th>By 2010</th>
<th>By 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients diagnosed and treated with correct anti-malarial drugs within 24 hours of onset of symptoms</td>
<td>At least 60%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>People at risk of malaria using effective vector control methods</td>
<td>At least 60%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Pregnant women receiving at least two doses of IPTp-SP</td>
<td>At least 60%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Challenges of ANC based approach of IPTp-SP Policy implementation**

It has been well documented that across Africa, an average of more than 70% of women attend antenatal clinics at least once during pregnancy, and many attend at least twice [6]. High antenatal clinic attendance in Africa therefore represents a unique opportunity for prevention of malaria along with other priority diseases affecting pregnant women. It was based on existence of this high antenatal coverage that the WHO targeted the ANC clinic as the site for the implementation of malaria prevention and control interventions during pregnancy [6, 66].

Despite high antenatal coverage, IPTp coverage of two or more doses of SP has consistently remained below 60% (The Abuja target) not to mention the revised 80%, or subsequent universal coverage target. A number of operational studies and systematic reviews assessed progress and operational challenges for ANC based IPTp-SP Policy.
implementation. Recent systematic reviews have summarized the findings from operational studies done sub-Saharan Africa [67-68]. Table eight summarises the common operational reasons why coverages of two or more doses of IPTp-SP are low (<60%) in sub-Saharan Africa despite high antenatal attendance.

**Table 8: Common reasons why coverages with two or more IPTp-SP doses are low in sub-Saharan Africa**

- Late antenatal clinic attendance. As many as one in four women start antenatal care in the third trimester
- Drug shortages
- Staff shortages at antenatal clinics
- Poor understanding and interpretation of IPTp Policy and Guidelines by health workers particularly concerning timing of SP doses
- Inadequate supportive supervision
- Staff shortage, lack of cups or clean water for directly observed therapy
- Lack of demand for high quality antenatal services
- Perceptions of drug safety including that the drug should be taken with food
- Long distance to ANC clinics
- User-fees

Out of 24 of 45 malaria endemic countries in sub-Saharan Africa that have adopted IPTp-SP Policy [67], only Malawi reached 60% coverage of two or more doses of SP according to population based national survey conducted in 2010 [69]. Malawi was the first country to adopt IPTp-SP Policy in 1993 followed by Kenya in 1998. It therefore took Malawi over sixteen years to achieve the Abuja target. Despite the constant high (>88%) ANC attendance (≥2 visits), the IPT-SP coverage in 2000, 2004 and 2010 was 29%, 47% and 60% respectively [69-74].

The above mentioned health system (rather than community) challenges that impede high coverage of IPTp-SP in the presence of high ANC attendance raised the justifiable need to explore other approaches that could supplement facility based surveillance of pregnancy outcomes and distribution of SP. One of such alternative is the use of community health workers.
Evidence that the use of community health workers in drug distribution and surveillance works

For decades, family planning, child health, onchocerciasis, lymphatic filariasis and other public health programmes have utilized community health workers (CHWs) as a way of reaching hard to reach populations and/or supplementing facility based efforts. Community health workers are sometimes known as lay health workers (LHWs). Numerous studies, randomized controlled trials and systematic reviews have been published on CHWs. A Cochrane systematic review provided evidence that child health (promotion of immunization uptake, breastfeeding) and Tuberculosis (TB) interventions undertaken by trained community/lay health workers were effective [75]. Two systematic reviews also shown that CHWs were utilized by programmes to provide a wide range services, ranging from provision of safe delivery, counseling on breast-feeding, management of uncomplicated childhood illnesses, from preventive health education on malaria, TB, HIV/AIDS, sexually transmitted infection and non-communicable diseases to their treatment and rehabilitation of people suffering from common mental health problems. The services offered by CHWs have contributed to the decline of maternal and child mortality rates and have also assisted in decreasing the burden and costs of TB and malaria [76-77].

The cost-effectiveness of using CHWs has been questioned as there is little evidence that it is a cost-effective approach [78]. A Cochrane review has also shown that effectiveness of CHWs is compromised when providing integrated health services compared to single special services [79].

In Malawi and other countries where Onchocerciasis (Oncho) is endemic, CHWs have been utilized for community directed intervention (CDI) approach to distribute Ivermectin for many years [80]. The Oncho CDI Control programme started in early 1990s and is present in eight districts in Malawi.

In summary, it is well documented that it is feasible, realistic and acceptable by the community to use CHWs for health promotion and drug distribution. It was based on this evidence therefore that a trial was conducted in rural southern Malawi to validate their effectiveness (chapter one of this thesis).

Monitoring and evaluation of malaria in pregnancy - developing a rational basis for control

Monitoring and evaluation (M & E) of malaria control in pregnancy is essential for assessing the efficacy and effectiveness of health interventions. The commonly used indicators for assessing efficacy and effectiveness of malaria interventions are therapeutic efficacy, maternal anaemia at delivery, low birthweight and placental malaria [46, 55, 81].

Traditionally, malaria drug therapeutic efficacy studies have been conducted in children under 5 years of age with clinical malaria. Results are used as proxy to parasitological response during pregnancy. Due to widespread SP resistance (≥25%) for clinical malaria in children, most countries in sub-Saharan Africa have changed their malaria treatment policy from SP to artemisinin combined therapy (ACT) for the treatment of clinical malaria,
Although SP is still used for IPTp in these countries. In view of this, SP therapeutic studies would be required in pregnant women where the drug is still used. The need for modifying the WHO in-vivo assessment protocol in order to take account of this has been highlighted [81]. Furthermore, a study in Ghana reported that parasitological failure rates in asymptomatic pregnant women and children with clinical malaria under 5 years of age differed significantly, with higher failure rates in children than in asymptomatic pregnant women [82].

Assessment of malaria in pregnancy impact indicators; percentage of low birthweight singleton livebirths and percentage of pregnant women screened for anaemia [46] may pose another challenge in settings where home delivery is common. In Malawi up to 44% of pregnant women deliver at home and this has been a chronic public health problem for years [70-72]. Using CHWs to measure birthweight and maternal haemoglobin in home deliveries could supplement health facility based M & E of these impact indicators and contribute to early detection and/or treatment of those at risk. There is limited available information on the role and use of CHWs for M & E of malaria interventions.

Monitoring and evaluation of malaria interventions during pregnancy may also be conducted using appropriate routinely collected health facility data. Such methods have infrequently been applied for this purpose, in part, because of concerns about the representativeness of health facility data and the potential for selection bias. However case coverage methods have been used to assess vaccine interventions and may have applicability for monitoring malaria interventions. This is based on a comparison of the proportion receiving the intervention amongst cases and amongst the population [83]. Application of this method for M & E of malaria interventions during pregnancy (IPTp-SP and ITNs) using birthweight, maternal anaemia or placental malaria data has been proposed [81]. Options for using low birthweight comparisons in primigravidae and multigravidae as malaria control indicators have also been proposed [81], and a comparable monitoring approach could be developed using anaemia prevalence. This is specifically assessed and reviewed in this thesis.

The World Health Organisation is currently promoting the integration (inclusion of programme activities in the broader health system with strong community involvement) and co-implementation (strategy of bringing two or more programme initiatives together to increase efficiency and avoid fragmentation) of malaria and neglected tropical diseases (NTDs) programmes [84]. Where community sentinel sites are available, establishment of integrated surveillance, M & E for malaria and NTDs is recommended. Malaria is being specifically targeted for integration and co-implementation with NTDs because ITNs which are primarily procured, distributed and used for malaria control have added benefits on Lymphatic filariasis (LF) control. LF is also transmitted by mosquitoes. Few studies have been published on the integrated surveillance, M & E for malaria and NTDs.
Study objectives

Primary objective
In a rural area of southern Malawi to evaluate the utility and effectiveness of a community health intervention to supplement antenatal care based distribution of IPTp-SP in pregnancy.

Secondary objectives

1. To assess the effect of using community health workers to distribute SP on the coverage of IPTp-SP and use of maternal facility based services.

2. To monitor trends in malaria in pregnancy and pregnancy outcomes among adolescents over a ten year period.

3. To determine the level of SP parasitological failure among asymptomatic pregnant women at a time when SP failure for the treatment of clinical malaria in children was high (≥25%)

4. To assess an integrated sentinel surveillance approach for malaria and neglected tropical diseases

5. To assess maternal anaemia as indicator for monitoring malaria in pregnancy in sub-Saharan Africa

6. To estimate the effectiveness of interventions for malaria control in pregnancy using the screening method.
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