Systematic assessment of factors affecting the delivery, access and use of interventions to control malaria in pregnancy in sub-Saharan Africa

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Chapter 1:
Introduction
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1. Background

1.1. Global distribution of malaria in pregnancy

Worldwide, an estimated 125 million pregnancies occurred in areas with *Plasmodium falciparum* and/or *Plasmodium vivax* transmission in 2007, resulting in about 83 million live births [1]. Of 85 million pregnancies in areas with *P. falciparum* transmission, 55 million occurred in areas with stable transmission and 30 million in areas with unstable transmission; 93 million occurred in areas with *P. vivax* transmission, 53 million of which occurred in areas in which *P. falciparum* and *P. vivax* co-exist and 40 million in temperate regions with *P. vivax* transmission only. *P. falciparum* is the most common species of malaria in sub-Saharan Africa, whereas *P. vivax* is more common in South East Asia, Latin America and the western Pacific.

The risks of malaria in pregnancy have long been recognized but the discovery that malaria occurs more frequently in pregnant women than in non-pregnant adults was made only about 75 years ago [2,3]. Pregnant women are particularly vulnerable to malaria as pregnancy alters a woman’s immune status, especially at the mother-foetal interface at the placenta, making her more susceptible to malaria as well as to other infections [4]. Pregnant women living in malaria endemic areas have an up to 1.2-fold higher risk of malaria infection during pregnancy compared with non-pregnant women [5] and have been reported to be more attractive to mosquitoes [6]. However, not all pregnant women who are infected with malaria parasites will develop clinical illness. The clinical manifestation of maternal infection with malaria depends on the malaria transmission intensity and the species of malaria parasite.

In areas of high, stable, *P. falciparum* malaria transmission, defined as annual parasite incidence (API) $\geq 0.1$ per 1,000 per year [7], women are exposed to malaria from childhood and acquire considerable levels of immunity, whereas women living in low transmission areas (API <0.1 per 1,000 per year) are less exposed and consequently have little or no acquired immunity. Maternal malaria infection is frequently asymptomatic but is associated with maternal anaemia and low birth weight (LBW; defined as birth weight of <2500g). The median prevalence of maternal malaria infection in sub-Saharan Africa in all gravidae determined by light microscopy was estimated to range from 26-28% [8,9], but is likely to be higher if more sensitive techniques that detect sub-microscopic parasitaemias are used [10].

In areas of low, unstable, and seasonal transmission or epidemic malaria, women infected with malaria are more likely to present with clinical malaria that is associated with severe disease (symptoms may include hyperpyrexia, hypoglycaemia, severe haemolytic anaemia, cerebral malaria and pulmonary oedema), high risk of maternal mortality and poor infant outcomes. Median prevalence of peripheral parasitaemia in low transmission settings in Africa is 13.7% compared to 6.2% outside Africa, and of placental parasitaemia, 6.7% and 9.6% respectively [10].
1.2. Risk groups and factors affecting malaria prevalence during pregnancy

Pregnant women are not equally susceptible to malaria; malaria prevalence is affected by both pregnancy and non-pregnancy related risk factors. Pregnancy related risk factors include gravidity and gestational age and important non-pregnancy related risk factors include transmission setting, HIV status, age, and location of residence.

In areas with moderate-to-high transmission, primigravidae are at highest risk of malaria infection followed by secundi-gravidae, the risk diminishing with each consecutive pregnancy. Malaria infection is more frequent and severe in primigravidae both during pregnancy and at the time of delivery [11]. This phenomenon is due to the development of parity-specific immunity during pregnancy, when the placenta provides a temporary blood-filled organ that permits sequestration of *P. falciparum* parasites [12]. The risk of maternal infection is highest during the second trimester of pregnancy [10] though a recent modelling study suggests the end of the first trimester is a key period during which 65% (credible interval [CrI], 61%–70%) of the potentially infected pregnancies first experience infection [13]. Primigravidae experience a high proportion 39% (95% CrI, 33%–46%) of the total potential malaria-attributable LBW burden [13], and this gravidity effect is less marked in low transmission areas [14] and is absent in areas with epidemics [15].

Human immunodeficiency virus (HIV) infection increases the risk of malaria parasite prevalence and density due to impairment of parity-specific immunity to malaria, hence the gravidity effect among HIV-infected women is less apparent [16]. The proportional increase of malaria prevalence during pregnancy attributed to HIV, regardless of gravidity, is estimated to be 5·5% and 18·8% for areas with an HIV prevalence of 10% and 40%, respectively. There is evidence of a synergistic action of malaria and HIV in pregnancy. HIV exacerbates malaria-associated anaemia so that co-infected women are at greater risk of severe anaemia and death [16-18]. Also, the consequences of co-infection on birth outcomes such as low birth weight, preterm delivery, and perinatal mortality are far worse than the effect of each infection separately [16,19].

Adolescence is an independent risk factor for malaria in pregnancy, with much higher prevalence of malaria in women aged 15-19 years [10], and younger adolescents might be at a higher risk than older adolescents due to immunological and hormonal factors [20]. Age-associated immunity appears to play an important role alongside parity-specific immunity in controlling maternal infection in areas of high transmission.

Other factors associated with higher malaria prevalence in the general population are also associated with higher malaria risk in pregnancy, such as rural versus an urban residence [21], and socio-economic status [22].

1.3. Impact on maternal health and birth outcomes

Malaria infection in pregnancy has adverse and often severe consequences for maternal, newborn, infant and child health (Figure 1). The presence of malaria parasites in peripheral blood contributes to maternal anaemia [23], malaria accounting for 26% (population attributable fraction) of all severe anaemia [10], and parasite sequestration in the placental vascular space results in infant LBW [24] through preterm delivery [25] and intrauterine growth retardation [25,26].
Figure 1. Effect of malaria in pregnancy on maternal health and birth outcomes

Abbreviations: LBW: low birth weight; IUGR: intrauterine growth retardation.

Malaria related anaemia alone is estimated to cause approximately 10,000 maternal deaths globally each year, with many more deaths either directly or indirectly related to malaria infections [27]. An autopsy study in Mozambique suggests malaria as a non-obstetrical cause in 10% of maternal deaths [28] and the range of maternal deaths due to malaria in a review of mainly hospital data in Africa was 0.5–23% [29]. Maternal mortality among cases of severe malaria is approximately 50%, which is considerably higher than in non-pregnant adults [30].

Miscarriage and stillbirths may result from complications of malaria during pregnancy, and placental malaria doubles the risk of stillbirths regardless of parity (odds ratio 2.19, 95% confidence interval (CI) 1.49-3.22) [31]. Although the pathology causing these outcomes is not completely understood [32], prevention of malaria in pregnancy substantially reduces spontaneous abortions and stillbirths [33,34].

In sub-Saharan Africa, malaria infection during pregnancy accounts for 20% of all LBW deliveries and 35% of preventable LBW births, regardless of the number of times a woman has been pregnant [9,10]. Primi- and secundi-gravid women are at higher risk of delivering LBW infants than multigravidae. LBW is the single most important risk factor for newborn and early infant mortality, with mortality in LBW infants being three-fold higher than in infants with normal birth weight [9]. Malaria in pregnancy is estimated to be responsible for up to 200,000 [8,35] (uncertainty interval (UI) 62,000–363,000) infant deaths in Africa every year due to the effects of malaria on both preterm births (associated with an 8%–36% risk of LBW) and intrauterine growth retardation (associated with a 13%–70% risk of LBW) [8]. Approximately 11% (100,000) of neonatal deaths are due to low birth weight (LBW) resulting from *P. falciparum* infections in pregnancy [10]. Surviving infants often experience lasting effects from infection in the womb that impede their development and learning [36].

In the absence of malaria control in pregnancy it is estimated that in sub-Saharan Africa in 2010, 11.4 million (95% credible interval (Crl), 10.7–12.1) pregnancies would have experienced *P. falciparum* placental infection at some stage of pregnancy, accounting for 41% of the estimated 27.6 million live births [13]. Combined with estimates of the relationship between placental infection and the risk of LBW, an estimated 900,000 (95% Crl, 530,000–1,240,000) LBW deliveries per year are caused by placental malaria. *P. falciparum* and HIV are independent risk factors for LBW and, among multigravidae, dual infection results in 9.59-fold (95% CI, 2.51-36.6) increase in the risk of LBW compared with uninfected multigravidae [19].

### 1.4. Economic burden

There is a paucity of data on the economic burden of malaria in pregnancy both for the pregnant woman and for pregnancy outcomes [37]. In terms of direct costs, it can be assumed that the cost of treating severe or complicated cases of malaria in pregnant women and malaria associated severe anaemia are high [38]. Where the quality of antenatal care services and/or access to these services are low, the outcome of malaria infection in pregnancy is likely to be poor. In turn, maternal death places a high economic burden on households as an indirect cost. The first economic evaluation of LBW in a low-income country, Mozambique, shows that reducing the prevalence of LBW would translate into important cost savings to the health system and the household [39]. Costs associated with LBW excess morbidity were calculated on the incremental number of hospital admissions in LBW
babies compared to non-LBW weight babies. Direct and indirect household costs for routine health care were US$24 (UI: US$22–26), and an increase in birth weight of 100g would cut these costs by half.

### 1.5. Control of malaria in pregnancy

In areas of stable, moderate-to-high transmission in sub-Saharan Africa, the World Health Organization (WHO) recommends a package of interventions for controlling malaria in pregnancy including two preventive strategies, intermittent preventive treatment and the use of insecticide treated nets, together with effective diagnosis and case management of clinical malaria and anaemia [40,41].

#### 1.5.1. Efficacy and effectiveness of preventive interventions

Intermittent preventive treatment of malaria in pregnancy (IPTp) consists of the administration of full, curative-treatment doses of an effective antimalarial drug at predefined intervals during pregnancy commencing in the second trimester, regardless of whether or not a woman is infected with malaria parasites. Sulphadoxine-pyrimethamine (SP) is currently the only drug recommended for IPTp in pregnancy for all areas of moderate-to-high transmission based on its efficacy and safety profile. The intervention has two malaria control properties: a) to clear existing parasites (treatment effect) and b) to prevent new infections (prophylactic effect). Systematic reviews of randomized control trials have shown that chemoprophylaxis or IPTp with SP (IPTp-SP) reduces the risk of severe maternal anaemia by 38%, low birth weight by 43%, and perinatal mortality by 27% among women in the first or second pregnancies, and also has positive effects on birth weight and possibly also perinatal death in low-parity women [33,42]. A more recent randomized placebo-controlled trial to evaluate the efficacy of 2-dose IPTp-SP in Mozambique, that followed about 1000 newborns until 12 months of age, found that IPTp reduced neonatal mortality by 61% (UI: 7%–83%) [43].

Increasing resistance to SP across several countries in Africa threatens the efficacy of IPTp with SP, however, with the exception of three foci of super-resistant parasites in East Africa [44], IPTp-SP remains an effective strategy in most parts of Africa [45]. Clinical trials to determine the efficacy, safety and tolerability of alternative drugs for IPTp have yet to identify suitable alternatives to SP [46,47]. Alternative strategies to IPTp are also being developed and tested, such as intermittent screening and treatment [48], a strategy which does not have the benefit of IPTp in controlling infections that cannot be detected by rapid diagnostic tests or microscopy but which may be more cost effective in areas of low or reduced transmission.

Cochrane systematic reviews of clinical trials in Africa show that insecticide treated net (ITN) use in the first few pregnancies reduces the risk of low birth weight by 23% (relative risk [RR] 0.77, 95% CI 0.61-0.98) and spontaneous abortions and stillbirths by 33% (RR 0.67, 0.47-0.97) [34,49]. As pregnant women normally sleep with their infants, ITN use in pregnancy confers additional protection to this group, reducing all cause child mortality by 17% compared to no nets (RR 0.83, 95% CI 0.76-0.90), and by 23% compared to untreated nets (RR 0.77, 95% CI 0.63 to 0.95), thereby saving an estimated 5.5 lives (95% CI 3.39-7.67) each year for every 1000 children protected with ITNs [50].
Effectiveness of IPTp and ITN use in pregnancy under routine malaria control programme conditions across sub-Saharan Africa has been recently demonstrated, showing substantial reductions in neonatal mortality and low birth weight. At 2012 coverage levels across 32 countries in sub-Saharan Africa, ITN or IPTp use among women in their first or second pregnancies was significantly associated with a decreased risk of neonatal mortality (incidence rate ratio 0.82; 95% CI, 0.698–0.96) and reduced odds of low birth weight (adjusted odds ratio 0.79; 95% CI 0.73–0.86), compared with newborn babies of mothers with no protection, after controlling for potential confounding factors [51].

1.5.2. Cost effectiveness of prevention interventions

Estimates of the cost effectiveness of IPTp and ITNs are relatively old, and new estimates are needed. In 2001, the incremental cost of adding IPTp with SP to an existing antenatal care service during first pregnancies was estimated to be US$ 1.10 per pregnancy in low-income countries, increasing to US$ 2.20 when adding service overheads [52]. The cost of providing IPTp to all mothers regardless of their previous number of pregnancies would substantially increase the total cost but would represent a relatively minor addition to existing government health expenditure and be easier to implement than targeting. When extended to include benefits to the mother as well as infants using modelling of trial data in 2006, the incremental cost–effectiveness ratio (ICER) for two to three doses of SP during pregnancy delivered to women in their first pregnancy in a low-income sub-Saharan African setting, allowing for the probability of attending each visit, the level of drug resistance and compliance ranged between US$ 9 and US$ 21 per disability-adjusted life year (DALY) averted (mean US$ 13). DALY is a measure of the number of years lost to ill-health, disability or early death.

A more recent analysis of the cost-effectiveness of IPTp-SP on maternal clinical malaria and newborn survival was estimated in the context of a clinical trial of IPTp-SP in Mozambique, where both intervention groups received an LLIN through ANC [53]. In 2007 US$, the ICER of IPTp-SP for maternal malaria was US$ 41 (UI: US$21–97) per DALY averted, and for the reduction in neonatal mortality was US$ 1.08 (UI: US$0.50–3.50). The ICER including both the effect maternal malaria and neonatal mortality was US$ 1.02 (UI: US$0.40–3.20) per DALY averted. The cost-effectiveness of IPTp-SP is dependent on ANC attendance [54].

In a very-low-income country, the cost-effectiveness range for provision of nets and insecticide treatment was $19-85 per DALY averted [52]. Estimates for the cost and cost–effectiveness of delivering ITNs have used varying methodologies and cost outputs, and have included other target groups, such as children under five years of age and pregnant women, leading to a lack of reliable estimates on any one specific intervention [55]. Previous estimates from 1999 of the cost–effectiveness of delivering free ITNs to the whole population for reducing all-cause child mortality ranged from US$19–85 per DALY, reducing to US$4–10 per DALY in areas where there is a moderately high level of pre-existing ITN coverage, as in several parts of Africa today [52]. ITNs are a highly cost-effective public health tool when compared to other interventions such as immunization, estimated at US$3-7 per DALY.

1.5.3. Case management of malaria in pregnancy

The range of antimalarial drugs available for treating malaria in pregnancy is more restricted than for non-pregnant adults as these drugs must first be proven to be safe and efficacious for both the mother
and foetus, and yet pregnant women are systematically excluded from clinical trials [56,57]. This is primarily due to the risks, costs and complexities of undertaking clinical trials in pregnant women. In order to fully evaluate safety and clinical outcomes in both mother and infant, clinical trials need to follow each participant throughout pregnancy and at delivery, and, ideally, the infant is followed throughout the first year of life. In addition, pregnancy can alter the pharmacokinetics (or disposition) of a drug so that additional pharmacokinetic studies are needed to determine optimal dosing to achieve comparable cure rates to those achieved in non-pregnant adults.

The artemisinin derivatives have been the subject of disproportionately more clinical trials and studies in pregnancy than any other drug used previously, and by contrast to the prevention studies, the majority of case-management studies have been undertaken in areas of low transmission in Asia [58], though the results of a multicentre trial in four countries in Africa are due to become available in late 2014. Use of artemisinin derivatives as monotherapies is explicitly discouraged by WHO, due to evidence of emerging drug resistance in Asia [59,60]. To prevent further spread of drug resistance, artemisinin derivatives are combined with another antimalarial, such as lumefantrine, amodiaquine, piperaquine or mefloquine, loosely termed artemisinin-combination therapies (ACTs). In areas with both *P. falciparum* and *P. vivax* transmission, artemether-lumefantrine and dihydroartemisinin-piperaquine, respectively, are currently the most cost-effective treatment options [54]. Treatment of severe malaria with artesunate is more cost effective compared with treatment with quinine.

1.6. Global malaria control policy

WHO first recommended the IPTp strategy in 2000 [41], and it was subsequently adopted as regional policy in the WHO Africa Region in 2004 [40]. The initial regimen consisted of at least two doses of IPTp-SP given one month apart in the second and third trimester. In September 2012, WHO issued an updated policy recommendation which recommends more frequent dosing, increasing the regimen to a dose of IPTp-SP given at every ANC visit in the second and third trimester at least one month apart [61,62], ideally administered as directly observed therapy. The new regimen was based on the findings of a meta-analysis of seven clinical trials showing that three or more doses were more effective than two [63]. HIV infected women receiving co-trimoxazole should not receive IPTp-SP, given the redundant mechanisms of action in preventing malarial infection and synergistic worsening of adverse drug reactions due to sulphur content in both drugs e.g. severe cutaneous adverse reactions [64].

The use of ITNs has been a core malaria prevention strategy for more than two decades [65,66], and distribution of ITNs has up until recently targeted biologically vulnerable groups such as pregnant women and children aged less than 5 years [67,68]. In 2008, the Roll Back Malaria (RBM) Partnership set a more ambitious target of universal coverage of LLINs, defined as universal access to, and use of, LLINs, removing the focus on targeting vulnerable populations [69-71]. In the African region, 34 countries have since adopted this refocused strategy and provide ITNs through a combination of population-wide campaigns and targeted efforts including pregnant women through antenatal clinics.

The prompt diagnosis and treatment of malaria illness in pregnancy is important in all malaria endemic regions. WHO recommends that adults, including pregnant women, should be treated for malaria on the basis of a parasitological diagnosis by quality-assured light microscopy or, where microscopy is unavailable, rapid diagnostic tests (RDTs) [72]. Since 2006, WHO has recommended quinine alone or plus clindamycin for the treatment of uncomplicated malaria in the first trimester, and artesunate (AS)
plus clindamycin for treatment failures [72]. In 2010, the policy was changed to artemisinin-based combination therapies (ACTs) known to be effective in the country/region for case management of uncomplicated malaria in the second and third trimesters [73]. Use of the artemisinin class of compounds, alone or in combination therapies, is not recommended in the first trimester of pregnancy because of insufficient safety data in early pregnancy in humans [57], unless this is the only treatment immediately available [72].

For treatment of pregnant women with severe malaria, parenteral antimalarials (i.e. rectal, intramuscular or intravenous administration) are recommended [74]. Parenteral artesunate is preferred over quinine in the second and third trimesters because quinine is known to reduce blood sugar level (hypoglycaemia). In the first trimester, the risk of hypoglycaemia is lower and the uncertainties over the safety of the artemisinin derivatives are greater. However, weighing these risks against the evidence that artesunate reduces the risk of death from severe malaria, both artesunate and quinine may be considered as options until more evidence becomes available.

1.7. Policy implementation in sub-Saharan Africa

1.7.1. Policy change process

Successful policy change and implementation at the national level has relied on the availability of a comprehensive evidence base, clear policy guidance and availability of evidence-based guidelines, strong communication between departments of reproductive health, medical services and malaria control, and stakeholder commitment and consensus [75]. African leaders readily adopted the ITN policy at the African Summit on Roll Back Malaria in 2000 [76] whereas IPTp policy adoption was phased into countries more slowly, starting in East and Southern Africa followed by West and Central Africa [77]. The reason for the earlier policy change process in East Africa was the availability in the 1990s of evidence from Kenya and Malawi to support adoption of IPTp-SP [78-81], and increasing pressure to change treatment and prevention policy due to high levels of chloroquine resistance in the region and the consequent failure of weekly chemoprophylaxis among vulnerable groups [82].

The majority of malaria endemic countries in sub-Saharan Africa (39 out of 44) have adopted IPTp-SP as policy, the earliest being Malawi in 1993, the most recent the Central African Republic in 2007 [83]. All malaria-endemic countries in sub-Saharan Africa provide ITNs or the newer generation of long-lasting insecticidal nets (LLINs) to pregnant women, with Niger and Senegal the first countries to introduce the policy in 1998, and the most recent the Central African Republic and Equatorial Guinea in 2007 [83]. According to WHO, all countries in sub-Saharan Africa have adopted ACTs as first line treatment for uncomplicated *P. falciparum* malaria however the treatment policy for pregnant women is not reported [84]. Many countries in high transmission settings have made ACTs available free-of-charge to pregnant women in efforts to achieve universal coverage [85], and RDTs are becoming increasingly available.

1.7.2. Context of programme delivery

Responsibility for the delivery of IPTp and ITNs, and of case management of malaria in pregnancy, lie with different departments within the Ministry of Health and, in some African countries, within different ministries. The delivery of IPTp-SP and ITNs lies principally with reproductive health, whereas
responsibility for case management of malaria in pregnancy lies with curative or medical services, with malaria control programmes providing technical oversight [75]. The relationship between the reproductive health department, medical services and the malaria programme is an important element of the success of implementation of malaria control policies [86]. Successful implementation requires strong inter-departmental communication from national through to sub-national levels of the health system, the wide availability of evidence-based guidelines [87], strong programme linkages, sustainable financing, adequate human resources and ongoing programme evaluation.

1.7.3. ANC platform

Malaria prevention interventions (IPTp-SP and ITNs) are delivered to pregnant women through routine ANC services as part of a comprehensive focussed antenatal care package. Focussed antenatal care (FANC) is a goal-oriented antenatal care approach, which was recommended by researchers in 2001 [88] and adopted by WHO in 2002 [89]. FANC aims to promote the health of mothers and their babies through: identification and treatment of disease, early detection of complications and referral of high risk pregnancies; prophylaxis and treatment for anaemia, malaria, and sexually transmitted infections including HIV and syphilis, urinary tract infections and tetanus; and counselling. WHO recommends four ANC visits during pregnancy as part of a continuum of care from adolescence, through pregnancy, childbirth, the postnatal period, and childhood [90]. Public sector ANC facilities predominantly provide IPTp free of charge, and ITNs are provided either free or subsidized, for example, through the use of vouchers [91,92], whereas private sector providers usually apply user fees.

1.7.4. Other delivery channels

Additional strategies for delivering malaria in pregnancy interventions are needed for women who do not access ANC. Community based promotion and distribution of IPTp-SP has been evaluated in Burkina Faso [93], Malawi [94], Nigeria [95] and Uganda [96,97] with mixed results, some studies identifying the potential pitfall of the strategy as diverting women away from ANC and consequently access to other essential antenatal care services delivered by trained health providers. Community-based financing and distribution of ITNs alongside other essential health services, under UNICEF’s Bamako initiative programme in Burundi, Guinea, Kenya, and Nigeria, was found to be highly dependent on local contextual factors, such as the degree of decentralisation of the health services, community views on paying for services, and competition from other ongoing initiatives [98]. More recently, periodic campaign delivery of ITNs has been adopted in many African countries with the objective of achieving universal coverage, however evaluation of pregnant women’s intra-household access to ITNs through this strategy is not always considered [99].

1.8. Coverage

The Roll Back Malaria (RBM) Partnership has set increasingly ambitious targets for malaria prevention interventions among pregnant women in sub-Saharan Africa, starting with the original Abuja target of at least 60% of all pregnant women at risk of malaria have access to IPTp-SP and use ITNs by 2005 [76], increasing to 80% by 2010 [69], and most recently to 100% by 2015 [100]. Based on national survey data for ANC attendance and tetanus toxoid vaccinations, most countries could have achieved the 2005 target of 60% coverage for ITNs were every women who made a first ANC visit given an ITN, and many countries also the IPTp-SP target, were every women who made an ANC visit in the second and
third trimester given IPTp-SP, and yet up until 2013 attainment of the 2005 and 2010 targets have for most countries in sub-Saharan Africa have remained elusive [84]. The disparity between ANC coverage versus IPTp-SP and ITN coverage points to a high proportion of missed opportunities at ANC clinics, and suggests failings in the translation of these two relatively simple policies into practice [75]. Indeed, according to a ‘Countdown to 2015 report’, in 20 countries with data, IPTp and ITN use in children together with case management of malaria during pregnancy had the lowest coverage among all interventions delivered across the continuum of care [101], though the data masks important variations at country level. Furthermore, national survey data do not address the quality of IPTp-SP or ITN provision, for example whether IPTp-SP was given by directly observed therapy or at the appropriate gestation or in relation to the previous dose and other antimalarials used for treatment of clinical episodes.

Reasons for the failure to achieve coverage targets for malaria in pregnancy interventions are complex, and involve a range of health systems, health provider and socio-economic and individual factors affecting pregnant women’s care seeking behaviour. A systematic examination of the socio-cultural, economic and health systems constraints to the delivery and uptake of malaria in pregnancy interventions in the context of other ANC services would provide a rational basis for increasing the effectiveness of antenatal clinics to provide these and related services. In addition, programme managers need rapid assessment tools that capture relevant data at district, facility, and community level, as part of health facility quality assessments, to detect bottlenecks early and facilitate the scale up and use of these highly cost-effective interventions to control malaria in pregnancy.

2. Research Objectives

The overall aim of the research was to explore the coverage of malaria in pregnancy interventions in sub-Saharan Africa and the key factors affecting delivery, access and use from provider and user perspectives, and to develop methods for measuring programme and community effectiveness of interventions in programme settings to provide a rational basis for strategies to improve coverage.

Specific Objectives:

1. To review progress with coverage of policy interventions to prevent malaria in pregnancy in sub-Saharan Africa (Chapters 2 and 3).
2. To review the evidence of key factors affecting delivery, access and use of interventions to control malaria in pregnancy from the perspectives of pregnant women, health providers and the health system (Chapters 4, 5 and 9).
3. To evaluate survey methods for assessing community and health systems effectiveness of IPTp-SP and ITNs, and to explore the predictors of IPTp and ITNs uptake (Chapters 6-8).
4. To explore the perceptions, views and experiences of pregnant women and other community groups on accessing ANC and malaria in pregnancy interventions (Chapter 8).
5. To provide local evidence on the factors affecting women’s access and provider practices for the control of malaria during pregnancy in Kenya and Mali (Chapters 6-8).
3. Study Context

The studies presented in this thesis were conducted under the auspices of the Public Health Impact theme of the Malaria in Pregnancy Consortium’s research strategy, which is funded through a grant from the Bill and Melinda Gates Foundation to the Liverpool School of Tropical Medicine, UK (http://www.mip-consortium.org/index.htm). The Liverpool School of Tropical Medicine is the coordinating centre of the Malaria in Pregnancy Consortium, established in 2007 and comprises 41 partner institutions in 29 countries. The partnership is undertaking a seven-year research programme to provide new evidence to improve the control of malaria in pregnancy across a range of transmission settings. The Consortium’s primary aims are several: First to identify at least two antimalarial treatments that are safe, effective and practical to use for the case management of malaria in pregnancy; Second, to identify new safe and effective antimalarial drugs for its prevention in pregnancy; Third, to identify new screening strategies with rapid diagnostic tests that can be used in rural settings to replace drug-based prevention strategies in areas with reduced/low transmission or high drug resistance; and Fourth, to better define the overall burden of malaria in pregnancy in Asia and Latin America, which have predominantly low levels of malaria transmission and a co-existence of P. vivax, which has the infamous dormant liver stage, and determine the optimal strategy for the control of malaria in pregnancy in these areas. In addition, we are conducting studies to increase women’s access to and use of care packages associated with malaria in pregnancy in different contexts under the Public Health Impact theme. This theme consists of a series of multi-disciplinary studies involving anthropology, economics and implementation research so that policy changes and other enablers can be employed to improve access to pregnancy trial interventions within the context of antenatal care programmes. The implementation research studies explore the factors from the user and provider perspective that impact upon access to and use of current services for malaria in pregnancy provided through ANC.

4. Methods

The studies comprise a series of three inter-related systematic reviews (4.1.1) and a series of field studies in Kenya and Mali, which were undertaken in collaboration with the London School of Hygiene and Tropical Medicine, UK; the Centers for Disease Control and Prevention, US; the Kenya Medical Research Institute, Kenya; and the Malaria Research and Training Centre, Mali (4.1.2).

4.1.1. Systematic reviews and meta-analyses

Despite clear documented evidence on the burden of malaria in pregnant women and the availability of proven effective interventions, as adopted/recommended in global and Africa Regional policies, coverage of malaria prevention in pregnant women in many malaria African endemic countries remains unacceptably low. Three systematic reviews were undertaken to:

4.1.1.1. Identify the extent of gaps in coverage of key malaria in pregnancy (MiP) interventions in countries in sub-Saharan Africa by updating an existing database with data from more recent national surveys. This involved an analysis of national survey data on coverage of intermittent preventive treatment (IPTp) and
insecticide treated bets (ITNs) at the subnational level, given some countries show high variation among regions. National level coverage data were examined by rural/urban strata and socio-economic status. For each country, information was extracted on policy processes, Global Fund applications for MiP content, progress made in coverage, and delivery strategies, e.g. type of ITN distribution used, payment policy for IPTp, training content and provision on IPTp, institutions supporting the malaria programme etc. Information was extracted using resources available on the internet e.g. Global Fund proposals, PMI plans, national malaria strategic plans, literature on coverage.

4.1.1.2. Systematically examine the existing scientific evidence for the determinants of access, delivery and use of IPTp and ITNs to define a set of priority categories for barriers and their resolution. This review examined factors from the user and provider/health system perspectives, and included quantitative, qualitative and mixed methods research studies. Analysis used narrative synthesis, content analysis and meta-analyses to explore the data and determine key emerging themes in terms of barriers to scale up of IPTp and ITNs.

4.1.1.3. Systematically examine the existing scientific evidence for access, delivery and use of case management of malaria in pregnancy to define a set of priority categories for barriers and their resolution. This review examined factors from the user and provider/health system perspectives, and included quantitative, qualitative and mixed methods research studies. Analysis used narrative synthesis, content analysis and meta-analyses to explore the data and determine key emerging themes in terms of barriers to access (user) and adherence to national treatment policy (providers) for malaria in pregnancy.

4.1.2. Field studies

The overall aim of the field study was to develop programme friendly rapid assessment tools to identify and quantify the major barriers to the scale up and use of interventions for the control of malaria in pregnancy. The study was undertaken in two countries in sub-Saharan Africa that represent different malaria (and HIV) epidemiological, health systems and cultural contexts - Kenya and Mali. A combination of survey techniques were used to assess barriers at the levels of ‘access’, ‘delivery’ and ‘use’, using household surveys and focus group discussions (presented in the thesis), and health facility surveys using observations of the ANC process, interviews with health staff at facility and district levels, and ANC exit interviews with pregnant women (published elsewhere). Analyses of quantitative and qualitative data are presented and findings used to explain the intervention coverage and consequent community effectiveness. Strengths and weaknesses of the study methods are discussed and used to illustrate how they can provide complementary information to improve delivery and uptake of interventions.

Study Areas

Kenya: Kenya has a strong history of primary health care, delivered through a decentralised health system governed by the County Health Management Teams. The national policy in Kenya is for pregnant women to receive a package of interventions through antenatal care at each of four recommended focussed ANC visits. Malaria in pregnancy interventions at the time of the study
included a free LLIN provided to all women at their first ANC visit, a minimum of two doses of IPTp-SP taken under DOT and prompt diagnosis and treatment of malaria episodes with an effective antimalarial alongside health education at ANC [102]. According to current national guidelines, the first dose of SP should be given to all women after quickening and subsequent dose(s) taken at least 4 weeks (one month) apart. HIV positive pregnant women taking daily cotrimoxazole should not be given IPTp-SP [102,103].

The study was conducted in Greater Nyando County (now subdivided into Nyando, Muhoroni and Nyakach counties) in Nyanza Province, Kenya, between February and March 2010. Greater Nyando County had a population of 355,800 (1999 census), with more than 90% living in rural areas. Malaria is perennial holo-endemic with a parasite prevalence of 8.3% among women of child-bearing age (2008 unpublished data, KEMRI/CDC), peaking between April to June and October to December. HIV prevalence among women aged 15-49 years is higher in Nyanza Province compared to all other provinces in the country, 18% compared to national average of 9% [104]. Greater Nyando had a total of 40 health facilities of which 60% (24) were owned by the government, 13% (5) by missions, 18% (7) privately owned and 10% (4) community run. The government facilities comprised one hospital, two sub-district hospitals, six health centres and 15 dispensaries, the mission owned one hospital, three health centres and one dispensary and the community-owned four dispensaries.

Figure 2. Map of the study site in Nyando County, Nyanza Province, Kenya. The red symbol shows the GPS coordinates of the households within 40 clusters included in the study. The red cross symbol shows the position of the 10 health facilities included in the parallel health facility survey. GPS data visualised using www.GPSVisualizer.com. Maps visualised using Google Earth 2013®

Mali: The health care system in Mali is severely under-resourced. The government funds health facilities down to district level only, comprising one hospital and one district level health centre termed the Centre de Santé de Reference (CSRef). All health facilities below this level, at what is termed the operational level, are funded by communities themselves through a concept developed
initially as the ‘Bamako Initiative’ [105]. This engagement was done to push external partners and the government to transfer responsibility to the community for the creation, organisation and management of community health services (CSCom) through the ASACO (community health association) created in each ‘health area’. Malaria in pregnancy services are provided through Consultation Prénatale (CPN, or ANC) and at the time of the study included two doses of IPTp-SP administered by DOT between month 4 and 8 (inclusive) gestation, with each dose given at least one month apart, and three doses for women who are HIV positive, and provision of a free LLIN to all women at first ANC visit in areas of high transmission [106].

The study was conducted in Segou District, Segou Region (Figures 3 and 4), in September 2009. Malaria in Segou Region is seasonal ranging from holo-endemic in the southern part of the district and meso-endemic to the north. HIV prevalence is 1.3% in the general population of Segou and 1.7% in women aged 15-49 years [107]. Segou District had a total population of 448,552 projected from the 1998 census, with more than 60% of this population living in rural areas. The most common ethnic groups are Bamanan and Sarakole/Soninke, and the main economic occupation of the occupants is subsistence agriculture. Segou District had a total of 26 functioning health structures, 18 of which were owned by the community (i.e. headed by a nurse paid by the community) and eight of which were headed by a physician paid by the government. The government facilities comprised one hospital and one district level health facility (CSRef) based in Segou town (district headquarters).

Figure 3. Map of the study site in Segou District, Segou Region, Mali. The red symbol shows the GPS coordinates of the households within 40 clusters included in the study. The red cross symbol shows the position of the 10 health facilities included in the parallel health facility survey. GPS data visualised using www.GPSVisualizer.com, Maps visualised using Google Earth 2013®

![Map of the study site in Segou District, Segou Region, Mali.](image-url)
5. Overview of chapters

Chapter 1 is a general introduction to the burden of malaria in pregnancy and its impact on maternal and newborn health. Global policies for controlling malaria in pregnancy are outlined and progress with policy implementation in the context of reproductive health in sub-Saharan Africa introduced.

Chapter 2 describes progress with the scale-up of IPTp in three countries in East Africa that had adopted IPTp by 2007, three years after the introduction of WHO’s first Africa regional strategy for malaria in pregnancy.

Chapter 3 provides an update of progress with coverage of IPTp and ITNs using a synthesis and meta-analysis of national survey data from across countries in sub-Saharan Africa.

Chapter 4 presents the results of a systematic review and meta-analysis of the factors and determinants affecting the delivery, access and use of interventions to prevent malaria in pregnancy in sub-Saharan Africa, providing the main obstacles to progress.

Chapter 5 provides a case for continuing the provision of ITNs to pregnant women through routine ANC services.

Chapters 6 and 7 assess the effectiveness of antenatal clinics to deliver IPTp and ITNs using household survey data from Kenya and Mali.
Chapter 8 provides a qualitative analysis of focus group discussions with pregnant women and other community groups of the factors affecting access and use of antenatal clinic and malaria in pregnancy interventions.

Chapter 9 presents the results of a systematic review and meta-analysis of women’s access and provider practices for the case management of malaria during pregnancy.

Chapter 10 discusses the implications of the main findings from the systematic reviews, meta-analyses and case studies in Kenya and Mali for policies and programmes. In addition, the potential of the methodologies used here and elsewhere to develop tools that can assist programme managers to improve service delivery are discussed.
Introduction

References

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