Interventions, surveillance and monitoring of malaria in pregnancy in rural southern Malawi
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Discussion

Introduction
The aims and specific objectives of this thesis were achieved. In the general introduction, the thesis highlighted the evidence that in malaria endemic areas, malaria in pregnancy is a significant cause of maternal and infant morbidity and mortality. For example, a study in Mozambique showed that the risk of dying during infancy was higher among infants born to women with acute placental infection (OR 5.08, 95%CI 1.77–14.53), parasitaemia in cord blood (OR 19.31, 95%CI 4.44–84.02), low birth weight (OR 2.82, 95%CI, 1.27–6.28) or prematurity (OR 3.19, 95%CI 1.14–8.95). Infants born to women who had clinical malaria during pregnancy (OR 1.96, 95%CI 1.13–3.41) or acute placental infection (OR 4.63, 95%CI 2.10–10.24) had an increased risk of clinical malaria during infancy [1]. Pregnant women at increased risk of malaria include: primigravidae, secundigravidae, HIV infected and/ or adolescents [2]. There are challenges facing the use of intermittent presumptive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) as one of the three World Health Organisation recommended interventions for malaria control during pregnancy. In sub-Saharan Africa, these challenges include low (<60%) coverage despite high (>80%) antenatal care clinic (ANC) coverage; widespread SP resistance (≥25%) for the treatment of uncomplicated symptomatic malaria as demonstrated in children under five years of age; and high (≥10%) HIV prevalence [3]. A recent (2007) estimate from a synthesis and analysis of national survey data from sub-Saharan countries showed that despite high antenatal care coverage of 77%, only 25% of pregnant women received at least one dose of IPTp-SP and ITN coverage was 39% [4]. This study therefore aimed to address some of these challenges by assessing monitoring and evaluation approaches. These included: feasibility, effectiveness and effects of community based distribution of IPTp-SP as a complementary approach to the routine ANC based system; 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 increasing (≥25%); an integrated sentinel surveillance approach for malaria and neglected tropical diseases (NTDs) in an area with a well established community drug distribution system for NTD control; trends in malaria in pregnancy and pregnancy outcomes among adolescents over a ten year period; the use of maternal anaemia as an indicator for monitoring malaria in pregnancy; and the effectiveness of assessing interventions for malaria control in pregnancy using a screening method which has previously been used in vaccine efficacy estimation. These objectives were achieved and the results presented in chapters one to six. Below is the summarised discussion of the key results, with some consideration of the future challenges and research needs.

Effect of community based distribution on IPTp-SP coverage
The community based study demonstrated the feasibility and acceptability of community based distribution of IPTp-SP as a supplemental activity to antenatal distribution of IPTp. Comparable findings were reported from Uganda in a study which demonstrated that community based IPTp-SP distribution by different community health workers (traditional birth attendants, drug-shop vendors, community reproductive health workers, and adolescent peer mobilizers) complemented the health facility based system. In the Ugandan study, coverage of IPTp-SP was significantly higher in community than in health facility based distribution areas (≥2 SP doses, 67.5% vs 39.9%, p<0.0001) [5]. In Burkina Faso where SP was made available through
nearest health facilities, uptake of two or more doses IPTp-SP was higher in areas with additional community promotion of IPTp-SP than in those areas not receiving this promotional campaign (70% vs 49%, *p*<0.014) [6].

**Effect of community based IPTp-SP distribution on antenatal care clinic (ANC) attendance**

Although IPTp-SP coverage was improved through the community based programme, the present study clearly demonstrated that community based distribution of IPTp-SP had negative effects on ANC and/or delivery attendance. In the intervention area, ANC attendance (≥2 visits) was reduced from 87% before to 66% (*p*<0.05) following introduction of the intervention, while in the control area it consistently remained high (over 90%). This may suggest that SP is one of the important incentives that motivate women to attend ANC, and as a consequence making it available at the community may reduce the perceived need for a health facility visit. Reduction in ANC attendance was also observed in the Ugandan study although specific details were not reported. In the Ugandan study, ANC attendance (≥4 visits) was lower in community than facility based IPTp-SP distribution areas (56.8% vs 76.1%). Key knowledge of malaria prevention during pregnancy (use of ITNs, and IPT with SP) was also lower in intervention than control areas (80.9% vs 89.3%, 59.2% vs 67.5% respectively) [7]. Community based IPTp-SP promotion in Burkina Faso had a greater impact in adult pregnant women as fewer adolescents (age <19 years) attended ≥3 ANC visits [8-9]. Reduced ANC attendance with community based IPTp-SP distribution would also lead to reduced coverage with other ANC interventions such as haematinic supplementation, ITNs, tetanus toxoid vaccination, HIV testing and counselling (HTC), prevention of mother to child transmission of HIV (PMCT) and possibly health awareness.

**Effect of community based IPTp-SP distribution and/or promotion on maternal anaemia, parasitaemia at delivery and low birthweight**

High coverage (>80%) of IPTp-SP (≥2 doses) in the study intervention area did not translate into reduced prevalence of maternal anaemia, peripheral parasitaemia at delivery, or low birthweight in comparison to the control area. Effect of higher IPTp-SP coverage may have been less marked due to the low ITN coverage and low haematinic supplementation that resulted as a consequence of lower antenatal clinic care attendance in the intervention group. Other studies have reported that IPTp-SP uptake (administered at the community or health facility level) had limited effectiveness for improved pregnancy outcomes [6, 8-10]. This may indicate that at community level, as with immunisation, very high coverage (>80%) is required in order to demonstrate effectiveness compared to lower coverage areas [6], or that IPTp-SP has lost its protective effect because of increasing SP resistance and/or ITN use.

**Community based IPTp-SP future directions**

Based on the negative effects of community based IPTp-SP distribution on ANC attendance demonstrated in both the Malawi and Uganda studies, there are clear concerns about its policy relevance and implications. The sustainability and cost effectiveness of using community health workers has also been questioned [11], and
their performance may be compromised with provision of integrated health services compared to a single special service [12]. Furthermore, drug distribution by community health workers will require regular supportive supervision and monitoring which is already a challenge in resource poor settings because of lack of transport, funds for fuel, staff and logistics. Improving existing health systems for delivering ANC based IPTp-SP is a priority. Better understanding and awareness of the benefits of ANC, in addition to its practical utility for delivering IPTp, should be promoted. Community based interventions which address this promotive approach should be developed and evaluated.

**Surveillance of pregnancy outcomes and monitoring of malaria interventions during pregnancy**

This research has shown that over a period of ten years (1993 to 2002) for participants living in the same study area, the burden of malaria in adolescent primigravidae decreased and their pregnancy outcomes improved. Prevalence of moderate/severe maternal anaemia (Hb<8.0g/dl) and peripheral parasitaemia at delivery decreased from 32% to 20% and 31% to 6% respectively. Prevalence of low birthweight decreased from 28% to 12% and mean birthweight increased from 2,679g to 2,947g. The decreasing trend of the burden of malaria in pregnancy and improvement in pregnancy outcomes has also been reported for urban Malawian women living around Blantyre [13]. Improved coverage of IPTp-SP and ITNs must have contributed to these changes. However, adolescent pregnant women remain a high risk group requiring specific health promotion interventions to improve antenatal attendance, IPTp-SP uptake, ITN coverage and health facility delivery attendance, as demonstrated in the present study, as well as by others [8-9, 14].

**SP failure in pregnancy, what next?**

Published studies on the *in-vivo* parasitological response to SP during pregnancy are rare and therefore our findings at the time when SP was being withdrawn for the treatment of clinical malaria for both adults and children although maintained for IPTp use provide essential baseline data. With reference to a similar study conducted in the same area, parasitological failure to SP during pregnancy increased from 5% to 20% at day 28 during the eight year period [15], and paralleled changes in SP drug resistance in children with symptomatic malaria during the same period. Lower parasitological failure rates in asymptomatic pregnant women than in symptomatic children under 5 years of age have been reported [16-17]. The *in-vivo* study contributed to mounting evidence on increasing SP failure in pregnancy. Parasitological failure in pregnancy of 33% at day 28 has been reported in a recent (2009-2010) study conducted in the same district (Chikwawa) as the present study, and also in peri-urban Blantyre, with failure rates in primigravidae and secundigravidae as high as 50% (Kalilani L et. al. personal communication). Longitudinal (1997-2006) malaria in pregnancy study in Blantyre demonstrated that IPTp-SP lost protective efficacy since 2002. Among women enrolled from 1997–2001, the number of IPTp-SP doses received were associated with protection against placental parasitaemia, maternal anaemia and low birth weight, with increased mean maternal haemoglobin level and birth weight. Whereas from 2002 onwards, these protective associations were not demonstrated [13]. At molecular level, the emergence and magnitude of resistance to SP is monitored by measuring the prevalence of single nucleotide polymorphisms (SNPs) in the *P. falciparum* dihydrofolate reductase (*Pfdhfr*) gene, responsible for pyrimethamine
resistance and the dihydropteroate synthetase (Pfdhps) gene, responsible for sulfadoxine resistance [18]. In Malawi, data on the trends of molecular markers of SP resistance are scarce. However, data from neighbouring Tanzania showed that prevalence of the *P. falciparum* dihydropteroate synthase (Pfdhps) gene 581G mutation increased from 12% in 2003 to 56% in 2007 (*P* < 0.001) in children and adolescents [18-19]. Continued use of SP in pregnancy in a setting of widespread resistance may be harmful as demonstrated by a study in Tanzania reported by Harrington *et al.* [20]. In the Tanzanian study, IPTp-SP uptake was associated with increased prevalence of parasitaemia at delivery, placental inflammation and the proportional fraction of parasites carrying the resistance allele dihydropteroate synthase (DHPS) codon 581 associated with high *in-vitro* SP resistance. The highest mean level of parasitaemia occurred after recent IPTp use. These findings supported a model of parasite release and facilitation, whereby the most highly resistant parasites out-compete less fit parasite populations and overgrow under drug pressure.

Although WHO is still recommending the continued use of SP for IPTp even in settings where SP parasitological failure in children under the age of 5 years is as high as 50% at day 14 [21], the increasing number of reports of SP parasitological failure in pregnancy, the loss of protective effects of IPTp-SP, and the potential harmful effects of IPTp-SP in settings with widespread SP resistance all pose questions on the duration of further SP utilisation, and on which drug(s) might provide appropriate alternatives. The possible next steps could be use of a new antimalarial drug combination for IPTp, an alternative control strategy, or a combination of both.

At least ten antimalarials drugs could be used during pregnancy. These include: chloroquine, amodiaquine, quinine, azithromycin, sulfadoxine-pyrimethamine, mefloquine, dapsone-chlorproguanil, artesiminin derivatives, atovaquone-proguanil, or lumefantrine. Antimalarial drugs that should not be used in pregnancy include halofantrine, tetracycline/doxycycline, and primaquine [22]. Several randomised control trials on efficacy of different combinations of these drugs for the treatment of malaria in pregnancy have been published and Cochrane and other reviews are available [23-25]. The challenge has been to find a combination of antimalarials to replace SP for IPTp taking into account many factors including, cost, tolerance, multiple dosing, lack of direct observed therapy, lack of co-formulation, short half life of some drugs, availability, acceptability, WHO approval, and limited data on safety [24, 26-27]. Monotherapy and combining a new drug with an old drug which once failed (such as chloroquine or SP) would be discouraged because resistance may develop rapidly. Although significant progress has been achieved in conducting antimalarial drug efficacy trials in pregnancy and substantial data on the efficacy and safety of different combinations is now available, there are still outstanding issues in establishing the ideal antimalarial combination for IPTp.

The second way forward could be developing a new strategy for administering effective drugs. Intermittent screening and treatment (IST) has been piloted in Ghana where women were screened for malaria using a rapid diagnostic test (OptiMal®) during focused antenatal care visits. Malaria positive women were treated with artesunate amodiaquine (ASAQ). Those who were negative received routine SP for IPT. This new IST strategy was acceptable to pregnant women, was as safe and effective as the standard IPTp-SP based on outcome assessments for maternal anaemia and low birth weight [27-28]. The artesunate amodiaquine combination has been shown as one of the most efficacious artemisinin-based combinations in pregnancy [29], and the drug is already registered in many countries in sub-Saharan Africa, either as first or second line...
drug for the treatment of uncomplicated malaria. In Malawi it is the second line drug with lumefantrine- artemether (L.A) as first line. With the implementation of universal coverage with effective vector control methods (insecticide treated nets and/or in door residual spray) it could be assumed that the proportion of women with placental malaria who would be missed by screening with rapid diagnostic tests would be minimal and therefore IST may be a recommendable alternative strategy. It could be integrated with existing haemoglobin testing, HIV testing and counselling, or syphilis screening. The challenge would be sustaining the availability, use and compliance of RDTs in all ANC clinics (static and outreach). In situations where the drug combination has a relatively long half-life and is the second line treatment (as in Malawi), or where it is not yet registered, then making it the first line choice in pregnant women may lead to confusion in policy implementation.

In summary, therefore, based on the challenges with different potential antimalarial combinations on cost, deliverability, tolerance, half-life, and multiple dosing, then IST could be an interim way forward provided operational issues to make RDTs available are overcome and their use and compliance in ANC clinics is addressed. The current Roll Back Malaria promotion for universal coverage would work in favour of IST. The application of screening both at first antenatal visits as well as before delivery should be assessed, as late pregnancy screening would enable detection of new infections acquired towards term, as well as drug resistant infections.

**Monitoring and evaluation of pregnancy outcomes in the context of malaria elimination and eradication goals**

In October 2007, the 1955 malaria eradication goal of Global Programme for Malaria Eradication, which was abandoned in 1969, was resurrected by the Melinda & Bill Gates Foundation and was subsequently endorsed by the WHO and by the Roll Back Malaria Partnership [30-33]. The 1955 goal used indoor residual spraying with DDT as a strategy and was successful in eliminating malaria in Europe. The reinvigorated malaria elimination and eradication goals promote universal coverage of effective case management, vector control methods (ITNs/LLNs and/or IRS), and IPTp-SP by 2010 (80% coverage) and 2015 (universal coverage) [34]. Malaria elimination is defined as reducing incidence to less than 1 per 1000 population, whereas eradication is reduction of incidence to zero [34]. As countries are scaling up interventions to achieve universal coverage, and sustain high coverage, there is a need for integrated monitoring and evaluation of the interventions. In settings where less than 40% of pregnant women deliver in health facilities, which is most parts of sub-Saharan Africa, the use of routine facility based data such as maternal anaemia at delivery and birthweight may not be representative of community outcomes. However data collected from health centres and/ or dispensaries, which are closer to the community, should be more representative than hospital data [35]. The need for effectively incorporating different M & E approaches including: assessments of therapeutic and prophylactic drug efficacy using the modified WHO protocol in pregnancy; proportional reductions in parasite prevalence; seasonal effects; rapid assessment methodologies; birthweight and/or anaemia nomograms; case-coverage methods; maternal mortality indices; operational and programmatic indicators; and safety and pharmacovigilance of antimalarials in pregnancy, in National Malaria Control Programmes has been highlighted [36].

This research has demonstrated that the screening method which has been used in assessing vaccine efficacy could be applied to assess malaria interventions in pregnancy using routinely collected appropriate data such as low birthweight and maternal...
anaemia at delivery. This method could be complementary to monitoring the protective effect of IPTp-SP (≥2 doses). The study has also demonstrated that it is feasible to implement an integrated sentinel surveillance approach for monitoring of interventions for both malaria and neglected tropical diseases thereby enhancing effective use of the limited available resources.

**Future surveillance and monitoring of malaria in pregnancy with falling malaria prevalence**

Globally, because of the scale up of effective malaria control interventions, the burden of malaria cases and deaths has declined significantly between 1990 to 2009 [37-39]. A study in Malawi by Feng *et. al.* showed that between 1990 and 2009, prevalence of placental and maternal peripheral parasitaemia at delivery declined from 25.2% to 6.8% and from 23.5% to 5.0% respectively [13]. Our findings (this thesis) of the analysis of trends for pregnancy outcomes (Chapter 2), *in-vivo* parasitological study (Chapter 3), and the integrated sentinel surveillance study (Chapter 4) are in agreement with these observations. As countries move towards malaria elimination with increasing universal coverage there is need to strengthen surveillance, monitoring and diagnosis of malaria. Microscopy has low sensitivity at low gametocytes levels. Application of highly sensitive, user-friendly molecular techniques such as the polymerase chain reaction (PCR) [33, 40], rapid diagnostic tests such as OptiMAL® [41], and serological tests [42] have been proposed for surveillance. In addition, the development of appropriate sampling methods for detection of malaria in situations where the prevalence of infection is low, including comparisons of active and passive case-detection techniques and development and/ or strengthening of monitoring systems to provide accurate information on the incidence of clinical malaria have been highlighted [33].

As the prevalence of malaria declines it will be important for malaria control programmes to strengthen their surveillance and monitoring systems including the widespread introduction of more sensitive and specific diagnostic tests to able to detect malaria cases even at low parasite densities.

**Surveillance and monitoring of adverse effects of antimalarial drugs during pregnancy: emphasis on the inadvertent use of artemisinins during the first trimester**

Reports from experimental animal trials showed that artemisinins were embryotoxic and teratogenic [43-44]. The limited available data in clinical trials that included first trimester pregnant women have so far showed that such toxic effects are rare [45-46]. A study from Zambia reported by Manyando *et. al.* showed that exposure to artether-lumefantrine during the first trimester was not associated with particular safety risks in terms of perinatal mortality, malformations, or developmental impairment of the infant [47]. Nevertheless, the current WHO guidelines recommend that for the treatment of uncomplicated malaria in pregnancy, ACTs should be used in the second and third trimesters of pregnancy. They should not be used in the first trimester unless they are the only treatment available, or if the patient’s life is threatened, or if treatment with quinine has failed [48-49]. The guidelines take into account the greater confidence regarding the safety of ACT exposure in the second and third trimesters, and the scarcity of data on first trimester exposure versus the risk of embryotoxicity. As countries adopt and scale up WHO recommendation on the use of ACTs for malaria treatment, inadvertent use of these drugs in the first trimester will not be uncommon either because the women may not be sure of pregnancy in the early weeks or of last date of normal menstrual period or the health worker may not ask for such information.
before prescribing the drug. National malaria control programmes therefore need to establish and/or strengthen pharmacovigilance system which will provide data on the adverse effects of ACTs including those that may result from inadvertent use during the first trimester. The pharmacovigilance system should be linked to antenatal, delivery, postnatal and neonatal care system to identify suspected cases of adverse events of ACTs from drug history during pregnancy.

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