Malaria and anaemia in pregnancy: importance, detection and prevention
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Summary

The work discussed in this thesis addresses the important topic of severe anaemia and malaria in pregnancy.

Initially the causes of severe anaemia in Kilifi Kenya were investigated, and malaria was found to be an important cause of severe anaemia in primigravidae in the population. Other major risk factors for the anaemia were iron deficiency and hookworm infestation (particularly in multigravidae).

This preliminary work was followed by intervention trials undertaken to investigate ways of preventing severe anaemia secondary to malaria in primigravidae.

**Insecticide Treated Bednets (ITBN)**

As part of a large community randomised trial of ITBN in Kilifi District, which addressed the impact of bednets on childhood mortality and severe morbidity, we investigated the impact of ITBN on malaria and anaemia in pregnancy. The ITBN had very little impact on anaemia and no impact on peripheral parasitaemia. Possible explanations for this include: pregnant women did not use the nets consistently, possibly due to uncomfortable heat; women went to bed after the peak biting time or frequently got out of bed in the night to pass urine; or that placental infection is not substantially reduced despite a reduction in transmission.

Other evidence on the lack of effectiveness of ITBN in preventing malaria or anaemia in pregnancy in this population, comes from the trial of intermittent SP (chapter 4) [1], as this was carried out in both a bed-netted population and a non-netted population. The magnitude of the impact of intermittent SP on severe anaemia and parasitaemia was similar in both the netted and the non-netted areas, confirming that in this setting, ITBN alone were not sufficient protection for pregnant women.

Work on the impact of bednets in pregnant women by other investigators has shown variable effects. In Ghana, in an area of perennial transmission, ITBN had no impact on maternal anaemia, malaria infection or birthweight [2]. However, in Thailand, in an area of low transmission [3], ITBN were associated with a halving of anaemia rates. In The Gambia [4], where transmission is limited to one short season a year, in the dry season women from villages with insecticide treated bednets had less severe anaemia than women from villages with untreated nets (OR 0.27, 95% CI 0.07-0.93), though there was no difference in the rainy season. There was an improvement in birthweight in the rainy season of $135\text{g}$ ($p = 0.04$) but a reduction in birthweight in the dry season of the same amount ($p = 0.05$). More recently, in an area of intense transmission, preliminary analysis of data have suggested that ITBN are associated with a reduction in low birthweight (adjusted OR 0.67 (0.53-0.85) (ter Kuile, personal communication).

Overall, the data suggest that in certain settings ITBN offer women substantial protection from some of the adverse outcomes of malaria in pregnancy. However, this impact is
not consistent. The difference seen may be due to differences in the usage of nets during pregnancy by different populations. In view of this, and in the light of the substantial benefit from intermittent treatment with SP in Kilifi District among the populations both with and without ITBN, some form of chemo-prevention (either as chemoprophylaxis or intermittent treatment) should be offered in addition to ITBN's.

**Preventative Intermittent Treatment with Sulfadoxine-Pyrimethamine (SP).**

The other intervention trial described in this thesis is a double blind, placebo controlled, randomised trial of intermittent SP. In this trial women received between one and three doses of SP depending on the gestation at which they first attended antenatal clinic. This regime resulted in a 39% reduction in severe anaemia at 34 weeks gestation and an 85% reduction in parasitaemia. Even women who received only one dose late on in the second or early third trimester benefited from this treatment.

A complimentary study was conducted by different investigators at a similar time in an area of Western Kenya with high malaria transmission [5]. In their study the primary outcome was placental parasitaemia and birthweight. Intermittent SP reduced placental parasitaemia and improved mean birth weight significantly in HIV negative women. However, they found that in this area of Western Kenya, where HIV prevalence is high, two doses of intermittent treatment with SP was inadequate to reduce placental parasitaemia in HIV positive women. In Malawi, where policy changed to intermittent SP in 1993 two operational effectiveness studies have shown that this preventative strategy is still effective at improving birthweight [6] [7].

**Which parities need preventative strategies**

The intervention trial of SP was undertaken in primigravidae (PG) only, because from the preliminary work it wasn't clear whether malaria was an important problem in multigravidae (MG) in this area. It therefore seemed unethical to subject MG to a drug from which they might not be expected to derive any benefit.

In order to determine whether or not MG suffer deleterious effects from malaria in pregnancy a large cross sectional study of women delivering in hospital was undertaken. The rationale was that if the intervention was found to be effective at reducing severe anaemia in primigravidae, it would be important to be able to make recommendations for women of other parities. This cross sectional study demonstrated that women of all parities are at significant risk of placental malaria and the presence of placental infection is as detrimental to multigravidae as it is to primigravidae in terms of both severe anaemia and low birthweight. In addition, an interesting interaction was observed whereby the presence of both severe anaemia and past or chronic placental malaria infection was associated with very profound reduction in birthweight. Having placental malaria in the absence of severe anaemia or having severe anaemia in the absence of placental malaria was not associated with a significant risk of low birthweight. This suggests that the impact of malaria on birthweight may be determined by the combined effect of severe anaemia and placental malaria in the population.

**Anaemia and General Health**

An anaemia specific health-status questionnaire was developed in order to determine the impact of severe anaemia on maternal physical, psychological and social wellbeing and so
to demonstrate the likely benefits of its reduction. Severe anaemia was shown to be an important contributor to ill health in all these areas.

**Screening for Severe Anaemia**

In addition to prevention, it is important that severe anaemia is detected and treated appropriately. Many health facilities (including District level hospitals) are unable to routinely screen for severe anaemia in pregnant women. Consequently, many women leave antenatal clinics without detection of their severe anaemia. We used pallor testing on a large number of women and determined its usefulness as a screening tool. We went on to develop a brief screening questionnaire, based on history, to see if this increased the sensitivity and specificity of pallor testing alone. Pallor testing alone had a sensitivity of 69% for detecting women with a haemoglobin of < 7g/dl. Interestingly, when the same midwife asked the screening questions before examining women for pallor, the sensitivity of the pallor test for detecting women with severe anaemia increased to 84%. This raises the hypothesis that a midwife’s awareness of the general health of a woman (by spending a few minutes talking to her prior to examination) increases the likelihood of detection of severe anaemia by pallor examination.

**Policy Implications and Dissemination**

**Kenya**

At the end of 1997, just as this work was being completed in Kilifi, researchers working in Kisumu, Western Kenya, convened a meeting to discuss malaria in pregnancy. The findings from the work on intermittent SP in both Kisumu and Kilifi were summarised and reported back to the Malaria Control Division in Nairobi.

I undertook additional dissemination of this work, with policy makers and advisors working with the Kenya Ministry of Health including personnel from the Reproductive Health Division and the Safe Motherhood Advisory Committee. Those working with antenatal services and reproductive health were particularly interested in the findings, as they considered severe anaemia in pregnancy to be a major public health problem in Kenya and a major contributor to maternal mortality. They had not been aware of the extent to which malaria in pregnancy caused severe maternal anaemia and were keen to convene a meeting to discuss the findings and policy implications with those working within the Division of Malaria Control. This was also the time that Kenya was changing its first line drug treatment from chloroquine to SP. A subsequent meeting resulted in a unanimous decision to adapt the policy on the prevention of malaria in pregnancy to include the use of intermittent treatment with SP. It was decided that the implementation of such a policy should primarily be the responsibility of the Division of Reproductive Health with technical input from the Malaria Control Division.

**Internationally**

Internationally I presented and discussed the results with the Safe Motherhood and Malaria Control Units at the World Health Organisation, so contributing to the current recommendations for the prevention of malaria in pregnancy. I also held discussions of the results with UNICEF. The results were also presented and discussed at the 2nd European Congress on Tropical Medicine held in Liverpool, UK, in 1998, the Multilateral Ini-
tiative on Malaria conference in Durban, South Africa in 1999, and at FIGO 2000 conference in Washington DC.

For the last couple of years, I have been involved with the Kenya Ministry of Health, supported by the UK Department for International Development (DFID) to assist with developing the strategy for implementation of the policy of intermittent SP in pregnancy. The challenge remains for this to be successfully implemented at every level of the health service. In addition, as resistance to SP is increasing, there is an urgent need to seek alternative antimalarial drugs that can be used safely as intermittent treatment or chemoprophylaxis to prevent malaria in pregnancy.

Since the work described in this thesis started, the profile of malaria (including malaria in pregnancy) has been greatly increased internationally with the WHO Roll Back Malaria initiative. Another potentially exciting initiative that has recently been established and has now received funding is the PREMA (Pregnancy Malaria and Anaemia) network. This aims to include researchers, policy makers and implementers of malaria and anaemia control strategies in pregnancy in developing countries.

The opportunity for co-ordinated action to reduce the burden of malaria and anaemia in sub-Saharan Africa is greater than ever before. The challenge is to ensure that this opportunity is not lost.
REFERENCES
