Malaria and anaemia in pregnancy: importance, detection and prevention
Shulman, C.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
A community randomised controlled trial of insecticide treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan Coast

C.E. Shulman¹,², E.K. Dorman²,³, A. O. Talisuna⁴, B. S. Lowe²,³, C. Nevill²,⁴, R.W. Snow²,³, H. Jilo⁵, N. Peshu², J.N. Bulmer⁶, S. Graham¹, K. Marsh²,³

1 London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT (¹ MSc student)
2 Kenya Medical Research Institute (KEMRI), CRC Kilifi Unit, P.O.Box 230, Kilifi, Kenya
3 University of Oxford, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DU
4 African Medical Research Foundation (AMREF), P.O.Box 30125, Nairobi, Kenya
5 Kilifi District Hospital, Kilifi, Kenya
6 University of Newcastle, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Adapted from: Tropical Medicine & International Health 1998, 3, 197-204
**SUMMARY**

The effectiveness of insecticide-treated bednets (ITBN) in preventing malaria and anaemia among primigravidae living in Kilifi District, Kenya, was assessed by a randomised controlled trial between September 1994 and November 1995. All residents within 28 community clusters received ITBN in July 1993, whilst residents of another 28 clusters served as contemporaneous controls. All resident primigravid women attending antenatal care at Kilifi District Hospital, with singleton pregnancies, were eligible for recruitment. 503 primigravidae were recruited. 91.4% were anaemic antenatally (Hb < 11g/dl): 91.0% from the intervention arm and 92.0% from the control arm. Severe anaemia (Hb < 7g/dl) was found among 15.1% of intervention women and 20.1% of control women (p = 0.28). No significant differences were observed in reports of febrile illness or the presence of chloroquine in the serum or peripheral parasitaemia during the third trimester between the two groups. In the women delivering in hospital (n=130), there was no association between placental malaria infection and the intervention: 77.4% of placentas from control women had evidence of past or active infection, compared with 72.0% of placentas from intervention women (p=0.76). Similarly, in the women delivering in hospital, ITBN did not improve birth weight, and there were no differences in perinatal mortality between the two study groups. Despite ITBN having a great impact on childhood severe malaria and mortality in this transmission setting, there was very little impact of ITBN on the morbidity associated with malaria infection in primigravidae. Alternative strategies are required to tackle this continued public health problem for pregnant women living in endemic areas similar to the Kenyan Coast.
INTRODUCTION

Where *Plasmodium falciparum* malaria is endemic, immunity to malaria develops over the first few years of life, and older children and adults rarely suffer severe complications of malaria. An exception is during pregnancy. It has long been recognised that malaria parasitaemia is more prevalent, with higher parasite burdens, in pregnant compared with non-pregnant women (McGregor 1984, Brabin 1983) and that the increase in prevalence and density of parasitaemia is greatest in primigravidae and decreases as gravidity increases (McGregor 1984, Steketee & Breman 1988).

In endemic areas, the most important effect of *P. falciparum* infection in pregnant women is on haemoglobin, and in much of sub-Saharan Africa malaria is the main cause of severe anaemia in pregnancy particularly in primigravidae (Gilles et al. 1969, Fleming 1989a Fleming 1989b, Shulman 1993). In a previous study in Kilifi (Shulman et al. 1986) we found the main risk factor for severe anaemia (Hb < 7g/dl) in primigravidae was concurrent peripheral malaria parasitaemia, this being associated with an average 2.23g/dl decline in haemoglobin. As anaemia in pregnancy due to malaria infection characteristically presents later than peak parasitaemia (Gilles et al. 1969, Brabin 1983), cross sectional studies such as these may under-estimate the relationship between parasitaemia and anaemia.

Malaria in pregnancy also affects the feto-placental unit, a mean birth weight approximately 150 gms lower being observed in primigravidae with parasitised placentas compared with primigravidae with non-parasitised placentas (McGregor 1983, Brabin 1991). Low birth weight is the most important risk factor for neonatal and early infant mortality (McCormick 1985, Greenwood et al. 1992).

In areas where malaria is epidemic and unstable, such as South East Asia, *P. falciparum* is associated with an increased incidence of spontaneous abortion and stillbirths (WHO 1991, Nosten et al. 1991). Data from endemic areas are few but higher stillbirth rates have been found in women with severe anaemia and concurrent malaria parasitaemia (Brabin 1991), and in Sudan the risk of stillbirth was increased among women who reported malaria attacks in the 1st and 2nd trimester (Taha E.L. & Gray 1993).

The mainstay of the prevention of malaria and the sequelae of malaria infection in pregnancy has been antimalarial chemoprophylaxis taken during pregnancy. Controlled trials have shown that such chemoprophylaxis given to primigravidae can result in a decrease in placental parasitaemia (Morley et al. 1964, Steketee et al. 1996a), reduce the incidence of low birth weight neonates (Morley et al. 1964, Steketee et al. 1996b, Mutabingwa et al. 1993) increase mean maternal haemoglobin (Greenwood et al. 1989) and if given early in the second trimester can prevent the development of severe haemolytic anaemia (Gilles et al. 1969, Kortmann 1972, Fleming & Ghatoura 1986). Although the benefits of prophylaxis with an effective drug seem clear, the problems of poor compliance (Heymann et al. 1990) and increasing antimalarial drug resistance have led to the search for alternative preventative strategies. Of particular interest are insecticide treated bednets (ITBN), which have led to major reductions in childhood morbidity and mortality when introduced to malaria endemic communities (Alonso et al. 1991, Neville et al. 1996, Binka et al. 1996). During a recent study of the effects of ITBN upon childhood mortality and severe malaria morbidity in Kilifi District (Nevill et al. 1996) we conducted this additional study on the effects of reducing parasite exposure upon the adverse consequences of malaria in pregnancy.
MATERIALS AND METHODS

Study area and population
This study was conducted between September 1994 and November 1995 in Kilifi District, 60km north of Mombasa on the coast of Kenya. Malaria transmission at Kilifi is typical of large parts of sub-Saharan Africa. There is perennial transmission of *Plasmodium falciparum* with two seasonal peaks in the principal vectors from the *An. gambiae* s.l. complex, between June - August and during November - December, coinciding with the 2 rainy seasons (Mbogo *et al.* 1995, Snow *et al.* 1993) On average, individuals can expect to receive 10 infective bites per person per annum (ranging from 1 every 2 years to nearly 60 per person per year).

The study women came from a rural population that had already been randomised to receiving or not receiving insecticide treated bed-nets as part of a trial assessing the effect of ITBN on childhood mortality and severe malaria in children (Nevill *et al.* 1996). As part of the trial, a surveillance system was established, which involved mapping and enumeration of over 5,000 households, as has been described elsewhere (Snow *et al.* 1993). The area was subdivided along administrative boundaries within its 3 divisions, into 56 zones of approximately 1000 individuals each. Within each division, zones were randomised into those where all households received bednets and those where no households received bednets. In households selected to receive bednets, sufficient nets were distributed for all members of the household. Green nets, size 190 x 180 x 150cm were impregnated with permethrin to achieve a target dose of 0.5g permethrin per m² of netting (Nevill *et al.* 1996). Randomisation and distribution of nets was completed by August 1993. Education regarding the correct hanging and handling of nets, was performed in the home at the time of and following distribution. Posters were used and group discussions were held throughout the trial, with school based plays and interactive learning sessions being introduced from June 1994 (Marsh *et al.* 1996). Nets were re-treated every 6 months, immediately before the rains in April and October. The bednet trial continued until October 1995, after which time, nets were distributed to all households in the control area.

The majority of the population live within 2 km of a bus stage with regular transport to Kilifi District Hospital. It is estimated that at least 90% of women attend for antenatal care at least once during their pregnancy in Kilifi District (Kirumbi *et al.* 1996). The majority of women from the study area attend for antenatal care at Kilifi District Hospital. There are, in addition, 2 dispensaries within the study area that provide antenatal care to women. These clinics carry out approximately 15% of the antenatal care within this area. Women attending for care at these dispensaries are referred at their first attendance, for investigations at the antenatal clinic at Kilifi District Hospital.

Recruitment and Data collection
Ethical clearance was granted by the Kenyan Medical Research Institute and by the Ethical Committee of the London School of Hygiene and Tropical Medicine. Women were recruited when they attended for antenatal care at Kilifi District Hospital. All primigravid women or women with a previous history of a pregnancy that had not gone beyond 12 weeks, with a singleton pregnancy, who came from the study area, were eligible for recruitment. 9.5% of the women recruited had been referred from one of the 2 dispensa-
ries. Informed consent was obtained from all women after explanation of the study in their first language.

At the recruitment visit, a questionnaire was completed with information on the woman's and her partner's education status, occupation and socio-economic status, along with bednet utilisation and pregnancy history. Gestational age was assessed by a midwife who asked about last menstrual period and measured symphysis-fundal height. A venous blood sample was taken for full blood count in the third trimester (between 28 and 34 weeks gestation) or at any time that a woman was suspected of being severely anaemic. At this time, a retrospective history was taken of drug use and illness episodes during the pregnancy (including both self and health personnel diagnosed malaria). Blood was also tested for malaria parasites and plasma was stored for measurement of chloroquine. HIV status was determined in all women with testing being anonymous with linkage only possible once the names of the women had been destroyed after completion of the study. All women with an Hb of less than 10g/dl were given haematinics and all women with a positive slide were treated with sulfadoxine-pyrimethamine (SP). All women found to be severely anaemic (Hb < 7g/dl) were also given SP irrespective of the result of their malaria smear, based on the assumption that some of those with a negative smear would be likely to have placental parasitisation.

For women delivering in hospital, maternal blood was taken for haemoglobin and peripheral parasitaemia, and a placental smear and biopsy were taken for parasitological and histological assessment of malaria. At the time of delivery, cord samples were taken for haemoglobin and malaria parasites, and birth weight recorded.

All women were visited at home at least 4 weeks (range 4 weeks to 9 months) after their expected date of delivery to ascertain birth outcome in terms of stillbirths, neonatal deaths and maternal deaths.

**Laboratory methods**

Full blood counts were performed on a model M530 Coulter Counter. Thick and thin blood films were prepared for the detection of malaria parasites, using standard Giemsa staining, counting parasites per 200 white cells, and calculating counts per microlitre from the white cell count. 100 high power fields were read to confirm a negative film. HIV testing was done using an IgG capture gelatin particle adherence test (GACPAT), (Parry & Mortimer 1989). Plasma chloroquine assay was performed using ELISA (Witte AM et al. 1990). Placental biopsies were prepared as described previously (Bulmer et al. 1993a and 1993b) and were categorised as showing: active malaria infection (where parasites in maternal erythrocytes in the intervillous space were seen, usually in association with pigment in erythrocytes and monocytes in the intervillous space); active-chronic infection in which pigment was also identified in fibrin; past-chronic infection in which malaria pigment was only seen within fibrin or cells within fibrin; or negative where neither parasites or pigment were seen.

**Statistical methods**

Data entry, validation and cleaning were carried out using D Base IV. Statistical analysis was carried out using STATA (release 4.0 1995, Stata Corporation, Texas, USA). Analysis was on an intention to treat basis. In addition, a comparison was carried out between women from the intervention arm who used their net at least 5 times in the previous week and control arm women without nets.
Table 1 Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control n = 231</th>
<th>Intervention n = 272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyramaa</td>
<td>228 (98.7%)</td>
<td>263 (96.7%)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional</td>
<td>86 (37.9%)</td>
<td>94 (34.9%)</td>
</tr>
<tr>
<td>Christian</td>
<td>113 (49.8%)</td>
<td>142 (52.8%)</td>
</tr>
<tr>
<td>Moslem</td>
<td>28 (12.3%)</td>
<td>33 (12.3%)</td>
</tr>
<tr>
<td>Female literacy (literate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman's education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no schooling</td>
<td>78 (33.8%)</td>
<td>87 (32.0%)</td>
</tr>
<tr>
<td>Primary education</td>
<td>146 (63.2%)</td>
<td>158 (58.1%)</td>
</tr>
<tr>
<td>post primary education</td>
<td>7 (3.0%)</td>
<td>27 (9.9%)</td>
</tr>
<tr>
<td>Husband's education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no schooling</td>
<td>14 (6.1%)</td>
<td>20 (7.4%)</td>
</tr>
<tr>
<td>Primary education</td>
<td>122 (53.3%)</td>
<td>132 (48.7%)</td>
</tr>
<tr>
<td>Secondary education</td>
<td>44 (19.2%)</td>
<td>57 (21.0%)</td>
</tr>
<tr>
<td>tertiary education</td>
<td>15 (6.6%)</td>
<td>18 (6.6%)</td>
</tr>
<tr>
<td>not known</td>
<td>34 (14.8%)</td>
<td>44 (16.2%)</td>
</tr>
<tr>
<td>Married</td>
<td>197 (85.7%)</td>
<td>230 (83.9%)</td>
</tr>
<tr>
<td>Ownership (at least one of: a cow, a bicycle, a radio a latrine)</td>
<td>143 (61.9%)</td>
<td>189 (69.5%)</td>
</tr>
<tr>
<td>Mid upper arm circumference (mean)</td>
<td>23.73 (SD 1.88)</td>
<td>23.87 (SD 2.01)</td>
</tr>
</tbody>
</table>

Because this was a community randomised trial, the analysis outcomes which applied to the whole study population were looked at by cluster with appropriate tests for the differences between intervention and control groups being based on between cluster information (Donner & Klar 1994). For each outcome of interest, the proportion of affected compared with non-affected were calculated for each cluster, and the mean proportion for the study groups determined. Odds ratios were calculated from the proportions and t tests used to assess significance (at the 5% level) of differences. For continuous variables, means of the different groups were computed per cluster and the overall mean in the study groups determined. To identify if there was any confounding, for each potential confounder an adjusted odds ratio was determined using the Mantel Haenzel technique and compared with the unadjusted odds ratio. The sample size was calculated to enable detection of a halving of the prevalence of severe anaemia, an increase in mean haemoglobin of 0.75g/dl and a 30% reduction in the prevalence of placental malaria infection with 80% power and 95% confidence.

RESULTS

503 primigravidae were recruited antenatally: 231 (45.9%) controls and 272 (54.1%) intervention women. 462 (91.8%) had a blood test in the third trimester for haemoglobin and peripheral parasitaemia. 130 (25.8%) delivered in hospital and 497 (98.8%) were followed up at least 4 weeks post delivery. Table 1 is a description of the socio-demographic characteristics of the women recruited.
**ANTENATAL**

**Maternal anaemia and malaria**

The effects of the intervention on anaemia and malaria are summarised in Table 2. This information is based on 219 (94.8%) women from the control arm and 243 (89.3%) women from the intervention arm who had a blood test.

### Table 2  Insecticide treated bednets and antenatal outcomes, analysed on an intention to treat basis, taking clustering into account.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ITBN</th>
<th>Odds Ratio (unadjusted) 95% CI</th>
<th>Odds Ratio (adjusted) 95% CI</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe anaemia (Hb &lt; 7g/dl)</td>
<td>20%</td>
<td>15%</td>
<td>0.69 (0.34, 1.38)</td>
<td>0.71 (0.44, 1.14)</td>
<td>0.15</td>
</tr>
<tr>
<td>peripheral parasitaemia</td>
<td>35%</td>
<td>31%</td>
<td>0.83 (0.48, 1.44)</td>
<td>0.75 (0.52, 1.10)</td>
<td>0.12</td>
</tr>
<tr>
<td>malaria / febrile illness</td>
<td>27%</td>
<td>31%</td>
<td>0.85 (0.47, 1.55)</td>
<td>0.95 (0.66, 1.37)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

* p value for adjusted OR

There was a high prevalence of anaemia in this population with 91.4% of women being anaemic (Hb < 11g/dl), 91.0% in control clusters and 92.0% in intervention clusters. 17.5% of women were severely anaemic overall (Hb < 7g/dl). There was less severe anaemia among the intervention clusters (15.1% intervention, 20.1% control), though this difference was not statistically significant (adjusted OR 0.71, 95% CI 0.44-1.14). Mean haemoglobin was 8.71g/dl (SE 0.12) within the intervention arm and 8.36g/dl (SE 0.21) within the control arm (95%CI -0.15-0.85, p=0.16).

There was little difference between the reporting of "malarial illness" (self and health personnel diagnosed) between the 2 groups (adjusted OR 0.95, 95% CI 0.66-1.37) or in the prevalence of peripheral parasitaemia in the third trimester (adjusted OR 0.75 95% CI 0.52-1.10).

There was an association between the reporting of malarial illness and positive serum chloroquine: 11% of women with a history of malarial illness were positive for chloroquine compared to 4% of those without (p=0.01), but there was no association between the presence of chloroquine in the blood and the intervention.

Table 3 shows the effect of the intervention comparing women from the intervention arm who used their nets more than 5 times in the previous week (n=183) compared with women from the control arm who did not have a net (n=207).

**Antenatal treatment**

30.9% of women in the control arm received sulfadoxine-pyrimethamine (SP) antenatally (for a positive malaria slide or Hb <7 at the time of this blood test) compared with 25.3% in the intervention arm (p = 0.48).

**Maternal HIV**

Of the 443 samples tested for HIV, 11 (2.7%) were positive. The prevalence was slightly higher in the intervention compared with the control women (3.4% compared with 1.9%) but this difference was not significant (adjusted OR 1.02, 95% CI 0.98-1.05). Controlling
Table 3  Insecticide treated bednets and antenatal outcomes, comparing net users from the intervention arm to controls without bednets.

<table>
<thead>
<tr>
<th></th>
<th>Control n = 207</th>
<th>ITBN n = 183</th>
<th>Odds Ratio (unadjusted) 95% CI</th>
<th>Odds Ratio (adjusted) 95% CI</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe anaemia (Hb &lt; 7g/dl)</td>
<td>20%</td>
<td>15%</td>
<td>0.72 (0.36, 1.43)</td>
<td>0.75 (0.44, 1.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>peripheral parasitaemia</td>
<td>35%</td>
<td>32%</td>
<td>0.87 (0.50, 1.53)</td>
<td>0.67 (0.42, 1.07)</td>
<td>0.09</td>
</tr>
<tr>
<td>malaria / febrile illness</td>
<td>31%</td>
<td>28%</td>
<td>0.90 (0.50, 1.61)</td>
<td>0.88 (0.50, 1.54)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* p value for adjusted OR

for HIV in the analysis did not alter the association between the intervention and anaemia or malaria.

DELIVERY
130 women delivered in hospital: 55 (23.8%) from control and 75 (27.6%) from the intervention areas. As the numbers were small, analysis was undertaken using individuals rather than community clusters as the unit of analysis.

Placental malaria infection
A blood smear was made from the placenta of 120 women at the time of delivery and a biopsy on 128 placentas (Table 4). Whilst only 12 (10.2%) placental blood smears were positive for either parasites and/or pigment, 95 (74.2%) placentas had histological evidence of placental malaria infection.

Table 4  Insecticide treated bednets and placental malaria infection

<table>
<thead>
<tr>
<th></th>
<th>Control n = 52</th>
<th>Intervention n = 71</th>
<th>Risk Ratio 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>placental smear positive</td>
<td>3 (5.8%)</td>
<td>9 (12.7%)</td>
<td>2.38 0.65-10.0</td>
<td>0.29</td>
</tr>
<tr>
<td>placental histology positive (total)</td>
<td>41 (77.4%)</td>
<td>54 (72.0%)</td>
<td>0.75 0.35-1.85</td>
<td>0.76</td>
</tr>
<tr>
<td>active alone</td>
<td>2 (3.8%)</td>
<td>13 (17.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>active/chronic</td>
<td>17 (32.1%)</td>
<td>18 (24.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chronic alone</td>
<td>22 (41.5%)</td>
<td>23 (30.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of the 118 placentas examined by both blood smear and histology only 11/43 (25.6%) of those with active infection by placental histology had a positive placental blood slide. Conversely, one placental smear showed pigment where placental histology was negative. All women with a peripheral parasitaemia at the time of delivery had positive placental histology: 13/15 having active infection and 2/15 having past chronic infection. Only 13/44 (29.5%) women with active placental infection had a concurrent positive peripheral parasitaemia. There was no statistical difference in the placental infection rates as judged by either parasitology or histology between intervention and control women (Table 4). 28.1%
(36/128) of the population who had placental histology performed had received SP at the time of their antenatal blood test. Controlling for the use of SP in the analysis made no difference to the effect of the intervention on placental malaria infection.

**Birth weight**

There was no association between the intervention and birthweight, mean birthweight being 2.8kg (SE 0.06) in both intervention and control women delivering in hospital. Controlling for use of SP antenatally did not alter this. Surprisingly, there was also no association detected between placental histological or smear findings and birthweight.

**Perinatal outcome**

Out of the 497 women followed up, there were 31 stillbirths, 41 perinatal deaths (stillbirths and deaths within the first 7 days of life) and 14 neonatal deaths (live births that died within the first 28 days of life). As only 4 of these neonatal deaths occurred after 7 days of age, and were split equally between intervention and control arms, data has been presented on perinatal deaths only. There were somewhat fewer reported stillbirths to women from the intervention compared with control clusters: 45 per 1000 women followed up compared with 70 per 1000 (adjusted OR 0.67, 95% CI 0.19-2.32, p = 0.51), although there was no difference in the perinatal death rate (stillbirths plus deaths within the first week of life): 75 per 1000 women followed up from intervention clusters and 80 per 1000 women followed up from control clusters.

**Maternal deaths**

There were 4 deaths among the women recruited antenatally. One death was from severe anaemia and malaria, in a woman who was recruited on the day of admission to hospital at 24 weeks gestation. One death was due to eclampsia (in-patient), one from breast cancer post-delivery and one was a road traffic accident during pregnancy.

**DISCUSSION**

The most important development in the control of malaria over recent years has been the introduction of insecticide treated bed-nets which have been shown to reduce severe morbidity and mortality from malaria in children under a range of endemicities (Alonso et al. 1991, Nevill et al. 1996, Binka et al. 1996). It has been unclear whether this form of malaria control is effective in pregnant women in sub-Saharan Africa. A study in a meso-endemic malarious area of the Thai-Burmese border found that insecticide treated bed-nets resulted in a significant reduction in maternal anaemia, despite a marginal effect on peripheral parasitaemia (Dolan et al. 1993). A recent study in The Gambia (where there is one single, short malaria season per year) demonstrated a reduction in severe anaemia in the dry season and fewer pre-term deliveries in the rainy season amongst women randomised to receive insecticide treated bednets (D’Alessandro et al. 1996). A study from Northern Ghana, where there is intense, seasonal malaria transmission, showed no impact of ITBN in pregnant women on maternal anaemia, peripheral parasitaemia or low birth weight (Browne, E.N.L., Abstract from 18th African Health Sciences Congress).

Similarly our study showed no statistically significant beneficial effect of ITBN on maternal anaemia, malaria infection or perinatal outcomes, despite the population having a high prevalence of: maternal anaemia (91.4% Hb < 11g/dl, 17.5% Hb < 7g/dl), placental malaria infection (74.2% by histology) and low birth weight (23.8% among women
delivering in hospital). Given the associations between malaria, severe anaemia and low birth weight, effective prevention of malaria in this population would be expected to have a major impact on the health of the women and their babies.

It could be argued that the observed difference in severe anaemia between the 2 groups (20.1% control, 15.1% intervention) may be a real finding, but that the power of the study to detect such a difference was too low. Indeed to detect a difference of this degree with 90% power would have needed a sample size of 2,500 primigravidae, i.e. the study would have needed to continue for 5 years or the population of the bednet study increased to 300,000. However, it seems unlikely that a true effect has been missed because there was also little difference between the groups, when a higher haemoglobin cut off (Hb < 8g/dl) was used: control 37%, intervention 32%, (RR 0.86, 95% confidence interval 0.67-1.11). Furthermore, given the lack of effect of the intervention on the prevalence of peripheral parasitaemia or placental malaria infection, it seems unlikely that a true effect on anaemia has been missed. There was also no effect when women who claimed to use their nets from the intervention arm were compared with women who did not own a net in the control arm, suggesting that the lack of effect was not due to poor compliance. These results contrast with the impressive impact of ITBN on infection rates (Snow et al. 1996), entomological inoculation rates (Mbogo et al. 1996) and childhood morbidity and mortality in this population (Nevill et al. 1996).

The findings in this study differ from those of the studies conducted in The Gambia, with its low and highly seasonal transmission, and the Thai-Burmese border, with its very low transmission, but are consistent with observations made in Ghana (intense seasonal transmission).

The most plausible explanation for this lack of effect is that in higher transmission settings or where there are prolonged seasons of *P. falciparum*, ITBN alone are not able to prevent the adverse effects of malaria in pregnancy. Bednets do not completely prevent transmission but reduce the incidence of new infections. In Kilifi this reduction is approximately 50% as measured by infant parasite and immunoglobulin M rates (Snow et al. 1996). Malaria associated childhood illness and death is an immediate consequence of transmission, and the major impact of bednets in children is by reducing the incidence of these acute infections. The situation in pregnancy is rather different: it has been suggested that the placenta is an immunologically privileged site which enables infection with malaria parasites to be amplified (Menendez et al. 1995). As pregnancy puts women at risk for a prolonged period of time, it seems likely that a much more complete reduction in transmission, probably following effective parasite clearance, is required to have any significant impact on malaria morbidity.

It is important that the effectiveness of ITBN in preventing childhood malaria deaths does not result in inappropriate assumptions regarding their effectiveness in pregnant women. This could lead to a dangerous neglect of the need to explore urgently other control strategies for this high risk group.

Acknowledgements

This paper is published with the permission of the Director of Kenya Medical Research Institute (KEMRI). This work received financial support from KEMRI, the Department for International Development (formerly the Overseas Development Administration); The Wellcome Trust; TDR/UNDP/World Bank/WHO special programme for research and training in Tropical Diseases; International Development and Research Centre,
African Medical Research Foundation. Many thanks to Elizabeth Breeze and David Smith for their help in the analysis. Thanks also to Dr John Parry, Hepatitis and Retrovirus Laboratory, Public Health Laboratory Service, London, for his assistance in the supply of kits and advice regarding the HIV testing, and to Dr Teunis Eggelte, Department Clinical Pharmacology, Amsterdam, for supplying the chloroquine ELISA kit. K. Marsh (631342) and R.W. Snow (033340) are Wellcome Trust Senior Research Fellows.
REFERENCES


Nevill CG, Some ES, Mung’ala VO et al. (1996). Insecticide treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine and International Health* 1(2):139-146.


Snow RW, Molyneux CS, Warn PA et al. (1996). Infant parasite rates and immunoglobulin M seroprevalence as a measure of exposure to *Plasmodium Falciparum* during a randomized controlled trial of insecticide-treated bed nets on the Kenyan Coast. *American Journal of Tropical Medicine and Hygiene* 55(2), 144-149.


