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Estimation of effectiveness of interventions for malaria control in pregnancy using the screening method

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Background The evaluation of the effectiveness of antimalarial drugs and bed net use in pregnant women is an important aspect of monitoring and surveillance of malaria control in pregnancy. In principle the screening method for assessing vaccine efficacy can be applied in non-vaccine settings for assessing interventions for malaria control in pregnancy.

Methods In this analysis field data on the proportion of placental malaria cases treated with two doses of sulphadoxine-pyrimethamine (SP) and the uptake of two doses of SP in the antenatal clinic was used in a case-coverage method to assess the protective effectiveness (PE) of intermittent preventive treatment with SP for malaria control in pregnancy. PE was assessed using placental malaria, low birthweight and maternal anaemia at delivery as outcome variables. The method was also applied to an evaluation of the protective effectiveness of self-reported use of impregnated bed nets (ITNs).

Results Effectiveness was highest for reduction of low birthweight in multigravidae (87.2%, 95% CI, 83.2–91.3%). PE was lower for placental malaria (61.6% primigravidae, 28.5% multigravidae), and maternal anaemia (Hb < 8.0 g/dl, 37.8% primigravidae, 29.6% multigravidae). Estimates for PE of self-reported use of ITNs gave values for all three outcome parameters that were much lower than for SP use. For women of all parties effectiveness estimates for reduction of low birthweight were 22% (95% CI, 17.7–26.4), prevention of placental malaria (all types) 7.1% (95% CI, 4.4–9.8), prevention of active placental infection 38.9% (95% CI, 27.4–50.4), and for maternal anaemia 8.8% (95% CI, 0–20.0).

Conclusions The case-coverage method could provide a useful and practical approach to routine monitoring and evaluation of drug interventions to control malaria in pregnancy and has potentially wide applications. Effectiveness estimates related

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to reported ITN use in pregnancy may be less reliable. The method should be further evaluated using currently available data sets.

Keywords Malaria, pregnancy, efficacy, antimalarials

Introduction

The routine evaluation of the effectiveness of antimalarial drugs in pregnant women is an important aspect of monitoring and surveillance of current efforts to control malaria in pregnancy, which is a priority strategy for the WHO Global Malaria Programme and several international organisations. WHO strategies for malaria control in pregnancy in Sub-Saharan Africa in areas with stable transmission recommend the use of intermittent preventive treatment (IPT) with sulphadoxine-pyrimethamine (SP), household use of insecticide-treated nets (ITNs) and effective case management of malarial illness.[1] These recommendations are based on controlled trials of effectiveness and protective efficacy for these interventions.[2–5] Despite this evidence many countries in poor malaria endemic areas lack the knowledge, capacity or health resources to deliver effective malaria control policies particularly during pregnancy. In addition in areas with stable transmission, malaria infection during pregnancy is often asymptomatic and of relatively low intensity, and women may not realize the need for effective malaria control in pregnancy which results in low coverage.[6] A further issue is the increasing prevalence of resistance of *Plasmodium falciparum* to SP.[7] However, antimalarial drug resistance in pregnancy has rarely been assessed directly using *in vivo* tests of parasitological or clinical response.[8] This is partly because such tests are usually carried out in children and these are then interpolated to pregnant women. This situation is unsatisfactory and there is a need to develop a practical method of assessing the effectiveness of malaria control in pregnancy which is not dependent on costly *in vivo* drug efficacy studies or population based studies of use of ITNs.

The most commonly used methods for assessing vaccine efficacy require detailed information on non-cases as well as cases, but for the purposes of routine monitoring, or if denominator data on individuals is unavailable, a screening method has been used as it requires data on individuals for cases only.[9] In principle the method could be applied for non-vaccine settings such as the assessment of antimalarial drug control in pregnancy. The method is based on a comparison of the proportion receiving the intervention amongst cases and amongst the population. Standardization is achieved using an estimate of coverage derived from external sources.[10] Its use as a tool for routine monitoring of vaccine effectiveness is well established especially with computerized vaccination records.[9,11]

Although it has limitations, external standardization is used in epidemiology and it is considered appropriate for routine monitoring of more complex and costly alternatives.[9] The aim of the present article is to assess the screening method as a surveillance tool for estimating the drug effectiveness of intermittent preventive antimalarial treatment with SP for malaria control in pregnancy. The method has not previously been evaluated outside its use for estimating vaccine effectiveness and could potentially provide a routinely available method for assessing malaria control for millions of pregnant women. The analysis also assesses the effectiveness of self-reported ITN use in pregnant women, using the same methodology.

Methods

The screening method

The protective effectiveness is given by the expression

$$PE\% = \frac{PPT - PCT}{PPT(1 - PCT)} \times 100$$

where:

PE = protective effectiveness

PCT = The proportion of pregnant women with placental malaria (cases) who have received two doses of SP

PPT = The proportion of the pregnant population who have received two doses of SP.

This expression is derived directly from the equation for vaccine effectiveness.[9]

Figure 1 shows PE estimates derived using the equation and for different values of percentage of cases treated (PCT) and percentage of population treated (PPT). For the estimation of self-reported ITN use, PCT was the proportion of pregnant women with placental malaria who reported using a ITN, and PPT the proportion of the pregnant population using ITNs.

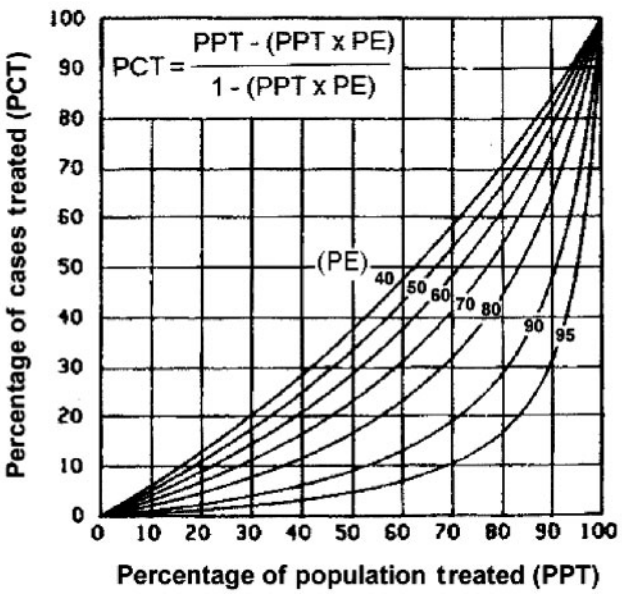

Figure 1 The relationship between the PCT and the PPT for seven different percentage values of PE

Study area and data sources for estimation of PCT and PPT

Field data to estimate PCT was available from a cross-sectional hospital-based study of placental malaria conducted at Montfort Hospital in Chikwawa District, Southern Malawi between September 2004 and May 2005 which covered the main rainfall period with increased malaria transmission. The primary purpose of this study was to describe histological placental malaria categories for women living under conditions of high malaria transmission. The placental histological categories used in the study have been previously described by Bulmer *et al*.[12] The epidemiology of malaria in pregnancy in this area has been well described.[13] The routine use of two intermittent treatment doses of SP has been the sole antimalarial drug control strategy promoted and available in this area since 1993.[14] and other antimalarials are not available through the health services or other outlets. The area provided a suitable site to evaluate SP effectiveness without confounding due to the restriction on use or availability of alternative antimalarials to this pregnancy study population. ITNs were available through antenatal clinics or from the Adolescent Girls Literacy Programme, a charity based in this area.

A total of 364 consecutive women were recruited at delivery. Information on the number of doses of SP taken during the antenatal period, maternal age and gravida was obtained from the antenatal card. ITNs ownership was determined by self-reporting. Birth weight (nearest 100 g), finger prick blood from the mother for haemoglobin and malaria smear, and placental biopsy for malaria histology were taken immediately after delivery. Haemoglobin concentration was determined using HemoCue (HemoCue AB, Angelholm, Sweden). Maternal peripheral parasitaemia was determined by thick blood film, air dried and stained with Field's stain and examined under light microscopy. Placental biopsy ($\sim 2 \times 2$ cm) was taken from the maternal side of the placenta after cleaning with normal saline. The biopsy was placed in 10% neutral buffer for formalin and transported to the histology laboratory, Pathology Department, College of Medicine, Blantyre. Placental malaria was categorized as acute, chronic, past or no infection.[12,15] The rationale for the histological classification is based on the different significance of haemozoin and parasites and on the assumption of the progression of the infection that is often left untreated. Thus, the presence of parasites indicates active infection whereas haemozoin deposition indicates chronic infection. Active infections, defined by the presence of parasitized red blood cells in the intervillous space of the placenta, includes two categories, acute infections (only parasites and minimal haemozoin deposition) and chronic infections (parasites and haemozoin deposition). The category 'past infection' includes cases with haemozoin, but no parasites.[15] Using this classification allowed protective effectiveness to be estimated for both past as well as active malaria infection.

Estimation of PPT was derived from the proportion of pregnant women receiving two doses of SP who were enrolled in the placental study. In the study area a concurrent village based SP distribution programme was in place which aimed to achieve full population coverage to pregnant women with SP.[16] It was assumed that values for either PCT or PPT were between 40% and 60%. The sample size required to estimate a 50% proportion to within 10% of the true value and with 95% CI is 385.

Definitions and data analysis

Gravida was stratified as primigravidae or multigravidae. Maternal age was grouped as adolescent (<20 years), or adult (≥20 years). Maternal anaemia was defined as a haemoglobin of <8 g/dl which is indicative of moderately severe anaemia. Low birthweight was defined as <2500 g. PE and 95% CI were calculated separately for prevention of placental malaria, or maternal anaemia (haemoglobin <8 g/dl), or low birthweight. A population estimate of ITN coverage for pregnant women was available from the village based survey. If PPT <PCT then PE would be estimated at <40% based on Figure 1. In the analysis we have assumed if these conditions applied, a best case scenario would be calculated as given by:

$$\mathrm{PE} = \frac{\text{Upper 95\% CI PPT} - \text{Lower 95\% CI PCT}}{\text{Upper 95\% CI PPT} \times (1 - \text{lower 95\% CI PCT})}$$

Ethical approval for both the study was obtained from the College of Medicine, Health Sciences Research Committee and the Ethics Committee of the Liverpool School of Tropical Medicine.

Results

The prevalence of maternal characteristics are summarized in Table 1 for the hospital placental malaria survey. A high proportion of women (78.6%) had received the recommended two doses of SP and an equivalent proportion reported ITNs ownership (77.7%). Placental malaria (acute, chronic or past) was present in 41.2% of primigravidae and 26.0% of multigravidae ($P = 0.005$), 45.3% of adolescents and 26.3% of adults ($P = 0.001$). The proportions with acute, chronic or past

Table 1 Prevalence of maternal characteristics

				Maternal Age	
Characteristics	**All**	**PG**	**MG**	**<20 years**	**≥20 years**
Sample size	364	114	250	86	278
ITNs ownership[a]	77.7	73.4	79.6	74.4	78.7
SP doses:					
0	3.0	1.8	3.6	2.3	3.2
1	18.4	21.9	16.8	22.1	17.3
≥2	78.6	76.3	79.6	75.6	79.5
Maternal Hb <8.0 g/dl	6.9	8.4	6.3	5.0	7.5
Maternal peripheral parasitaemia at delivery	3.0	5.3	2.0	5.8	2.2
Placenta malaria[b]	30.8	41.2[c]	26.0	45.3[c]	26.3
Low birthweight	7.7	14.0[c]	4.8	12.8[c]	6.1

[a] Sample size: primigravida 109, multigravidae 240.
[b] Acute (17.9%), chronic (2.7%) and past (10.2%) malaria infection.
[c] Primigravidae vs multigravidae, or adolescent vs adult: $P < 0.05$.
PG: primigravidae.
MG: multigravidae.

placental malaria infection were 17.9%, 2.7% and 10.2%, respectively. Low birthweight prevalence was higher in first than later pregnancies (14.0% vs 4.8%, $P = 0.003$).

Table 2 summarizes the estimates for PE and 95% CI, for use of two or more doses of SP based on placental malaria, low birthweight, or maternal anaemia at delivery as pregnancy outcomes. Effectiveness was highest for reduction of low birthweight in multigravidae (87.2%, 95% CI, 83.2–91.3), which was higher than in primigravidae (6.8%, 95% CI, 2.2–11.4), ($P < 0.001$). For placental malaria (all types) and anaemia outcomes, primigravidae showed consistently higher PE than multigravidae, (placental malaria 61.6% vs 28.5%, $P < 0.001$, and maternal anaemia 37.8% and 29.6%, $P = 0.14$).

The equivalent estimates for effectiveness of reported ITN use during pregnancy are summarized in Table 3. Estimates for all three outcome parameters are much lower than those calculated for SP use, and the overall estimate for women of all parities was always below 40%. There were no differences between primigravidae and multigravidae except for reduction in low birthweight which was significantly higher in multigravidae ($P = 0.02$).

Discussion

This analysis estimated the effectiveness of two or more doses of SP for three critical pregnancy outcomes related to the effectiveness of malaria control in pregnancy (low birthweight, placental malaria and maternal anaemia). A secondary analysis of the effectiveness of self-reported ITN use was also possible utilizing the same data set. The accuracy of the reported estimates is dependent on the validity of using the principle of

Table 2 Coverage and effectiveness of SP intermittent preventive treatment in pregnancy based on low birthweight, placental malaria or maternal anaemia outcomes

Outcome	All	Primigravidae	Multigravidae
Sample size	364	114	250
PPT (%)	78.6 (74.4–82.8)	76.3 (68.5–84.1)	79.6 (74.6–84.6)
PCT (%)			
Low birthweight	57.1 (38.8–75.4)	75.0 (53.8–96.2)	33.3 (6.6–60.0)
Placental malaria (all types)	83.9 (77.1–90.7)	78.7 (67.0–90.4)	87.7 (79.7–95.7)
Placental malaria (acute + chronic)	82.7 (74.1–81.3)	77.8 (62.1–93.5)	85.4 (75.4–95.4)
Hb <8.0 g/dl	70.8 (52.6–89.0)	66.7 (35.9–97.5)	73.3 (50.9–95.7)
Effectiveness (%)			
Low birthweight	63.8 (58.9–68.7)	6.8 (2.2–11.4)	87.2 (83.2–91.3)[a]
Placental malaria (all types)	30.1 (25.4–34.8)	61.6 (52.9–70.5)	28.5 (22.9–34.1)[a]
Placental malaria (acute + chronic)	40.6 (29.5–51.7)	69.0 (51.6–86.5)	44.2 (30.2–58.3)
Hb <8.0 g/dl	34.9 (15.8–54.0)	37.8 (6.1–69.5)	29.6 (6.5–52.7)

Values in paranthesis denote: 95% confidence interval.
[a] Difference between primigravidae and multigravidae, $P < 0.001$.

Table 3 Coverage and effectiveness of self-reported ITN use in pregnant women for malaria control in pregnancy, based on low birthweight, placental malaria or maternal anaemia outcomes

Outcome	All	Primigravidae	Multigravidae
Sample size	359	109	250
PPT (%)	77.7 (73.3–82.1)	73.4(65.1–81.7)	79.6 (74.5–84.5)
PCT (%)			
Low birthweight	73.1 (68.5–77.8)	71.4 (62.9–79.9)	75.0 (69.5–80.5)
Placental malaria (all types)	76.4 (72.0–80.9)	68.9 (60.2–77.6)	82.0 (77.1–86.9)
Placental malaria (acute + chronic)	82.6 (73.–91.6)	80.0 (64.3–95.7)	84.1 (73.4–94.9)
Hb <8.0 g/dl	91.7 (80.7–100)	88.9 (68.4–100)	93.3 (80.7–100)
Effectiveness (%)			
Low birthweight	22.0 (17.7–26.4)	9.5 (4.0–15.0)	23.1 (17.8–28.4)[a]
Placental malaria (all types)	7.1 (4.4–9.8)	19.2 (12.2–27.2)	18.5 (13.5–23.3)
Placental malaria (acute + chronic)	38.9 (27.4–50.4)	59.7 (40.5–78.9)	49.4 (34.6–64.2)
Hb <8.0 g/dl	8.8 (0–20)	51.5 (18.9–84.2)	23.3 (1.9–44.7)

Values in parentheses denote: 95% confidence interval.
[a] Difference between primigravidae and multigravidae, $P = 0.02$.

the screening method, designed for use in evaluating vaccine effectiveness, in a non-vaccine setting. Careful thought needs to be given to its application outside immunization studies. The methodology as applied in this analysis is actually a case-coverage study as it combines surveillance data on incident cases with a coverage estimate, rather than using the screening method in which you take an assumed total population coverage.

The coverage estimates in the present analysis were derived from the hospital antenatal record data. It would be preferable if these were estimated from a community coverage survey for the catchment population of pregnant women served by the hospital. A separate cross-sectional total village survey of pregnant women in an area 20–30 km away from the district hospital used in the present study observed comparable SP coverage to that reported by pregnant women in this analysis (70–80%).[16] This separate estimate of population SP coverage obtained at the same time as the present survey increases the reliability of the effectiveness estimates.

There is an important issue around the time and length of protection afforded by the intervention, as for each incident case, particularly when the effect of the intervention is short lasting, it is necessary to have an estimate of the population coverage at that time-point. Using data from a population coverage survey, an assumption can be made that population exposure is constant over the surveillance period. This would be the case for an intervention such as a vaccine, or SP use in pregnancy, however it may well be time-varying for an intervention such as ITNs. The effectiveness estimates related to reported ITN use in pregnancy may therefore be less reliable.

Other issues (probably less major) relate to the selection of the coverage sample and cases as these may not totally overlap and assumptions need to be made regarding comparability. The potential for confounding should be tackled by stratifying the data by possible confounders such as age and location. Also if coverage levels vary in populations then these could be stratified. In pregnant women stratification by parity is important as primigravidae are much more susceptible to *P. falciparum* malaria than multigravidae in women living under holoendemic conditions for malaria.[17] Young maternal age and adolescence may also be an independent risk factor for malaria in pregnancy. In this analysis SP effectiveness was greater in primigravidae for clearance of placental malaria (all types) but not current parasitaemia (i.e. acute plus chronic placental infection). This may indicate late pregnancy-reinfection with malaria following the second or last SP dose which is usually taken between 32 and 34 weeks gestation.

The low effectiveness for reduction of low birthweight in primigravidae (6.8%, Table 2) was surprising, as higher reductions have been reported previously in relation to frequency of SP use in pregnancy in the study area.[18] However, it is possible that SP drug resistance has increased since the time of these previous surveys (1993–1995). Separate estimates of *in vivo* SP drug efficacy in pregnant women were undertaken in this study population in 1996 ($n = 62$) and 2004 ($n = 74$) which showed an increasing rate of parasitological failure from 5% in 1996 to 20% in 2004.[19,20] These rates refer to clearance of peripheral (not placental) parasitaemia during pregnancy over a 28 day follow-up period following SP ingestion. Although there was a measurement difference with the present survey, which used placental malaria prevalence, the overall data suggests that SP drug resistance in pregnancy in this population is increasing. This parallels reported increases in SP parasitological failure in children in this region.[7] Other contributory factors including maternal nutritional status, anaemia or HIV infection may influence birthweight outcomes and some malaria intervention studies have shown a less clear-cut impact on improving birthweight.[21]

There is an urgent need for rapid methods of monitoring and surveillance of drug effectiveness for malaria control in pregnancy as >25 million pregnant women are exposed to this parasite annually in Africa. The estimation of effectiveness using the vaccine screening method, offers an innovative approach to this applied field problem. Further studies are required to assess the representativeness of the methodology as coverage estimates are not likely to be uniform. Its role and possible application to evaluating ITN effectiveness should be considered and currently available data sets could be used to assess this retrospectively.

In practical terms it would be simpler to measure placental malaria prevalence from a placental intervillous blood sample rather than from placental histology. Histology was used in the present study as this analysis was nested within a larger study for which this data was required. The antenatal record of SP use, as well as a placental malaria smear from a representative sample, are the minimum requirements necessary to allow an estimate of effectiveness to be calculated. Focussing solely on positive placental malaria histology (for PCT estimation), as the main evaluation indicator may give an underestimate of the true prevalence of maternal malaria, as prior treatment of peripheral parasitaemia may lead to normal placental histopathology. For example evidence from an area with low malaria transmission (Thailand) showed that placental malaria blood films were positive in only 6.9% of women who had malaria treated at any time during their pregnancies.[22] In the same study placental histopathology detected malaria parasites in only 21.3% of women who had had documented and treated peripheral parasitaemia during pregnancy. The extent of this underestimation in high transmission areas is uncertain, but for this reason estimates of effectiveness using this methodology should be considered minimum values.

Additional data on maternal haemoglobin at delivery and birthweight allow estimates of clinical effectiveness. The possibility of providing two clinical estimates for effectiveness, low birthweight and maternal anaemia, as well as a separate estimate of parasitological clearance makes this case-coverage method an attractive option for rapid surveillance that could be obtained at relatively low cost. Current malaria control monitoring and evaluation efforts rely mostly on costly, logistically difficult, population-based surveys and practical alternatives are required. Despite certain limitations of the case-coverage approach it may provide a useful and practical alternative. Because it utilizes facility-based data it is less representative of the general population of pregnant women. Its main value could be in coupling the method with other

KEY MESSAGES

- A modification of the screening method for assessing vaccine efficacy can be applied in non-vaccine settings for assessing interventions for malaria control in pregnancy.
- The method, which is a case-coverage approach, has practical utility, is low cost, and provides crude estimates of effectiveness of interventions for both parasitological and clinical outcomes.
- Its main value would be in coupling the method with national surveillance activities.

routine surveillance indicators undertaken in national surveys such as the Malaria Indictor Survey (MICS) which has been recently developed.[23]

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