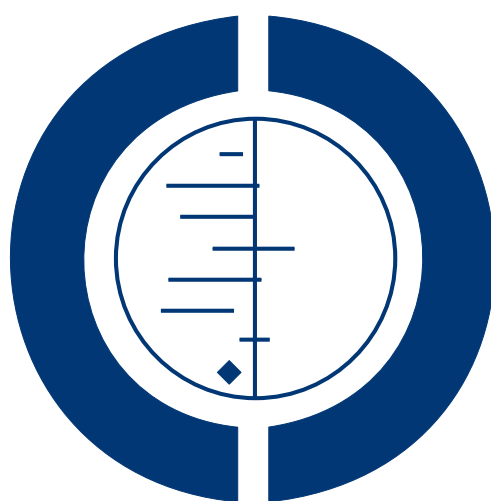# Insecticide-treated nets for preventing malaria in pregnancy (Review)

Gamble CL, Ekwaru JP, ter Kuile FO

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Insecticide-treated nets for preventing malaria in pregnancy

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A B S T R A C T

Background

Malaria in pregnancy is associated with adverse consequences for mother and fetus. Protection with insecticide-treated nets (ITNs) during pregnancy is widely advocated, but evidence of their benefit has been inconsistent.

Objectives

To compare the impact of ITNs with no nets or untreated nets on preventing malaria in pregnancy.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (February 2009), CENTRAL (*The Cochrane Library* 2009, Issue 1), MEDLINE (1966 to February 2009), EMBASE (1974 to February 2009), LILACS (1982 to February 2009), and reference lists. We also contacted researchers working in the field.

Selection criteria

Individual and cluster randomized controlled trials of ITNs in pregnant women.

Data collection and analysis

Three authors independently assessed the risk of bias in the trials and extracted data. Data were combined using the generic inverse variance method.

Main results

Six randomized controlled trials were identified, five of which met the inclusion criteria: four trials from sub-Saharan Africa compared ITNs with no nets, and one trial from Asia compared ITNs with untreated nets. Two trials randomized individual women and three trials randomized communities. In Africa, ITNs, compared with no nets, reduced placental malaria in all pregnancies (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.63 to 0.98). They also reduced low birthweight (RR 0.77, 95% CI 0.61 to 0.98) and fetal loss in the first to fourth pregnancy (RR 0.67, 95% CI 0.47 to 0.97), but not in women with more than four previous pregnancies. For anaemia and clinical malaria, results tended to favour ITNs, but the effects were not significant. In Thailand, one trial randomizing individuals to ITNs or untreated nets showed a significant reduction in anaemia and fetal loss in all pregnancies but not for clinical malaria or low birthweight.

Authors' conclusions

ITNs have a beneficial impact on pregnancy outcome in malaria-endemic regions of Africa when used by communities or by individual women. No further trials of ITNs in pregnancy are required in sub-Saharan Africa. Further evaluation of the potential impact of ITNs is required in areas with less intense and *Plasmodium vivax* transmission in Asia and Latin America.

PLAIN LANGUAGE SUMMARY

Insecticide-treated nets for preventing malaria in pregnancy

In endemic areas, malaria in pregnancy is a major public health problem. It contributes to severe anaemia in the mother and low birth weight for babies, which are associated with poor infant health and early infant death. Also the unborn child and the pregnant woman may die from malaria in pregnancy. Protection with insecticide-treated bednets (ITNs) during pregnancy is widely advocated, but evidence of their benefit has been inconsistent. This review found five trials of ITNs in pregnant women. The four trials in sub-Saharan Africa compared ITNs with no nets and showed a benefit from ITNs in terms of fewer malaria infections, low birthweight babies, and fewer babies died before delivery. The effects on severe anaemia in the mothers were inconclusive. The one trial from Asia compared ITNs with untreated nets and showed a beneficial effect on anaemia in women and fewer babies died before delivery, but it had no impact on other outcomes. ITNs have been shown to be beneficial and should be included in strategies to try to reduce the adverse effects of malaria in pregnant women in endemic areas of the world.

BACKGROUND

Approximately 50 million pregnant women are exposed to malaria each year. Women are more susceptible to malaria when they become pregnant, placing both the mother and fetus at risk of the adverse consequences (Brabin 1983; Lindsay 2000; Steketee 2001). In areas of low and unstable malaria transmission, such as in many regions in Asia and the Americas, women do not acquire substantial antimalarial immunity and are susceptible to episodes of acute and sometimes severe malaria, and fetal and maternal death (Nosten 2004). In areas with stable malaria transmission, such as in most of sub-Saharan Africa, infection with *Plasmodium falciparum* during pregnancy is characterized by predominantly low-grade, sometimes sub-patent, persistent, or recurrent parasitaemia. These frequently do not result in acute symptoms but cause maternal anaemia (Guyatt 2001a) and contribute to low birthweight (Brabin 1983; Steketee 2001), and thus may contribute to early infant mortality (Guyatt 2001b; van Geertruyden 2004). Because most of these infections remain asymptomatic, and therefore undetected and untreated, prevention of malaria in pregnancy is viewed as being especially important in these settings.

The World Health Organization advocates a three-pronged approach to malaria control in pregnancy that includes the use of insecticide-treated nets (ITNs) and antimalarial drugs, either through intermittent preventive therapy (IPT) or case management (treatment) (WHO 2000). Another Cochrane Review concluded that the prevention of malaria in pregnancy through chemoprophylaxis or IPT is associated with reductions in placental malaria, low birthweight, severe maternal anaemia, and perinatal mortality in the first two pregnancies (Garner 2002). In areas of stable malaria transmission in sub-Saharan Africa, ITNs are highly effective in reducing childhood mortality and morbidity from malaria (Lengeler 2004). Although ITNs are being promoted as a major tool in the fight against malaria in pregnancy, the available evidence about their effect in pregnancy appears inconsistent. In this review, we summarize the available evidence to date from randomized controlled trials of the impact of ITNs on the health of pregnant women and the birth outcome. We do not cover the current debate on the mechanisms of delivering ITNs.

OBJECTIVES

To compare ITNs with no nets or untreated nets on preventing malaria in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

Individual and cluster randomized controlled trials.

Types of participants

Pregnant women in malaria endemic areas.

Types of interventions

Intervention

Insecticide-treated nets.

Control

No nets or untreated nets.
Women in both arms may also receive malaria chemoprophylaxis or IPT.

Types of outcome measures

Primary

Anaemia during pregnancy

- Severe maternal anaemia (haemoglobin < 70 or 80 g/L, or haematocrit < 21% and 25%).
- Any anaemia (haemoglobin < 10 or 11 g/dL, or haematocrit < 30%).
- Mean haemoglobin or haematocrit.

Measures of birthweight

- Low birthweight (< 2500 g).
- Mean birthweight.

Secondary

- Clinical malaria illness during pregnancy (parasitaemic and febrile, or a history of fever).
- Peripheral parasitaemia (presence of malaria parasites determined by finger prick).
- Parasite density (geometric mean).
- Placental parasitaemia.
- Preterm delivery (< 37 weeks of gestation).
- Abortion or stillbirth (fetal loss).
- Neonatal death (death within first 28 days after birth).
- Infant death.
- Maternal death.
- Illness warranting hospitalization.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (February 2009); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2009, Issue 1); MEDLINE (1966 to February 2009); EMBASE (1974 to February 2009); and LILACS (1982 to February 2009).

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	malaria	malaria	malaria	malaria
2	pregnan*	pregnan*	pregnan*	pregnan*	pregnan*
3	woman	woman	woman	woman	woman
4	women	women	women	women	women
5	3 or 4	3 or 4	3 or 4	3 or 4	3 or 4

Table 1. Detailed search strategies   *(Continued)*

6	1 and 2 and 5	1 and 2 and 5	1 and 2 and 5	1 and 2 and 5	1 and 2 and 5
7	net*	net*	net*	net*	net*
8	ITN*	ITN*	ITN*	ITN*	6 and 7
9	ITM*	ITM*	ITM*	ITM*	-
10	7 or 8 or 9	7 or 8 or 9	7 or 8 or 9	7 or 8 or 9	-
11	6 and 10	6 and 10	6 and 10	6 and 10	-

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or EMTREE heading; lower case: free text term.

Researchers

We contacted individual researchers working in the field for unpublished and ongoing trials. We managed to identify two PhD theses, the work of which had only partially been published (Shulman 1998; Njagi 2002).

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Paul Ekwaru (PE) scanned the results of the literature search for potentially relevant trials. The full articles were retrieved, and Carrol Gamble (CG) and PE independently assessed them for inclusion in the review using an eligibility form based on the inclusion criteria. We planned to resolve disagreements through discussion or by contacting a mediator (Aika Omari (AO)). Although there were no disagreements, AO helped clarify some clinical definitions and terminology.

Data extraction and management

CG and PE independently extracted data relating to characteristics of the trials and participants, and the reported outcome measures.

We planned to resolve any discrepancies in the extracted data by referring to the original paper and through discussion; there were no disagreements.

Where possible we extracted data to allow an intention-to-treat analysis. If the number randomized and the numbers analysed for each outcome were inconsistent, we calculated the percentage loss to follow up and recorded this information.

For dichotomous outcomes, we recorded the number of participants experiencing the event in each group. For the continuous outcomes, we extracted means (arithmetic and geometric) and a measure of variance (standard deviation, standard error, or confidence interval) for each group.

Where trials had been randomized using clusters, we recorded whether the analysis accounted for the clustering effect and, when available, extracted results that adjusted for the clustering. This means extracted data were comparative outcome measures (risk ratios (RR), odds ratios (OR), hazard ratios) with 95% confidence intervals (CI). We also recorded the method used to adjust for clustering and whether the analysis adjusted for additional covariates.

Assessment of risk of bias in included studies

CG, PE, and Feiko ter Kuile (FK) independently assessed the risk of bias in the trials by describing the methods used to generate the allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We considered blinding by recording whether the participants, investigators, or outcome assessors were aware of the treatment group allocation

and recorded the studies description of blinding (open, single, or double) when provided. We considered inclusion of all randomized participants in the analysis as adequate (90% or more of the participants randomized included in the analysis), unclear (not reported), and inadequate (less than 90% participants randomized into the trial included in the analysis).

Data synthesis

CG entered the data into Review Manager 5. We anticipated four types of study design:

1. Cluster randomized: villages randomized and nets intended for the whole community.

2. Cluster randomized: villages or antenatal clinics randomized, but only the pregnant women are allocated to nets or no nets.

3. Individually randomized: pregnant women randomized to nets or no nets.

4. Individually randomized: as 3. but pregnant women are a subgroup of all those randomized.

A mass effect related to the area-wide killing of the malaria transmitting mosquitoes is expected to exist with an intervention for the whole community (Hawley 2003), as in 1. Studies that randomized communities (villages or antenatal clinics) need to account for clustering in the analysis. Ignoring the clustering leads to too narrow confidence intervals and small P values, and is likely to produce wrong conclusions (Kerry 1998). The decision was made a priori not to combine trials with different comparator groups (no nets or untreated nets).

All cluster randomized trials reported comparative outcome measures with 95% confidence intervals adjusted for clustering, unless otherwise stated. The chosen outcome measure varied between cluster randomized trials. It is not meaningful to combine hazard ratios with odds ratios or risk ratios. In trials that randomize individuals it is possible to convert odds ratios to risk ratios and vice versa if information is available about the probability of the event in each group (Deeks 2001). A similar approach was considered using average event rates across clusters, but this information was not available. Alternatively, odds ratios approximate risk ratios if the event is rare (Deeks 2005). Where event rates were presented with odds ratios, we considered them to approximate risk ratios if the event rate was less than 10%. Where meta-analysis was possible, we combined outcomes using the generic inverse variance method.

We assessed heterogeneity amongst trials by inspecting the forest plots, using the chi-squared test for heterogeneity with a 10% level of statistical significance, and using the I^2 statistic with a value of 50% representing moderate heterogeneity. We planned to perform subgroup analyses to explore the following potential sources of heterogeneity although in most cases there were too few trials to permit this: inclusion of trials randomizing individuals or clusters (herd effect); women of different gravidity; use of co-interventions

such as IPT; and differences in transmission intensity due to season and geographical location. In the presence of heterogeneity of trial effects, and where it remained clinically logical to combine trials we used the random-effects model; otherwise we used the fixed-effect model.

Because parity was considered the greatest potential modifier of the effect of ITNs (with the greatest effect of ITNs anticipated in women with fewer previous pregnancies), we aimed to stratify the analyses by groups according to the number of previous pregnancies (less than three, and three or more) whenever details were provided. One trial included women with no previous pregnancies only and one included no or one previous pregnancy only. Of the three trials that included women regardless of the number of previous pregnancies, ter Kuile 2003 reported details of the magnitude of effect by two groups, one for women with in their first pregnancy with those with up to three previous pregnancies and one for women with at least four previous pregnancies. Browne 2001 provided subgroups by no, one, and two or more previous pregnancies for all continuous outcome measures (birthweight, haemoglobin, and parasite densities), but not for the dichotomous outcomes. Although Browne 2001 provided proportions grouped by the number of previous pregnancies, cluster-adjusted estimates of the precision of effect were only available for the overall effect and not by gravidity groups. Shulman 1998 only included women in their first pregnancy, and Njagi 2002 included women in their first or second pregnancy. Dolan 1993 did not provide estimates by the number of previous pregnancies, except for the effect on birthweight.

To consider the effect of ITNs and IPT alone and in combination, we conducted a secondary analysis that excluded those trials that also used IPT (analyses not shown).

We pooled the data for women with two or more previous pregnancies in Browne 2001 with those from women with four or more previous pregnancies in ter Kuile 2003 to obtain summary estimates. Similarly we pooled data from women with no to three previous pregnancies from ter Kuile 2003 with the data for women in their first or second pregnancy from Shulman 1998, Browne 2001, and Njagi 2002.

We planned to consider publication bias using a funnel plot, but there were too few trials. Funnel plot asymmetry could be caused by publication bias, differences in design (cluster or individual randomization), methodological quality, or heterogeneity of results.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Eligibility

Seven studies of ITNs in pregnant women were identified, of which six were randomized controlled trials of ITNs in pregnancy that were potentially eligible for inclusion (Dolan 1993; D'Alessandro 1996; Shulman 1998; Browne 2001; Njagi 2002; ter Kuile 2003). The other was a social marketing study (Marchant 2002). We excluded D'Alessandro 1996, a cluster randomized controlled trial from The Gambia of women in their first pregnancy, for the reasons given in the 'Characteristics of excluded studies'. This left five trials that met the inclusion criteria (see ' Characteristics of included studies').

All five trial reports were published in English. Three trials (all in Africa) randomized entire communities and reported on pregnant women as a subgroup (Shulman 1998; Browne 2001; ter Kuile 2003), while the other two randomized individual pregnant women (Dolan 1993; Njagi 2002). All three trials that randomized entire communities (cluster randomized) took the clustering effect into account in their analysis, and the data supplied allowed the meta-analysis to take design effects into account.

Setting

The included trials were conducted in Kenya (Shulman 1998; Njagi 2002; ter Kuile 2003), northern Ghana (Browne 2001), and in refugee camps for the Karen people on the Thai-Burmese border (Dolan 1993). Malaria transmission rates varied, as described in the 'Characteristics of included studies'.

Participants and methods

The trials included a total of 6759 pregnant women. Three trials recruited women of all parity groups (Dolan 1993; Browne 2001; ter Kuile 2003), one trial recruited women having their first or second baby (Njagi 2002), and one trial recruited women having their first baby (Shulman 1998). In the cluster randomized trials, Browne 2001 included 1961 women (96 clusters), ter Kuile 2003 included 2991 pregnant women of all gravidity (79 clusters), and Shulman 1998 included 503 women (56 clusters). In the individually randomized trials, Dolan 1993 included 341 women and Njagi 2002 included 963 women.

The trials distributed the nets at different times: one year before the start of the nested study in pregnant women in Shulman 1998 and Browne 2001; by the start of the trial, January 1997, in ter Kuile 2003; and as they randomized individuals at the time of recruitment in Njagi 2002 and Dolan 1993. As the distribution of nets was completed well in advance of the start of the trials in Shulman 1998 and Browne 2001, women at any stage of their pregnancy who attended the study clinic or hospital were included. ter Kuile 2003 included women at any stage of pregnancy but excluded those with an expected delivery date before 12 July 1997 a priori from the analysis to allow sufficient time for the nets to impact on intrauterine growth and gestational age. Njagi 2002

considered women eligible if the gestational age was estimated to be between 12 and 24 weeks. Dolan 1993 recruited women as soon as they attended the antenatal clinic and reported that this was usually at the end of the first trimester.

Clinical management of anaemia and malaria during follow up

The frequency of blood tests to detect parasitaemia and haemoglobin and/or haematocrit levels varied between the trials. Dolan 1993 provided weekly antenatal care during which blood films were taken for malaria and measured haematocrit levels fortnightly. *P. falciparum* infections were treated with oral quinine if uncomplicated or with intravenous quinine if severe. *P. vivax* infections were treated with chloroquine. Women with haematocrit levels below 30% received ferrous sulphate and folic acid until delivery.

In Shulman 1998, a blood sample was taken in the third trimester (between 28 and 34 weeks) or at any time that a woman was suspected of being severely anaemic. All women with haemoglobin levels less than 10 g/dL received haematinics, and those with parasitaemia were treated with sulfadoxine-pyrimethamine. Women found to be severely anaemic (haemoglobin < 70 g/L) were also given sulfadoxine-pyrimethamine.

Browne 2001 reported that the clinic visits followed the same pattern as routine antenatal care; further details are not provided. Njagi 2002 treated women with sulfadoxine-pyrimethamine if they developed an episode of symptomatic malaria during pregnancy. All women received standard care during routine antenatal clinic visits plus routine iron and folic acid supplementation according to antenatal clinic guidelines. Women with haemoglobin levels less than 80.0 g/L were also given treatment doses of ferrous sulphate (6 mg/kg/day) and folic acid (0.5 mg/day) until delivery. The trial by ter Kuile 2003 was conducted in two contiguous areas: a 'non-cohort' area (60 villages) and a 'cohort' area (the remaining 19 villages) where a birth-cohort study was conducted. Birth outcomes were collected in all clusters, but only in the cohort area were women followed monthly throughout pregnancy to determine the incidence of malaria and anaemia. Women with clinical malaria were treated with sulfadoxine-pyrimethamine. Women with haemoglobin levels less than 80 g/L were given ferrous sulphate supplementation and those with levels less than 50 g/L were referred to hospital. Routine antenatal care was available in the noncohort villages.

IPT with sulfadoxine-pyrimethamine had not yet been introduced as policy for the prevention of malaria in pregnancy in any of the study areas at the time of the trial, with the exception of Njagi 2002. This trial provided IPT with sulfadoxine-pyrimethamine to half of the women as part of the study design, and the other half received placebo IPT.

Timing of outcome collection

In determining whether it is reasonable to combine data for particular outcomes the timing of the outcomes also needs to be considered. Malaria and anaemia outcome measures may be determined by blood tests during pregnancy or by blood tests taken at the time of delivery. Shulman 1998 and Browne 2001 reported haemoglobin and parasitaemia outcomes based on a blood test during the third trimester, while Njagi 2002 and ter Kuile 2003 took measurements at the time of delivery. We pooled the results of the peripheral malarial smears and the haematological assessment in the third trimester from Shulman 1998 and Browne 2001 with the respective assessments conducted at the time of birth from Njagi 2002 and ter Kuile 2003 and reported these in the text only. ter Kuile 2003 also took measurements throughout follow up and reported hazard ratios to account for participants lost during the follow-up period and those who were followed up for variable lengths of time. Dolan 1993 took weekly blood films for malaria and conducted fortnightly tests for haematocrit levels, and reported their incidence during follow up and at the time of delivery.

Sample size calculations

The outcome measures used for the sample size calculations varied between the trials. Shulman 1998 powered the study to detect a halving in the prevalence of severe anaemia, an increase in mean haemoglobin of 7.5 g/L, and a 30% reduction in the prevalence of placental anaemia with 80% power and 95% confidence. Full parameters required to replicate the sample size calculations are not provided.

Browne 2001 based the sample size on a 40% reduction in parasite prevalence, which was estimated at 50% in the no nets group. They used 90% power, 95% confidence, and inflated the sample size by 15% for clustering and 10% for losses to follow up.

Njagi 2002 powered the study to detect differences based on mean haemoglobin and birthweight. They considered an increase in haemoglobin of 5 g/L (from a 100 g/L mean with a standard deviation of 15 g/L) and an increase in birthweight of 150 g (from a mean of 3000 g standard deviation of 500 g) to signify an important difference. They used 80% power and 95% confidence, and inflated sample size calculations by 25% to allow for losses to follow up.

ter Kuile 2003 was designed to detect a 25% reduction in the prevalence of adverse birth outcomes, defined as low birthweight, preterm birth, or small for gestational age deliveries among women in their first or second pregnancy with 80% power and 95% confidence. This allows for a design effect (clustering) of 1.2 assuming that data would be collected on 80% of the deliveries within 96 hours of birth. The proportion used for adverse birth outcomes in the sample size calculations is not stated.

Dolan 1993 had 90% power and 95% confidence to detect a change in malaria incidence of 37% in the untreated nets groups to 15% in the treated nets group.

Interventions

All four trials conducted in Africa compared ITNs with no nets (Shulman 1998; Browne 2001; Njagi 2002; ter Kuile 2003). The remaining trial, conducted in Thailand, compared ITNs with untreated nets (Dolan 1993). All trials used the widely available insecticide permethrin (500 g/m^2), except Njagi 2002, which used cyfluthrin.

Dolan 1993 randomized individuals to receive either ITNs, untreated nets, or no nets. In the 'no-nets' arm, a large proportion of women received nets from another donor independent to the trial, and the researchers split the results in this control arm into women using donor nets and women not using donor nets. Because this compromised the validity of the control arm, we only present the comparison of ITNs versus untreated nets.

The trial by Njagi 2002 used a factorial design comparing the effect of ITNs with IPT plus sulfadoxine-pyrimethamine. Women were allocated to four groups: nets plus IPT, IPT alone, ITNs alone plus placebo IPT, or placebo IPT alone (case management). Shulman 1998, Browne 2001, and ter Kuile 2003 all provided multiple bed nets to allow use by all members of the households. Shulman 1998 and Njagi 2002 used nets that were 190 cm (width) by 180 cm (length) by 150 cm (height), while Browne 2001 provided four different sizes ranging from 100 cm to 190 cm in width. ter Kuile 2003 did not provide the size of the nets other than that they were a large family size (Phillips-Howard 2003). Dolan 1993 used single-sized nets that were relatively small in size, 70 cm (width) by 180 cm (length) by 150 cm (height). Thus while in both Dolan 1993 and Njagi 2002 pregnant women were provided with nets as part of antenatal care, only in Njagi 2002 were they of a sufficient size to allow more than one person to sleep under them.

Study subgroups

Three trials presented the results in subgroups. Browne 2001 used six subgroups, each divided according to the number of pregnancies (one, two, and three or more) and season (wet or dry). Njagi 2002 used subgroups based on the use of IPT. ter Kuile 2003 used two subgroups based on the number of pregnancies, one to four, and five or more.

Risk of bias in included studies

See Table 2.

Three of the included trials (Shulman 1998; Browne 2001; ter Kuile 2003) are linked to trials included in another Cochrane Review of ITNs that excluded pregnant women (Lengeler 2004). In assessing the risk of bias in these trials for this review, information

has been drawn from publications and also from Lengeler 2004 who had access to additional unpublished information.

Table 2. Risk of bias assessment[a]

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of all randomized participants in the analysis
Dolan 1993	Method not described	Not described	Double blind (participants, antenatal clinic staff, and supervising physician) for ITNs versus untreated nets comparison	Adequate
Shulman 1998	Adequate	Adequate	Open	Adequate for number with a third trimester blood sample Inadequate for number women who delivered in hospital Adequate for number followed up at least 4 weeks after delivery Adequate for number with a third trimester blood sample Inadequate for number women who delivered in hospital Adequate for number followed up at least 4 weeks after delivery
Browne 2001	Adequate	Adequate	Open	Adequate for number with blood taken in third trimester for malaria and haemoglobin Inadequate for number with pregnancy outcomes reported
Njagi 2002	Adequate	Not described	Open for ITNs versus no nets comparison Double blind for sulfadoxine- pyrimethamine (SP) versus SP placebo comparison Open for ITNs versus no nets comparison Double blind for sulfadox-	Inadequate for number evaluated at delivery

Table 2. Risk of bias assessment[a] *(Continued)*

			ine-pyrimethamine (SP) versus SP placebo comparison	
ter Kuile 2003	Adequate	Adequate	Open	Adequate number for birth outcomes and analysis of outcomes assessing the impact of nets during pregnancy

[a]Details of methods used in individual trials are in the 'Characteristics of included studies'.

Generation of allocation sequence

Four trials used random-number tables or open lotteries to generate the allocation sequence; the methods for the cluster randomized trials are described in more detail elsewhere (Binka 1996; Nevill 1996; Phillips-Howard 2003; Lengeler 2004). One trial does not describe the method used (Dolan 1993).

Allocation concealment

Three trials used adequate methods to concealed allocation. Two did not report on this (Dolan 1993; Njagi 2002).

Blinding

Dolan 1993 achieved double blinding in the comparison between ITNs and untreated nets, but it was open for the comparison with no nets (not included in this review). Blinding was not possible in the remaining four trials that compared ITNs with no nets and were classified as open. Njagi 2002 achieved double blinding between sulfadoxine-pyrimethamine and placebo.

Inclusion of all randomized participants in the analysis

The number of participants followed up was adequate (90% or more) in four of the five trials for at least one outcome. In Browne 2001, data from 92% of the 1961 participants were available for analysis of one of the primary outcomes (haematological impact in the third trimester), but birthweight and birth outcome data were available for only 847 women due to the change from active to passive surveillance of deliveries after six months because of resource constraints. In Shulman 1998, 91.8% had a third trimester blood sample taken, and 98.8% were followed up at least four weeks after delivery, but only those giving birth in hospital (25.8%) contributed to birthweight outcomes.

Effects of interventions

1. ITNs versus no nets

Anaemia during pregnancy

Severe anaemia (haemoglobin < 70 or 80 g/L)

Three cluster randomized controlled trials reported on severe anaemia (Shulman 1998; Browne 2001; ter Kuile 2003), *see* Analysis 1.1. As the occurrence of severe anaemia was not a rare event, we could not combine the risk ratio in ter Kuile 2003 with the odds ratios presented in Shulman 1998 and Browne 2001. Insufficient details were available to allow stratification by gravidity for Browne 2001. The pooled odds ratio of Shulman 1998 and Browne 2001 shows a non-significant trend towards fewer with severe anaemia in the ITNs group (0.77, 95% CI 0.56 to 1.08). Similar non-significant trends were seen with ter Kuile 2003 for women in their first to fourth pregnancy (measured at the time of delivery: RR 0.80, 95% CI 0.48 to 1.33; and with the hazard ratio of 0.70 (95% CI 0.42 to 1.16) reflecting the delay in time to first severe anaemic episode during pregnancy. Confidence intervals in all trials were wide. The direction of effect for women in their fifth or greater pregnancy in ter Kuile 2003 favoured the use of no nets but again the confidence interval width was wide.

Any anaemia (haemoglobin < 100 or 110 g/L)

Three trials, two cluster randomized, reported any anaemia, *see* Analysis 1.2. Overall the point estimate was in the direction of protection, and this was significant in the incidence data from ter Kuile 2003 for women in their first to third pregnancy.

Combining odds ratios based on blood tests during the third trimester (Browne 2001) with those at the time of delivery (Njagi 2002 +SP; Njagi 2002 -SP) gave a pooled odds ratio of 0.91 (95% CI 0.67 to 1.24, fixed-effect model; analysis not shown). This changed to an odds ratio of 0.83 (95% CI 0.68 to 1.02) when we excluded women randomized to receive IPT with sulfadoxine-pyrimethamine (Njagi 2002 +SP).

Haemoglobin (g/L)

Four trials, of which three were cluster randomized (Shulman 1998; Browne 2001; ter Kuile 2003), reported haemoglobin levels in late pregnancy or at delivery.

Shulman 1998 and Browne 2001 reported results based on a blood test during the third trimester while Njagi 2002 and ter Kuile 2003 reported results at the time of delivery, *see* Analysis 1.3. There is a large degree of uncertainty in the estimates, with no obvious consistency of direction apparent.

For haemoglobin results at the time of the delivery, the cluster-randomized ter Kuile 2003 included women in their first to fourth pregnancy while the individually randomized Njagi 2002 included women in their first or second pregnancy. Excluding Njagi 2002 +SP from this meta-analysis to allow a comparison of ITNs alone gave a mean difference of 4.06 (95% CI 0.52 to 7.59; analysis not shown).

Combining results for women in their first or second pregnancy (ter Kuile 2003 included women in their first to fourth pregnancy) taken during the third trimester with those at the time of delivery gave a pooled mean difference of 0.64 (95% CI -1.50 to 2.78, fixed-effect model; analysis not shown). When we excluded women randomized to receive IPT with sulfadoxine-pyrimethamine (Njagi 2002 +SP) this changed to 1.17 (95% CI -1.14 to 3.47; analysis not shown).

Measures of birthweight

Low birthweight

Two cluster randomized (Browne 2001; ter Kuile 2003) and one trial randomizing individuals (Njagi 2002) reported low birthweight; *see* Analysis 1.4. Browne 2001 presented results as odds ratios adjusted for clustering for all gravidity (OR 0.87, 95% CI 0.63 to 1.20; analysis not shown). As low birthweight in Browne 2001 is a common event and results are for all gravidity, we did not consider the odds ratios to approximate risk ratios to allow a meta-analysis with ter Kuile 2003.

As Njagi 2002 randomized individuals, we could express the results as risk ratios for pooling with ter Kuile 2003. The pooled result for women in their first or second pregnancy (ter Kuile 2003 also included women in their third and fourth pregnancies) shows a statistically significant effect of ITNs (RR 0.77, 95% CI 0.61 to 0.98). Excluding the trial arm that used IPT (Njagi 2002 +SP) from the meta-analysis to allow comparison of ITNs alone gave a risk ratio of 0.71 (95% CI 0.54 to 0.92; analysis not shown).

There was no apparent benefit of ITNs for women in their fifth or greater pregnancy or where both groups received sulfadoxine-pyrimethamine. The wide confidence intervals include potentially clinically important effects which could not be ruled out by these results.

Birthweight (kg)

Four trials, of which three were cluster randomized (Shulman 1998; Browne 2001; ter Kuile 2003), reported birthweights; *see* Analysis 1.5. Although the directions of the individual point estimates vary, the individual confidence intervals overlap. The statistically significant overall pooled result favours ITNs (mean difference 0.06 kg, 95% CI 0.02 to 0.09). Excluding the trial arm that used IPT (Njagi 2002 +SP) from the meta-analysis of women in their first or second pregnancy to allow a comparison of ITNs alone gave a mean difference of 0.07 kg (95% CI 0.03 to 0.10; analysis not shown).

Clinical malaria illness during pregnancy

Two trials, both cluster randomized, reported data on the episodes of clinical malaria; *see* Analysis 1.6.

Shulman 1998 reported an odds ratio of 0.85 (95% CI 0.47 to 1.54) for women in their first pregnancy. Malaria illness was self and health personnel diagnosed.

ter Kuile 2003 reported a hazard ratio of 0.72 (95% CI 0.19 to 2.75), which was based on monthly blood tests during follow up for women in their first to fourth pregnancy with clinical malaria, defined as any parasitaemia with fever. There were not enough episodes of clinical malaria to allow an estimate of the hazard ratio in women in their fifth or greater pregnancy.

Peripheral parasitaemia (presence of parasites determined by finger prick)

Four trials, three cluster randomized (Shulman 1998; Browne 2001; ter Kuile 2003), reported peripheral parasitaemia;*see* Analysis 1.7. Two trials based results on a blood test in the third trimester, either for women in their first pregnancy only (Shulman 1998) or for all pregnancies (Browne 2001). ter Kuile 2003 reported hazard ratios split by the number of pregnancies (one to four, and five or more) based on monthly blood tests throughout follow up and risk ratios at the time of delivery. Njagi 2002 randomized individual women in their first or second pregnancy and

based results on a blood test at the time of delivery. All pooled results support the use of ITNs, with the risk ratio at the time of delivery and the hazard ratio achieving statistical significance. Excluding the results for ter Kuile 2003 with five or more pregnancies at the time of delivery, to allow comparison of results within women with lower numbers of pregnancies, changed the risk ratio to 0.76 (95% CI 0.66 to 0.85; analysis not shown). By further excluding the trial arms that used IPT (Njagi 2002 +SP) to allow comparison of ITNs alone within these women, the risk ratio changed to 0.74 (95% CI 0.65 to 0.85; analysis not shown).

Parasite density (geometric mean)

Browne 2001 (cluster randomized) and Njagi 2002 reported details on parasite density; *see* Analysis 1.8. A geometric mean ratio looks at how many times bigger or smaller the geometric mean of parasite density in the ITNs group is compared with the no nets group. This means that the value of no difference between the groups is one. The pooled result for women in their first or second pregnancy favoured the use of ITNs although the result was not statistically significant (geometric mean ratio 0.82, 95% CI 0.66 to 1.02). For women in their third or greater pregnancy, the direction of the result favoured no nets, but the confidence intervals were wide (geometric mean difference 1.28, 95% CI 0.90 to 1.82). By excluding the trial arm that used ITNs plus IPT (Njagi 2002 +SP) from the meta-analysis of women in their first or second pregnancy to allow a comparison of ITNs alone, the geometric mean ratio changed to 0.92 (95% CI 0.71 to 1.20; analysis not shown). ter Kuile 2003 reported that maternal and placental parasite densities were identical in parasitaemic women from the ITN and control villages, but insufficient details were provided for inclusion in this analysis.

Placental parasitaemia

Two cluster randomized trials (Shulman 1998; ter Kuile 2003) and one individually randomized trial (Njagi 2002) reported placental parasitaemia; *see* Analysis 1.9.

Shulman 1998 reported results based on women in their first pregnancy who delivered in hospital. A placental smear was available for 120 women (9/71 ITNs and 3/52 no nets) and a placenta histology for 128 women (54/75 ITNs and 41/53 no nets), but the results were not adjusted for clustering because of the small number of women.

Analysis 1.9 shows the pooled risk ratio using the placental smear results for Shulman 1998. Although the chi-squared test for heterogeneity and I^2 value are of borderline significance, there is visual evidence of heterogeneity and hence we used the random-effects model, giving a combined risk ratio of 0.82 (95% CI 0.61 to 1.11) for first or second pregnancy. Excluding the trial arm that used ITNs plus IPT (Njagi 2002 +SP) to allow comparison of ITNs alone gave a risk ratio of 0.76 (95% CI 0.54 to 1.07; analysis

not shown) for women in their first or second pregnancy and 0.74 (95% CI 0.59 to 0.92) overall parity.

Using the histology data from Shulman 1998 instead of the placental smear results gave a combined risk ratio of 0.82 (95% CI 0.68 to 1.00; analysis not shown) for first or second pregnancy with overall pooled risk ratio of 0.81 (95% CI 0.69 to 0.95; analysis not shown). Excluding the trial arm that used ITNs plus IPT (Njagi 2002 +SP) to allow comparison of ITNs alone gave a risk ratio of 0.79 (95% CI 0.65 to 0.97; analysis not shown) for women in their first or second pregnancy and 0.79 (95% CI 0.63 to 0.98) overall parity.

Results from ter Kuile 2003 favoured the use of ITNs in women on their fifth or greater pregnancy, but they were not statistically significant.

Preterm delivery (< 37 weeks of gestation)

ter Kuile 2003 compared preterm deliveries for women living in villages provided with ITNs and control villages without nets. There was no statistically significant difference for women in their first to fourth pregnancy (RR 0.66, 95% CI 0.34 to 1.29; analysis not shown) or those in their fifth or greater pregnancy (RR 1.02, 95% CI 0.33 to 3.15; analysis not shown).

Fetal loss

Four trials, three of them cluster randomized (Shulman 1998; Browne 2001; ter Kuile 2003), reported the frequency of fetal loss; *see* Analysis 1.10. Each trial reported on this outcome measure slightly differently: Shulman 1998 reported an odds ratio for stillbirth in women in their first pregnancy (45/1000 (ITNs group) women followed up compared with 70/1000 (no nets); ter Kuile 2003 reported a risk ratio for abortion and stillbirth split by number of pregnancies (one to four, and five or more); Browne 2001 reported 15 stillbirths and 18 abortions without giving the breakdown by intervention groups or gravidity; and Njagi 2002 reported on abortions and stillbirths in women in their first or second pregnancy in the ITNs plus sulfadoxine-pyrimethamine group (8/205), sulfadoxine-pyrimethamine group (11/191), ITNs alone group (12/206), and no intervention group (17/1880).

As the event is rare (< 10%), the odds ratio reported by Shulman 1998 will approximate a risk ratio, and we have combined it with the risk ratios reported by Njagi 2002 and ter Kuile 2003. For women in their first or second pregnancy (ter Kuile 2003 includes women in their third to fourth pregnancy) there is a statistically significant decrease in the risk of fetal loss (RR 0.67, 95% CI 0.47 to 0.97). Excluding the trial arm that used both ITNs and IPT (Njagi 2002 +SP) from this meta-analysis to allow comparison of ITNs alone gave a risk ratio of 0.67 (95% CI 0.45 to 1.00; analysis not shown). There was no evidence of a decrease in women with four or more previous pregnancies.

Neonatal death (death within first 28 days after birth)

Shulman 1998 observed 14 neonatal deaths, of which four occurred after seven days of age, and reported that they were spilt equally between the ITNs and no nets groups.

Infant death (death within one year of birth)

This outcome measure was not reported.

Maternal death

Njagi 2002 reported four maternal deaths, two in the ITNs plus sulfadoxine-pyrimethamine group, one in the sulfadoxine-pyrimethamine group, and one in the placebo group. Shulman 1998 reported four deaths but not the groups the deaths occurred in; one was due to each of severe anaemia and malaria, eclampsia, breast cancer, and a road accident.

Illness warranting hospitalization

This outcome measure was not reported.

2. ITNs versus untreated nets

One individual randomized controlled trial compared ITNs with untreated nets (Dolan 1993).

Any anaemia during pregnancy

ITNs were associated with a reduction in anaemia (haematocrit < 30%) in all the refugee camps (study sites) and women of all gravidae. After adjusting for number of pregnancies and the refugee camps, the risk ratio was 0.63 (95% CI 0.42 to 0.93; analysis not shown) for ITNs compared with untreated nets providing a statistically significant result favouring the ITNs.

Measures of birthweight

Low birthweight

There was no statistically significant difference between the women using ITNs (15/94) compared with those using untreated nets (13/85) (RR 1.04, 95% CI 0.52 to 2.07; analysis not shown).

Birthweight

Dolan 1993 reported no statistically significant difference for birthweight. Although the trial report presents means and standard deviations for women in their first pregnancy (ITNs 2493 g (544 g) versus untreated nets 2676 g (464 g)) and those with one or more previous pregnancies (ITNs 2940 g (436 g) versus untreated nets 2945 g (473 g)), the number of participants was not provided, which means that a 95% confidence interval for the difference in means could not be calculated.

Peripheral malaria parasitaemia

Risk ratios of the incidence of *P. falciparum* per 1000 person weeks were 0.39 (95% CI 0.37 to 0.82) for the Shoklo camp and 1.1 (95% CI 0.57 to 2.12) for the Bono and Maesalit camps; analyses not shown. The presented results are adjusted for gravidity.

Preterm delivery

Dolan 1993 reported that 13/80 (16%) women in the ITNs group and 13/73 (18%) women in the untreated nets group delivered prematurely (RR 0.92, 95% CI 0.45 to 1.88; analysis not shown).

Fetal loss

Fetal loss amounted to 2/102 (2%) in the ITNs group and 10/97 (10%) reported in the untreated nets group. The risk ratio shows a protective effect of ITNs over the untreated nets (RR 0.21, 95% CI 0.05 to 0.92; analysis not shown).

Infant death

Dolan 1993 reported 11/50 (18%) deaths in the ITNs group and 10/64 (16%) in the untreated nets group (RR 1.33, 95% CI 0.61 to 2.93; analysis not shown).

Maternal death

There were two deaths among the untreated nets groups. One woman died of severe malaria and the other of eclampsia, both after being absent from the antenatal clinic for at least one week.

Illness warranting hospitalization

Five women were hospitalized; three were referred to hospital at the time of delivery for abnormal presentation of fetus (two from the ITNs group, one in the untreated nets group), and two were treated for post-partum haemorrhage (both in the ITNs group).

DISCUSSION

Despite over 80 studies of ITNs (reviewed in Lengeler 2004), only six were randomized controlled trials that addressed the effect on malaria in pregnancy, half of which were conducted in Kenya. All six trials used the widely available insecticide permethrin (500 g/m^2), except one trial that used cyfluthrin (Njagi 2002). The first cluster randomized controlled trial in sub-Saharan Africa was conducted in The Gambia in the early 1990s (D'Alessandro 1996),

but it was excluded from this review for reasons described in the 'Characteristics of excluded studies'.

Although the aim was to present meta-analysis results subgrouped by women in their first or second pregnancy and those in their third or greater pregnancy, this was not possible. Browne 2001 presented detailed results only by number of pregnancies for continuous outcome measures, and ter Kuile 2003 presented results by number of previous pregnancies (none to three, and four or more). The results could be stratified by combining women with none to three previous pregnancies from ter Kuile 2003 with the women in their first or second pregnancy in the other trials, and by combining the women in their third or greater pregnancy in the trial from Ghana (Browne 2001) with the women in their fifth or greater pregnancy from the trial in western Kenya (ter Kuile 2003). Despite these limitations, when we combined the results from the four trials in Africa, ITNs were associated with significant reductions in peripheral and placental malaria parasitaemia, low birthweight, and fetal loss. This effect was only evident in the subgroups of women with few previous pregnancies; there was no evidence for a statistically significant beneficial effect in women with at least two or more previous pregnancies.

Malaria infection: ITNs reduced the frequency of placental malaria and peripheral parasitaemia at the time of delivery. The peripheral parasite densities among infected women were lower in those in their first or second pregnancy, but this was not seen in women with at least two previous pregnancies. There was no significant reduction in the occurrence of self reported or microscopically confirmed episodes of clinical malaria.

Birthweight and preterm delivery: ITNs were associated with a mean increase of 50 grams (95% CI 20 to 90 grams) in birthweight in women with few previous pregnancies and a 23% reduction in low birthweight. There was no evidence for a beneficial effect on low birthweight in women with at least two previous pregnancies or in women protected by IPT with sulfadoxine-pyrimethamine. No significant decrease in the number of babies delivered prematurely was observed in the single trial that assessed this outcome.

Fetal loss: The risk of fetal loss decreased with the use of ITNs by women in their first or second pregnancy, but again this decrease was not seen in women with at least two previous pregnancies.

Anaemia: The methodology used to determine and analyse the impact on haemoglobin and anaemia varied considerably between the trials, which limited the ability to combine the results. The overall impact of ITNs on haemoglobin levels or anaemia was inconclusive. There is some support from the two trials in western Kenya that ITNs provide beneficial effects on mean haemoglobin levels in women with few previous pregnancies at the time of delivery. However, no significant beneficial effect on severe anaemia was seen in the other two trials from Africa that assessed haemoglobin in the third trimester, although the effect estimate was in favour of ITNs.

The results from this review are consistent with a non-randomized study of the effect of socially marketed ITNs conducted in an area with intense perennial malaria transmission in southern Tanzania (Marchant 2002), and with the excluded randomized controlled trial by D'Alessandro 1996 conducted in The Gambia, which has low and highly seasonal transmission malaria. This supports the current recommendations from the World Health Organization to provide ITNs for pregnant women in all regions with stable malaria transmission throughout sub-Saharan Africa regardless of the degree of malaria transmission intensity.

Mass effect versus individual barrier protection: ITNs may be implemented as a community control measure, where they are distributed to the whole population, or as personal protection, where pregnant women are specifically targeted to use nets. Four of the five included trials were cluster randomized and used villages as the unit of randomization. The other trial assessed the effect of ITNs when distributed as part of antenatal care and thus randomized individual women. The effect of ITNs in the cluster randomized trials reflects the combined effects of personal protection (individual barrier protection) and area-wide reductions in malaria transmission (community or mass effect). It is possible that the mass killing effect on mosquito populations will have resulted in stronger treatment effects supporting ITNs in the three cluster randomized trials than would be seen in trials randomizing individuals, as women in villages randomized to receive ITNs may have benefited from the area wide reduction of the malaria vector. The KEMRI/CDC ITNs trial conducted in western Kenya suggested that the community effect can be substantial (Hawley 2003). Similar considerations apply to the Dolan 1993 trial from the Thai-Burmese border. Although this trial randomized individual women rather than communities, all the women lived in the same densely populated refugee camps and some mass-effect by the treated nets cannot be excluded.

Extrapolation of results from cluster randomized trials to predict the impact in programmes that distribute ITNs to individual pregnant women, such as part of antenatal care, or vice versa without taking the effect of coverage into account should be done with care. The three community randomized trials and the two individually randomized trials also differed in the duration of protection during pregnancy. The community randomized trials distributed ITNs to all members of a community regardless of whether they were pregnant, while the individual randomized trials enrolled women when they were, on average, in their second trimester. Most women included in the community randomized trials became pregnant after the intervention was distributed and were as such protected throughout pregnancy, unlike those in individual randomized trials who would be protected only from the second trimester onwards. The risk of peripheral malaria parasitaemia is greatest in the first 20 weeks of gestation, with malaria infection rates at delivery approximating the levels in the postnatal period (Brabin 1983). The most recent included trial from western Kenya,

Njagi 2002, is informative in this respect. This is the only trial that compared the effects of ITNs with no nets using simple randomization by individual allocated through antenatal clinics in an area with low ITN coverage (little or no mass effect). This trial was conducted in an area of western Kenya that was contiguous with the location of ter Kuile 2003. They shared similar levels of malaria transmission, socioeconomic and educational status, and ethnicity of the population. They were also conducted at the same time period. The effect estimates in the two trials were remarkably similar, suggesting that ITNs may work equally well when provided to individuals as part of antenatal care in the second trimester as when provided to entire communities.

The World Health Organization recommends the use of IPT as well as ITNs for the prevention of malaria in pregnancy in areas where malaria is endemic in Africa (WHO/AFRO 2004). Njagi 2002 is also the only trial that simultaneously assessed the effect of ITNs and IPT with sulfadoxine-pyrimethamine using a factorial design that allows the comparison of the effects of each single intervention and the combined use of ITNs and IPT. The results suggest that the additional clinical benefits of combined approaches on birthweight and maternal anaemia are small, if any. ITNs provided no additional benefit to women also receiving the two-dose regimen of IPT with sulfadoxine-pyrimethamine. The benefit of ITNs in this group is likely to be restricted to the effects on the infants after birth with continued use of the net by mother and newborn. Additional studies are required to evaluate the cost-effectiveness of programmes that use single interventions compared with those that use multipronged approaches to malaria control.

Four of the five trials were conducted in areas of African where malaria is endemic. The only trial conducted in Asia compared ITNs with untreated nets on the Thai-Burmese border. There was a statistically significant reduction in anaemia and fetal loss, but there was no evidence of a beneficial effect on birthweight or gestational age. Further efficacy studies are required before ITNs can be recommended for the prevention of malaria in pregnancy in Asia and Latin America.

Several limitations should be taken in account when considering the results of the meta-analyses:

• For birth outcomes (haemoglobin, malaria, and birthweight), the results of the cluster-randomized Shulman 1998 were based on women who delivered in hospital (75 used ITNs and 55 had no nets). As numbers were small the results were not adjusted for clustering and it is plausible that the women who delivered in hospital were different to those who delivered at home, which means they are unlikely to be representative of all those randomized.

• In Shulman 1998 all women were visited at home at least four weeks (range four weeks to nine months) after their expected date of delivery to ascertain birth outcome in terms of stillbirths, neonatal deaths, and maternal deaths. This range means that there maybe variability in the reliability of the data collected.

• For birth outcomes, the results from Browne 2001 are based on 847/1961 (43%) participants in the study due to passive surveillance of birth outcomes.

• Njagi 2002 and Dolan 1993 randomized individuals whereas the other trials were cluster randomized and may have a herd effect present.

• ter Kuile 2003 presented results for women with no to three previous pregnancies, and those with four or more previous pregnancies. The results for the first group were combined with subgroups considering women in their first or second pregnancy, while Browne 2001 did not present results grouped by gravidity for the dichotomous outcome measures. This means that stratification by gravidity could not always be presented as desired.

• Detection and treatment of anaemia and parasitaemia during follow up varied between trials and is likely to have impacted on associated outcome measures. If the intensity of detection and treatment of haemoglobin levels and parasitaemia is greater within the clinical trial than in routine clinical practice, this could potentially reduce the effect of ITNs on these outcomes. Dolan 1993 performed weekly blood tests and ter Kuile 2003 tested monthly, which would rarely be part of routine antenatal clinic care. Shulman 1998 and Njagi 2002 tested and treated women only if they were suspected of being anaemic or of having malaria, while procedures in Browne 2001 are unclear.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

The use of ITNs reduces peripheral and placental parasitaemia, increases maternal haemoglobin concentrations, increases mean birthweight, and decreases the risk of fetal loss in the women in their first to fourth pregnancies. The effects were apparent in the community (cluster) randomized trials in which women benefited from protection throughout pregnancy and from area-wide killing of malaria vectors (community effect), and in individual protection studies where ITNs were distributed to individuals as part of antenatal care in the latter half of pregnancy. ITNs should be an integral part of strategies to prevent malaria in pregnant women living in areas of Africa where malaria is endemic.

Implications for research

No further trials of ITNs in pregnancy are required in sub-Saharan Africa and research efforts should focus instead on improving their coverage in pregnant women. Further research is required of the

benefits of combining IPT and ITNs in a multipronged approach to prevent malaria in pregnant women. Further research is also required before this recommendation can be extended to Asia and Latin America.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Browne 2001

Methods	Cluster randomized controlled trial: 96 clusters, 48 per group Generation of allocation sequence and allocation concealment: determined by "open ballot of community leaders" Blinding: open Inclusion of randomized participants in analysis: 1806/1961 (92%) had blood taken in the third trimester for malaria and haemoglobin outcomes; 847/1961 (43%) had pregnancy outcomes reported
Participants	1961 pregnant women (1033 intervention and 928 control) of any parity who had attended the study clinic at least once
Interventions	1. ITNs Insecticide: permethrin (500 g/m²) Size: rectangular; 4 sizes ranging between 190 cm and 100 cm in width and by 180 cm in length and 150 cm in height 2. No nets
Outcomes	1. Malaria infection 2. Antenatal parasitaemia (by parity and season) 3. Antenatal anaemia 4. Low birthweight 5. Mean and standard deviation of birthweight 6. Haemoglobin 7. Placental parasitaemia 8. Stillbirth
Notes	Location: living compounds in Kassena-Nankana district, Ghana Date: June 1994 to April 1995 Malaria transmission: hyperendemic and perennial with peaks in the rainy season Trial assessed the impact of ITN use on malaria and anaemia in pregnancy as a supplementary study in a major cluster randomized trial of bed nets supported by WHO/TDR Active surveillance was used to track all deliveries of the recruited women, but this had to be abandoned in favour of passive surveillance after 6 months because of resource constraints

Browne 2001 G1, dry

Methods	Browne 2001 results for women in first pregnancy during the dry season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Browne 2001 G1, wet

Methods	Browne 2001 results for women in first pregnancy during the wet season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Browne 2001 G2, dry

Methods	Browne 2001 results for women in second pregnancy during the dry season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Browne 2001 G2, wet

Methods	Browne 2001 results for women in second pregnancy during the wet season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Browne 2001 G3+, dry

Methods	Browne 2001 results for women in third or greater pregnancy during the dry season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Browne 2001 G3+, wet

Methods	Browne 2001 results for in third or greater pregnancy during the wet season
Participants	-
Interventions	-
Outcomes	-
Notes	-

Dolan 1993

Methods	Individual randomized controlled trial Generation of allocation sequence and allocation concealment: states "randomized", but the methods not described Blinding: ITNs versus untreated nets comparison double blind (participants, antenatal clinic staff, and supervising physician) Inclusion of randomized participants in analysis: of 223 enrolled into ITN and untreated groups 203 (91%) completed
Participants	Pregnant women of all parity 341 women enrolled; 34 were excluded from the analysis because they either delivered within 2 weeks of enrolment or were lost to follow up
Interventions	1. ITNs Insecticide: permethrin (500 g/m^2) Size (cm): 70 wide by 180 long by 150 high Material: nylon, mesh size 196, denier 70 2. Untreated nets 3. No study nets, but some women in this group had their own family-size untreated nets supplied by the Consortium of Christian Relief Organizations and Interaid Additional interventions: women with uncomplicated *Plasmodium falciparum* were treated with quinine sulphate (30 mg salt/kg/d in 3 divided doses for 7 d), and *Plasmodium vivax* infections with chloroquine (25 mg/kg base over 3 d); severe cases of *P. falciparum* were treated with intravenous quinine in a local hospital
Outcomes	1. Malaria infection during pregnancy 2. Antenatal parasitaemia 3. Illness warranting hospitalization 4. Antenatal anaemia 5. Premature delivery 6. Stillbirth 7. Infant mortality 8. Low birthweight 9. Birthweight
Notes	Location: 3 camps (Shoklo, Bonoklo, and Maesalit) for displaced people of the Karen ethnic minority, Thailand Date: recruitment between October 1990 and September 1992 Malaria transmission: mesoendemic with estimated attack rates of 1.0/year in the under 10 years age group and 0.8/year in older children and adults In the published results the 'no study nets group' was split into those who had no nets and those who had received nets from the charity: we felt the validity of the no study nets control group was compromised and decided to use

Dolan 1993 (*Continued*)

	data only on the treated versus untreated nets comparison

Njagi 2002

Methods	Individual randomized controlled trial Generation of allocation sequence: enrolled women randomized into the 4 arms in blocks of 12 using computer-generated random numbers; randomization numbers were prepared before the trial started and kept at each recruitment centre until the end of the trial Allocation concealment: method not described Blinding: open for ITNs versus no nets comparison; double blind for sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine placebo comparison Inclusion of randomized participants in analysis: 963 women were recruited, out of which 752 (78%) were followed up to completion
Participants	Women in their first or second pregnancy
Interventions	1. ITNs plus sulfadoxine-pyrimethamine 2. ITNs 3. Sulfadoxine-pyrimethamine 4. Placebo Net size (cm): 190 wide by 180 long by 150 high Net material: polyester
Outcomes	1. Malaria infection 2. Maternal death 3. Antenatal parasitaemia 4. Spontaneous miscarriage 5. Maternal anaemia 6. Haemoglobin 7. Stillbirth 8. Birthweight
Notes	Location: Bondo District Nyanza province, Kenya Date: July 1997 to September 1999 Malaria transmission: perennial with 2 peaks coinciding with the rainy seasons with 90 to 400 infective bites per person annually

Njagi 2002 +SP

Methods	Njagi 2002 results for ITNs nets plus sulfadoxine-pyrimethamine versus no nets plus sulfadoxine-pyrimethamine
Participants	-
Interventions	-
Outcomes	-

Njagi 2002 +SP (*Continued*)

Notes	-

Njagi 2002 -SP

Methods	Njagi 2002 results for ITNs plus placebo versus placebo
Participants	
Interventions	-
Outcomes	-
Notes	-

Shulman 1998

Methods	Cluster randomized controlled trial: 56 clusters (28:28) each of approximately 1000 individuals Generation of allocation sequence and allocation concealment: determined by "open ballot "; information received via personal communication from Christian Lengeler Blinding: open Inclusion of randomized participants in analysis: of 503 recruited 462 (91.8%) had third trimester blood sample, 130 (25.8%) delivered in hospital, and 497 (98.8%) followed up at least 4 weeks after delivery
Participants	503 women pregnant for the first time with singleton pregnancies or history of previous pregnancy that did not go beyond 12 weeks
Interventions	1. ITNs Insecticide: permethrin (500 g/m^2) Size (cm): 190 wide by 180 long by 150 high Material: green 2. No nets Additional interventions: all women with haemoglobin < 10 g/dL were given haematins and those with a positive slide for malaria were treated with sulfadoxine-pyrimethamine; all women with severe anaemia also given sulfadoxine-pyrimethamine irrespective of the results of their malaria smear, based on the assumption that those with negative smear would be likely to have placental parasitaemia Sufficient nets provided for all members of randomized households
Outcomes	1. Malaria infection 2. Antenatal parasitaemia 3. Antenatal anaemia 4. Haemoglobin 5. Placental parasitaemia 6. Stillbirth 7. Birthweight 8. Perinatal mortality 9. Neonatal mortality

Shulman 1998 (*Continued*)

Notes	Location: resident in rural populations Kilifi District, Kenya Date: September 1994 to November 1995 Malaria transmission: endemic and perennial with peaks in the 2 rainy seasons with individuals on average receiving 10 infective bites per person per year (ranging from 1 every 2 years to nearly 60 per person per year) The trial recruited pregnant women who came from a rural population that had already been randomized to receiving or not receiving nets treated with permethrin (500 g/m^2) as part of a trial assessing the effect of ITNs on childhood mortality and severe malaria in children; randomization and distribution of nets had been finished by August 1993, and this study was conducted between September 1994 and November 1995

ter Kuile 2003

Methods	Cluster randomized controlled trial 79 villages: 60 villages described as 'non cohort' with delivery data only, and 19 villages described as 'cohort' with outcomes collected prior to delivery and at delivery Generation of allocation sequence and allocation concealment: "open lottery" Blinding: open Inclusion of randomized participants in analysis: birth outcomes for 2754/2991 (92%); minimum of 764/780 (98%) included in analysis of outcomes assessing the impact of nets during pregnancy
Participants	2991 pregnant women of all parity
Interventions	1. ITNs Insecticide: permethrin; pretreated at distribution and re-treated biannually to maintain a target dose of 500 mg/m^2 Size: not provided Note: multiple nets provided to large households according to bed space measurements and baseline demographic data, providing an intervention ITN coverage ratio of 1.5 persons per ITN 2. No nets
Outcomes	1. Malaria infection 2. Antenatal parasitaemia 3. Spontaneous miscarriage 4. Maternal anaemia 5. Haemoglobin 6. Premature delivery 7. Stillbirth 8. Birthweight
Notes	Location: Rarieda Division (Asebo), Siaya district, Kenya Malarial transmission: intense perennial transmission with 60 to 300 infected bites per person annually with peaks in the 3 rainy seasons Conducted within the context of a large community-based randomized controlled trial designed to assess the impact of ITNs on mortality in children < 5 years of age. The mortality in children trial consisted of two main sites, Asebo and Gem, but the study on the impact of ITNs in pregnancy was conducted in Asebo area only (200 km^2). The trial involved randomizing villages to the intervention group, in which all households received ITNs during the fourth quarter of 1996 or control group which received ITNs in April 1999 after the trial was completed

ter Kuile 2003 G1-4

Methods	ter Kuile 2003 results for women in their first to fourth pregnancy
Participants	-
Interventions	-
Outcomes	-
Notes	-

ter kuile 2003 G5+

Methods	ter Kuile 2003 results for women in their fifth or greater pregnancy
Participants	-
Interventions	-
Outcomes	-
Notes	-

ITN: insecticide-treated net; WHO/TDR: World Health Organization/United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Characteristics of excluded studies *[ordered by study ID]*

D'Alessandro 1996	1. Cluster randomized trial that did not adjust for clustering in the analysis 2. Substantial proportions of missing data: of the 651 women in their first pregnancy recruited, only 358 (55%) had blood samples collected at 32 weeks gestation that were used in the analysis; 537 (82%) were available for the pregnancy outcomes but only 380 (58%) were available for birthweight with 289 (44%) available with placenta biopsy; 319 (49%) had information on survival

DATA AND ANALYSES

Comparison 1. Insecticide-treated nets versus no nets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe anaemia	4		Various (Fixed, 95% CI)	Subtotals only
1.1 Odds ratio (third trimester)	2		Various (Fixed, 95% CI)	0.77 [0.56, 1.08]
1.2 Risk ratio (at delivery)	2		Various (Fixed, 95% CI)	0.98 [0.63, 1.52]
1.3 Hazard ratio	2		Various (Fixed, 95% CI)	0.89 [0.61, 1.31]
2 Any anaemia	5		Various (Random, 95% CI)	Subtotals only
2.1 Odds ratio (third trimester)	1		Various (Random, 95% CI)	0.88 [0.71, 1.10]
2.2 Odds ratio (at delivery)	2		Various (Random, 95% CI)	0.95 [0.50, 1.79]
2.3 Hazard ratio	2		Various (Random, 95% CI)	0.90 [0.71, 1.13]
3 Haemoglobin (g/L)	11		Mean difference (Random, 95% CI)	Subtotals only
3.1 Third trimester: first or second pregnancy	5		Mean difference (Random, 95% CI)	-0.04 [-2.41, 2.33]
3.2 Third trimester: third or greater pregnancy	3		Mean difference (Random, 95% CI)	0.30 [-3.38, 3.97]
3.3 At delivery: first or second pregnancy	3		Mean difference (Random, 95% CI)	1.95 [-2.61, 6.51]
4 Low birthweight	4		Various (Fixed, 95% CI)	0.80 [0.64, 1.00]
4.1 Risk ratio: first or second pregnancy	3		Various (Fixed, 95% CI)	0.77 [0.61, 0.98]
4.2 Risk ratio: fifth or greater pregnancy	1		Various (Fixed, 95% CI)	1.12 [0.56, 2.24]
5 Birthweight (kg)	10		Mean difference (Fixed, 95% CI)	0.06 [0.02, 0.09]
5.1 First or second pregnancy	8		Mean difference (Fixed, 95% CI)	0.05 [0.02, 0.09]
5.2 Third or greater pregnancy	2		Mean difference (Fixed, 95% CI)	0.08 [-0.13, 0.28]
6 Clinical malaria illness during pregnancy	2		Various (Fixed, 95% CI)	Totals not selected
6.1 Odds ratio	1		Various (Fixed, 95% CI)	Not estimable
6.2 Hazard ratio	1		Various (Fixed, 95% CI)	Not estimable
7 Peripheral parasitaemia	6		Various (Fixed, 95% CI)	Subtotals only
7.1 Odds ratio: third trimester	2		Various (Fixed, 95% CI)	0.88 [0.73, 1.06]
7.2 Risk ratio: at delivery	4		Various (Fixed, 95% CI)	0.76 [0.67, 0.86]
7.3 Hazard ratio	2		Various (Fixed, 95% CI)	0.67 [0.52, 0.86]
8 Parasite density	8		Geometric mean ratio (Fixed, 95% CI)	0.93 [0.77, 1.11]
8.1 First or second pregnancy	6		Geometric mean ratio (Fixed, 95% CI)	0.82 [0.66, 1.02]
8.2 Third or greater pregnancy	2		Geometric mean ratio (Fixed, 95% CI)	1.28 [0.90, 1.82]
9 Placental parasitaemia	5		Risk Ratio (Random, 95% CI)	0.79 [0.63, 0.98]
9.1 First or second pregnancy	4		Risk Ratio (Random, 95% CI)	0.82 [0.61, 1.11]
9.2 Fifth or greater pregnancy	1		Risk Ratio (Random, 95% CI)	0.72 [0.48, 1.08]
10 Fetal loss	5		Risk Ratio (Fixed, 95% CI)	0.68 [0.48, 0.98]
10.1 First or second pregnancy	4		Risk Ratio (Fixed, 95% CI)	0.67 [0.47, 0.97]
10.2 Fifth or greater pregnancy	1		Risk Ratio (Fixed, 95% CI)	1.02 [0.17, 6.23]

Analysis 1.1. Comparison 1 Insecticide-treated nets versus no nets, Outcome 1 Severe anaemia.

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 1 Severe anaemia

Study or subgroup	log [Various] (SE)	Various IV,Fixed,95% CI	Weight	Various IV,Fixed,95% CI
1 Odds ratio (third trimester)				
Browne 2001	-0.2231 (0.1904)		77.9 %	0.80 [0.55, 1.16]
Shulman 1998	-0.3711 (0.3574)		22.1 %	0.69 [0.34, 1.39]
Subtotal (95% CI)			**100.0 %**	**0.77 [0.56, 1.08]**
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² =0.0%				
Test for overall effect: Z = 1.52 (P = 0.13)				
2 Risk ratio (at delivery)				
ter Kuile 2003 G1-4	-0.2231 (0.2592)		75.1 %	0.80 [0.48, 1.33]
ter kuile 2003 G5+	0.59 (0.45)		24.9 %	1.80 [0.75, 4.36]
Subtotal (95% CI)			**100.0 %**	**0.98 [0.63, 1.52]**
Heterogeneity: Chi² = 2.45, df = 1 (P = 0.12); I² =59%				
Test for overall effect: Z = 0.09 (P = 0.93)				
3 Hazard ratio				
ter Kuile 2003 G1-4	-0.3567 (0.2592)		57.3 %	0.70 [0.42, 1.16]
ter kuile 2003 G5+	0.2151 (0.3004)		42.7 %	1.24 [0.69, 2.23]
Subtotal (95% CI)			**100.0 %**	**0.89 [0.61, 1.31]**
Heterogeneity: Chi² = 2.08, df = 1 (P = 0.15); I² =52%				
Test for overall effect: Z = 0.57 (P = 0.57)				
Test for subgroup differences: Chi² = 0.76, df = 2 (P = 0.68), I² =0.0%				

```
        0.2   0.5   1   2    5
      Favours ITNs    Favours no nets
```

Analysis 1.2. Comparison 1 Insecticide-treated nets versus no nets, Outcome 2 Any anaemia.

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 2 Any anaemia

Study or subgroup	log [Various] (SE)	Various IV,Random,95% CI	Weight	Various IV,Random,95% CI
1 Odds ratio (third trimester)				
Browne 2001	-0.1278 (0.113)		100.0 %	0.88 [0.71, 1.10]
Subtotal (95% CI)			**100.0 %**	**0.88 [0.71, 1.10]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.13 (P = 0.26)				
2 Odds ratio (at delivery)				
Njagi 2002 +SP	0.2776 (0.2246)		47.1 %	1.32 [0.85, 2.05]
Njagi 2002 -SP	-0.3711 (0.2081)		52.9 %	0.69 [0.46, 1.04]
Subtotal (95% CI)			**100.0 %**	**0.95 [0.50, 1.79]**
Heterogeneity: Tau² = 0.16; Chi² = 4.49, df = 1 (P = 0.03); I² =78%				
Test for overall effect: Z = 0.16 (P = 0.87)				
3 Hazard ratio				
ter Kuile 2003 G1-4	-0.2357 (0.0995)		46.3 %	0.79 [0.65, 0.96]
ter kuile 2003 G5+	0 (0.0807)		53.7 %	1.00 [0.85, 1.17]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.71, 1.13]**
Heterogeneity: Tau² = 0.02; Chi² = 3.38, df = 1 (P = 0.07); I² =70%				
Test for overall effect: Z = 0.94 (P = 0.35)				

```
        0.2    0.5    1    2    5
        Favours ITNs    Favours no nets
```

Analysis 1.3.   Comparison 1 Insecticide-treated nets versus no nets, Outcome 3 Haemoglobin (g/L).

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 3 Haemoglobin (g/L)

Study or subgroup	Mean difference (SE)	Mean difference IV,Random,95% CI	Weight	Mean difference IV,Random,95% CI
1 Third trimester: first or second pregnancy				
Browne 2001 G1, dry	1.8 (2.551)		20.9 %	1.80 [-3.20, 6.80]
Browne 2001 G1, wet	-1.4 (2.7117)		19.1 %	-1.40 [-6.71, 3.91]
Browne 2001 G2, dry	-3.2 (3.0718)		15.7 %	-3.20 [-9.22, 2.82]
Browne 2001 G2, wet	-1.7 (2.3519)		23.5 %	-1.70 [-6.31, 2.91]
Shulman 1998	3.5 (2.551)		20.9 %	3.50 [-1.50, 8.50]
Subtotal (95% CI)			**100.0 %**	**-0.04 [-2.41, 2.33]**
Heterogeneity: Tau² = 0.44; Chi² = 4.25, df = 4 (P = 0.37); I² =6%				
Test for overall effect: Z = 0.03 (P = 0.98)				
2 Third trimester: third or greater pregnancy				
Browne 2001 G3+, dry	3.8 (2.551)		31.5 %	3.80 [-1.20, 8.80]
Browne 2001 G3+, wet	-0.3 (1.8038)		49.6 %	-0.30 [-3.84, 3.24]
ter kuile 2003 G5+	-3.8 (3.52)		18.9 %	-3.80 [-10.70, 3.10]
Subtotal (95% CI)			**100.0 %**	**0.30 [-3.38, 3.97]**
Heterogeneity: Tau² = 4.33; Chi² = 3.35, df = 2 (P = 0.19); I² =40%				
Test for overall effect: Z = 0.16 (P = 0.87)				
3 At delivery: first or second pregnancy				
Njagi 2002 +SP	-2 (2)		41.4 %	-2.00 [-5.92, 1.92]
Njagi 2002 -SP	3 (2.2398)		35.8 %	3.00 [-1.39, 7.39]
ter Kuile 2003 G1-4	6 (3.036)		22.8 %	6.00 [0.05, 11.95]
Subtotal (95% CI)			**100.0 %**	**1.95 [-2.61, 6.51]**
Heterogeneity: Tau² = 10.45; Chi² = 5.69, df = 2 (P = 0.06); I² =65%				
Test for overall effect: Z = 0.84 (P = 0.40)				

-10   -5   0   5   10

Favours no nets   Favours ITNs

Analysis 1.4. Comparison 1 Insecticide-treated nets versus no nets, Outcome 4 Low birthweight.

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 4 Low birthweight

Study or subgroup	log [Various] (SE)	Various IV,Fixed,95% CI	Weight	Various IV,Fixed,95% CI
1 Risk ratio: first or second pregnancy				
Njagi 2002 +SP	0.0862 (0.2775)		17.0 %	1.09 [0.63, 1.88]
Njagi 2002 -SP	-0.3857 (0.2609)		19.2 %	0.68 [0.41, 1.13]
ter Kuile 2003 G1-4	-0.3285 (0.1568)		53.3 %	0.72 [0.53, 0.98]
Subtotal (95% CI)			**89.5 %**	**0.77 [0.61, 0.98]**
Heterogeneity: Chi² = 1.98, df = 2 (P = 0.37); I² =0.0%				
Test for overall effect: Z = 2.17 (P = 0.030)				
2 Risk ratio: fifth or greater pregnancy				
ter kuile 2003 G5+	0.1133 (0.3536)		10.5 %	1.12 [0.56, 2.24]
Subtotal (95% CI)			**10.5 %**	**1.12 [0.56, 2.24]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.32 (P = 0.75)				
Total (95% CI)			**100.0 %**	**0.80 [0.64, 1.00]**
Heterogeneity: Chi² = 2.99, df = 3 (P = 0.39); I² =0.0%				
Test for overall effect: Z = 1.95 (P = 0.052)				
Test for subgroup differences: Chi² = 1.01, df = 1 (P = 0.32), I² =1%				

```
        0.2    0.5    1    2    5

       Favours ITNs      Favours no nets
```

Analysis 1.5. Comparison I Insecticide-treated nets versus no nets, Outcome 5 Birthweight (kg).

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 5 Birthweight (kg)

Study or subgroup	Mean difference (SE)	Mean difference IV,Fixed,95% CI	Weight	Mean difference IV,Fixed,95% CI
1 First or second pregnancy				
Browne 2001 G1, dry	0.1 (0.149)		1.3 %	0.10 [-0.19, 0.39]
Browne 2001 G1, wet	-0.16 (0.1225)		1.9 %	-0.16 [-0.40, 0.08]
Browne 2001 G2, dry	0.05 (0.1036)		2.7 %	0.05 [-0.15, 0.25]
Browne 2001 G2, wet	0.14 (0.1121)		2.3 %	0.14 [-0.08, 0.36]
Njagi 2002 +SP	-0.03 (0.0459)		13.6 %	-0.03 [-0.12, 0.06]
Njagi 2002 -SP	0.07 (0.0459)		13.6 %	0.07 [-0.02, 0.16]
Shulman 1998	0 (0.0849)		4.0 %	0.0 [-0.17, 0.17]
ter Kuile 2003 G1-4	0.0776 (0.0222)		58.1 %	0.08 [0.03, 0.12]
Subtotal (95% CI)			**97.4 %**	**0.05 [0.02, 0.09]**
Heterogeneity: Chi² = 8.74, df = 7 (P = 0.27); I² =20%				
Test for overall effect: Z = 3.19 (P = 0.0014)				
2 Third or greater pregnancy				
Browne 2001 G3+, dry	-0.14 (0.1975)		0.7 %	-0.14 [-0.53, 0.25]
Browne 2001 G3+, wet	0.16 (0.1227)		1.9 %	0.16 [-0.08, 0.40]
Subtotal (95% CI)			**2.6 %**	**0.08 [-0.13, 0.28]**
Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² =40%				
Test for overall effect: Z = 0.73 (P = 0.46)				
Total (95% CI)			**100.0 %**	**0.06 [0.02, 0.09]**
Heterogeneity: Chi² = 10.45, df = 9 (P = 0.32); I² =14%				
Test for overall effect: Z = 3.27 (P = 0.0011)				
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² =0.0%				

```
          -1    -0.5    0    0.5    1
        Favours no nets      Favours ITNs
```

Analysis 1.6. Comparison 1 Insecticide-treated nets versus no nets, Outcome 6 Clinical malaria illness during pregnancy.

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 6 Clinical malaria illness during pregnancy

Study or subgroup	log [Various] (SE)	Various IV,Fixed,95% CI	Various IV,Fixed,95% CI
1 Odds ratio			
Shulman 1998	-0.1625 (0.3044)		0.85 [0.47, 1.54]
2 Hazard ratio			
ter Kuile 2003 G1-4	-0.3285 (0.6845)		0.72 [0.19, 2.75]

0.1 0.2 0.5 1 2 5 10

Favours ITNs   Favours no nets

Analysis 1.7. Comparison 1 Insecticide-treated nets versus no nets, Outcome 7 Peripheral parasitaemia.

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 7 Peripheral parasitaemia

Study or subgroup	log [Various] (SE)	Various IV,Fixed,95% CI	Weight	Various IV,Fixed,95% CI
1 Odds ratio: third trimester				
Browne 2001	-0.1165 (0.0999)		88.7 %	0.89 [0.73, 1.08]
Shulman 1998	-0.1863 (0.2803)		11.3 %	0.83 [0.48, 1.44]
Subtotal (95% CI)			**100.0 %**	**0.88 [0.73, 1.06]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%				
Test for overall effect: Z = 1.32 (P = 0.19)				
2 Risk ratio: at delivery				
Njagi 2002 +SP	0 (0.2627)		6.1 %	1.00 [0.60, 1.67]
Njagi 2002 -SP	-0.3567 (0.182)		12.7 %	0.70 [0.49, 1.00]
ter Kuile 2003 G1-4	-0.2877 (0.0783)		68.7 %	0.75 [0.64, 0.87]
ter kuile 2003 G5+	-0.3011 (0.1841)		12.4 %	0.74 [0.52, 1.06]

0.2 0.5 1 2 5

Favours ITNs   Favours no nets

(*Continued* . . .)

Study or subgroup	log [Various] (SE)	Various IV,Fixed,95% CI	Weight	Various IV,Fixed,95% CI
Subtotal (95% CI)			**100.0 %**	**0.76 [0.67, 0.86]**
Heterogeneity: Chi² = 1.34, df = 3 (P = 0.72); I² =0.0%				
Test for overall effect: Z = 4.32 (P = 0.000015)				
3 Hazard ratio				
ter Kuile 2003 G1-4	-0.478 (0.1506)		73.7 %	0.62 [0.46, 0.83]
ter kuile 2003 G5+	-0.1863 (0.2521)		26.3 %	0.83 [0.51, 1.36]
Subtotal (95% CI)			**100.0 %**	**0.67 [0.52, 0.86]**
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² =0.0%				
Test for overall effect: Z = 3.10 (P = 0.0019)				
Test for subgroup differences: Chi² = 3.36, df = 2 (P = 0.19), I² =41%				

```
        0.2    0.5    1    2    5
        Favours ITNs    Favours no nets
```

Analysis 1.8. Comparison 1 Insecticide-treated nets versus no nets, Outcome 8 Parasite density.

Review: Insecticide-treated nets for preventing malaria in pregnancy

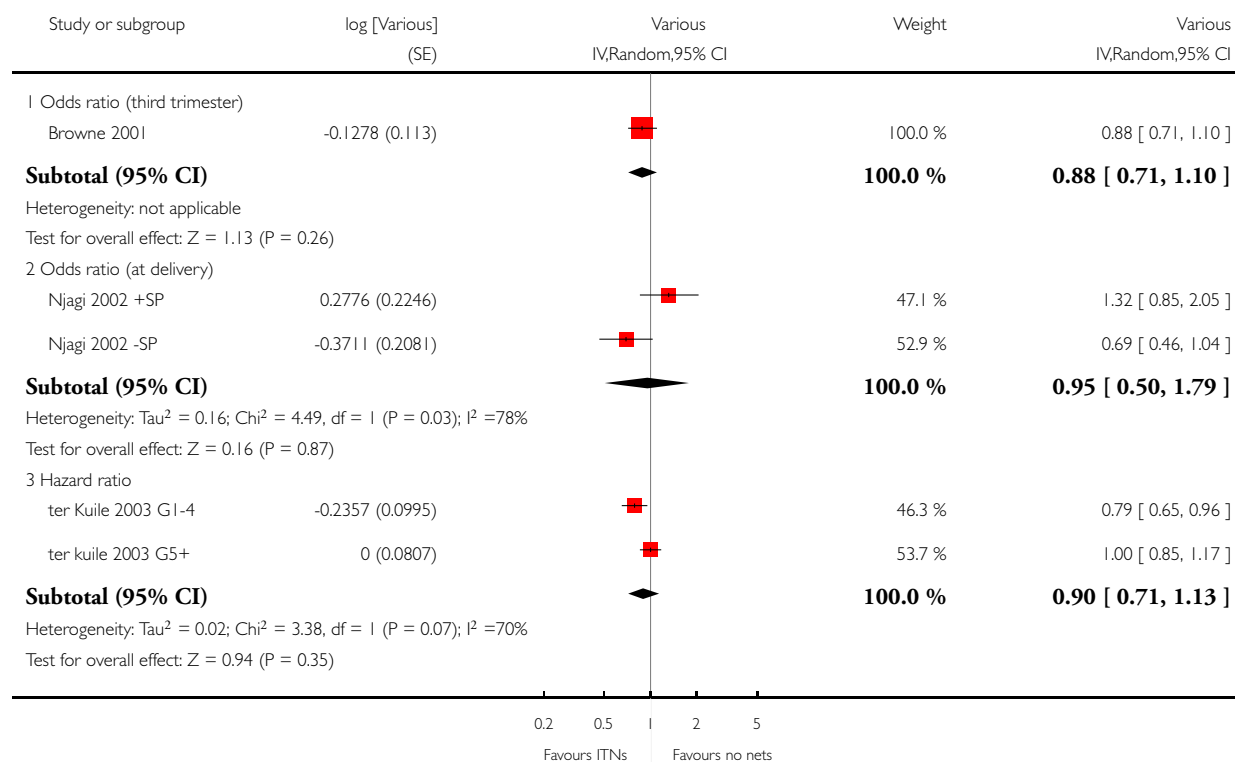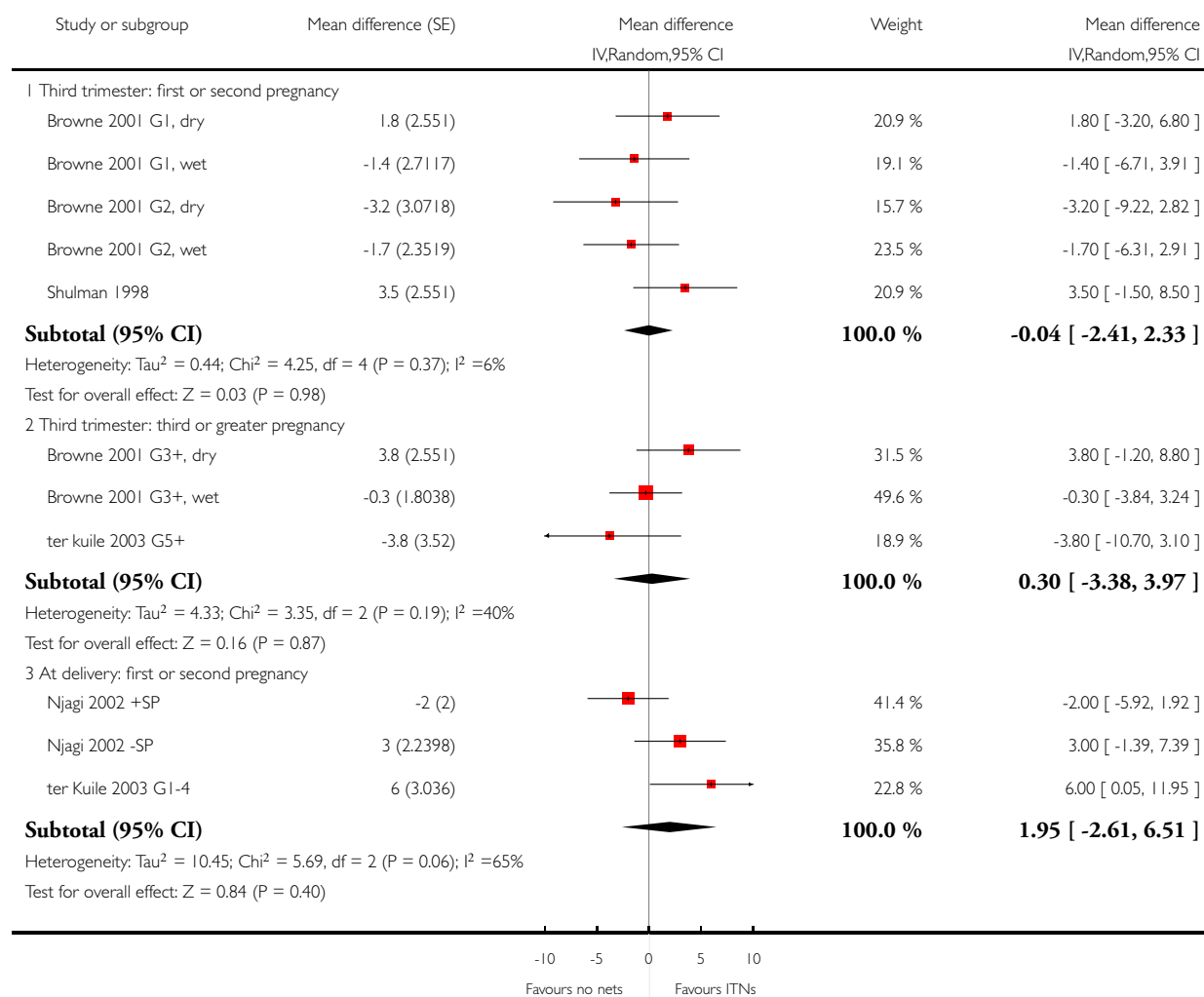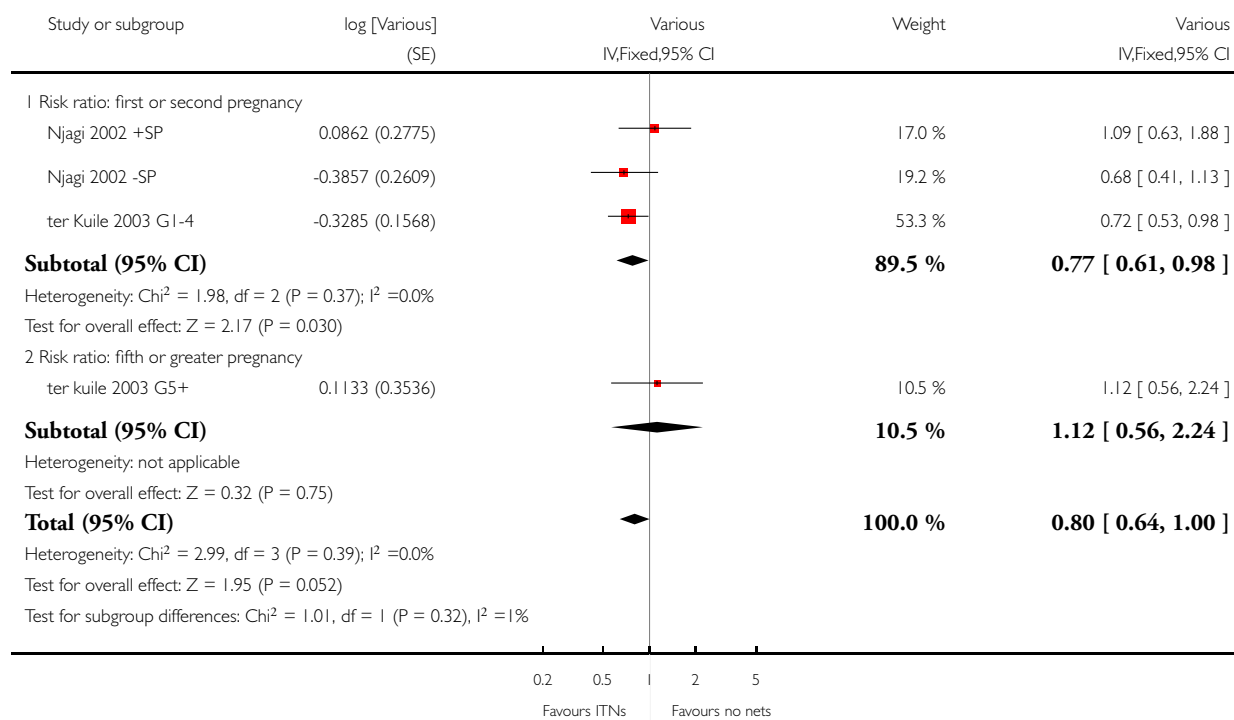Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 8 Parasite density

Study or subgroup	log [Geometric mean ratio] (SE)	Geometric mean ratio IV,Fixed,95% CI	Weight	Geometric mean ratio IV,Fixed,95% CI
1 First or second pregnancy				
Browne 2001 G1, dry	0.5971 (0.4337)		4.7 %	1.82 [0.78, 4.25]
Browne 2001 G1, wet	0.181 (0.3477)		7.3 %	1.20 [0.61, 2.37]
Browne 2001 G2, dry	-0.561 (0.4418)		4.5 %	0.57 [0.24, 1.36]
Browne 2001 G2, wet	-0.2029 (0.3953)		5.7 %	0.82 [0.38, 1.77]
Njagi 2002 +SP	-0.4577 (0.1966)		22.9 %	0.63 [0.43, 0.93]
Njagi 2002 -SP	-0.1591 (0.1785)		27.7 %	0.85 [0.60, 1.21]
Subtotal (95% CI)			**72.8 %**	**0.82 [0.66, 1.02]**
Heterogeneity: Chi² = 7.02, df = 5 (P = 0.22); I² =29%				
Test for overall effect: Z = 1.80 (P = 0.072)				
2 Third or greater pregnancy				
Browne 2001 G3+, dry	-0.0054 (0.3598)		6.8 %	0.99 [0.49, 2.01]

```
        0.2    0.5    1    2    5
        Favours ITNs    Favours no nets
```

(*Continued* . . .)

Study or subgroup	log [Geometric mean ratio] (SE)	Geometric mean ratio IV,Fixed,95% CI	Weight	Geometric mean ratio IV,Fixed,95% CI
Browne 2001 G3+, wet	0.3304 (0.208)		20.4 %	1.39 [0.93, 2.09]
Subtotal (95% CI)			**27.2 %**	**1.28 [0.90, 1.82]**
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² =0.0%				
Test for overall effect: Z = 1.37 (P = 0.17)				
Total (95% CI)			**100.0 %**	**0.93 [0.77, 1.11]**
Heterogeneity: Chi² = 12.11, df = 7 (P = 0.10); I² =42%				
Test for overall effect: Z = 0.82 (P = 0.41)				
Test for subgroup differences: Chi² = 4.44, df = 1 (P = 0.04), I² =77%				

```
        0.2    0.5    1    2    5
          Favours ITNs    Favours no nets
```

Analysis 1.9. Comparison 1 Insecticide-treated nets versus no nets, Outcome 9 Placental parasitaemia.

Review: Insecticide-treated nets for preventing malaria in pregnancy

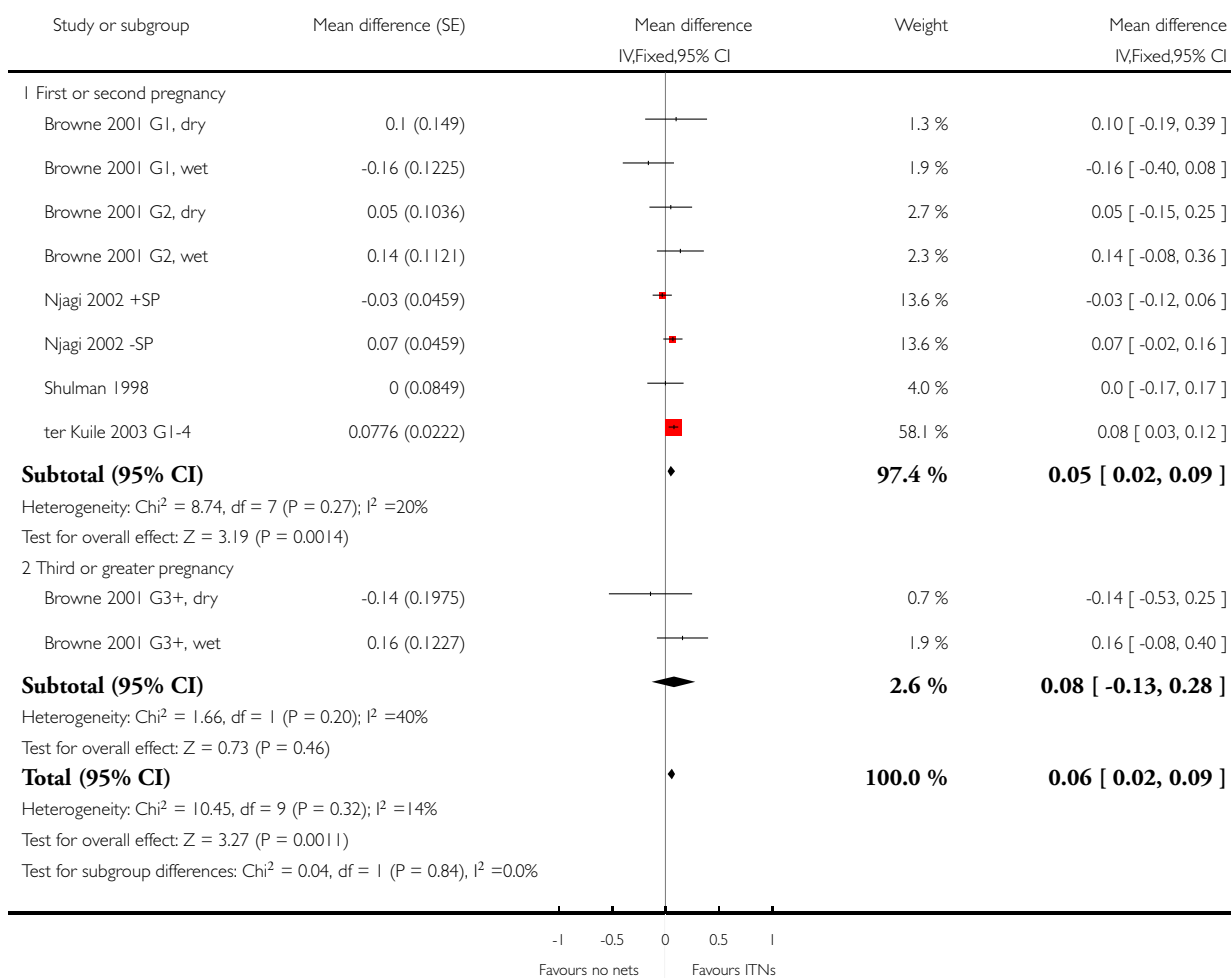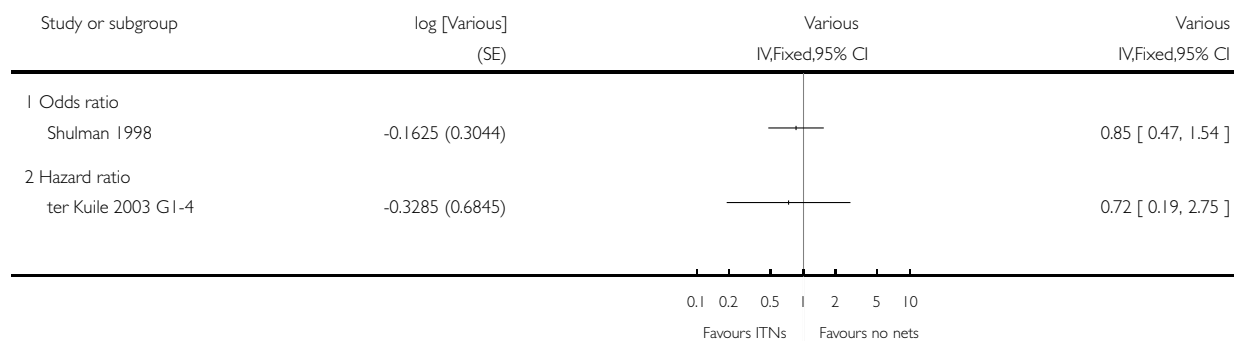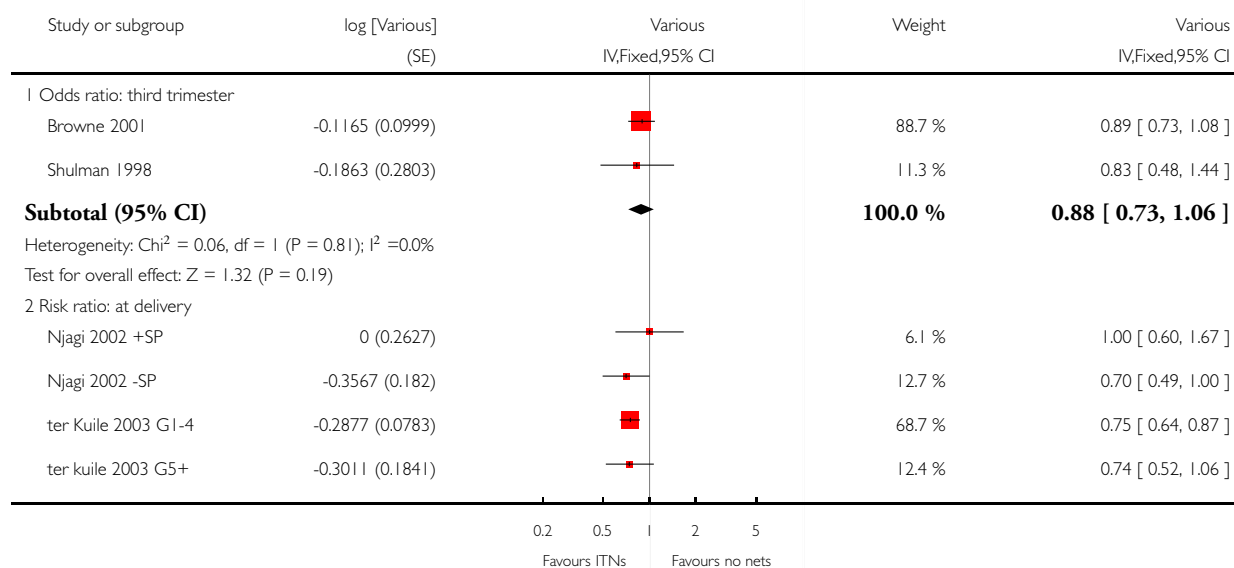Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 9 Placental parasitaemia

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 First or second pregnancy				
Njagi 2002 +SP	0.0953 (0.2602)		14.6 %	1.10 [0.66, 1.83]
Njagi 2002 -SP	-0.4943 (0.1944)		21.9 %	0.61 [0.42, 0.89]
Shulman 1998	0.7885 (0.6392)		3.0 %	2.20 [0.63, 7.70]
ter Kuile 2003 G1-4	-0.2614 (0.1021)		40.5 %	0.77 [0.63, 0.94]
Subtotal (95% CI)			**80.0 %**	**0.82 [0.61, 1.11]**
Heterogeneity: Tau² = 0.04; Chi² = 5.99, df = 3 (P = 0.11); I² =50%				
Test for overall effect: Z = 1.27 (P = 0.20)				
2 Fifth or greater pregnancy				
ter kuile 2003 G5+	-0.3285 (0.2085)		20.0 %	0.72 [0.48, 1.08]
Subtotal (95% CI)			**20.0 %**	**0.72 [0.48, 1.08]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.58 (P = 0.12)				
Total (95% CI)			**100.0 %**	**0.79 [0.63, 0.98]**
Heterogeneity: Tau² = 0.02; Chi² = 6.12, df = 4 (P = 0.19); I² =35%				
Test for overall effect: Z = 2.12 (P = 0.034)				

```
     0.1  0.2   0.5   1   2   5   10
          Favours ITNs    Favours no nets
```

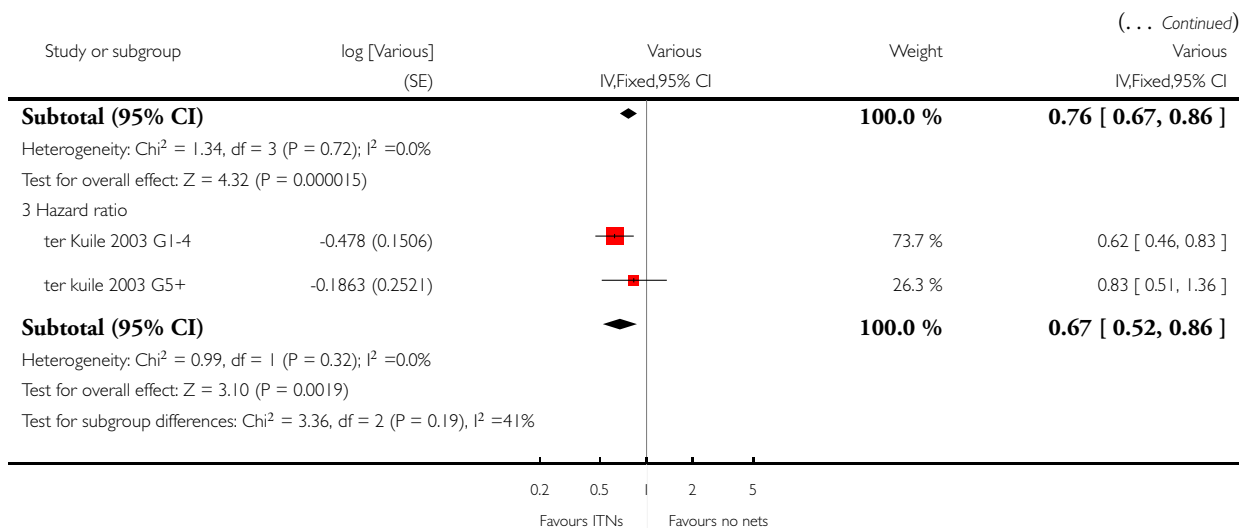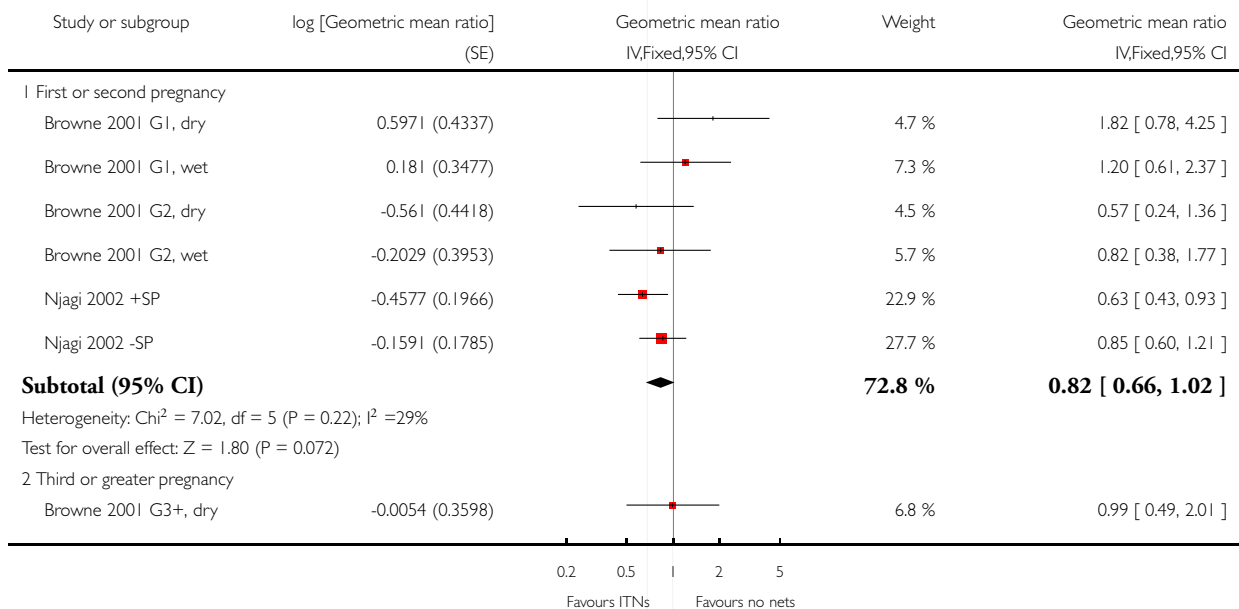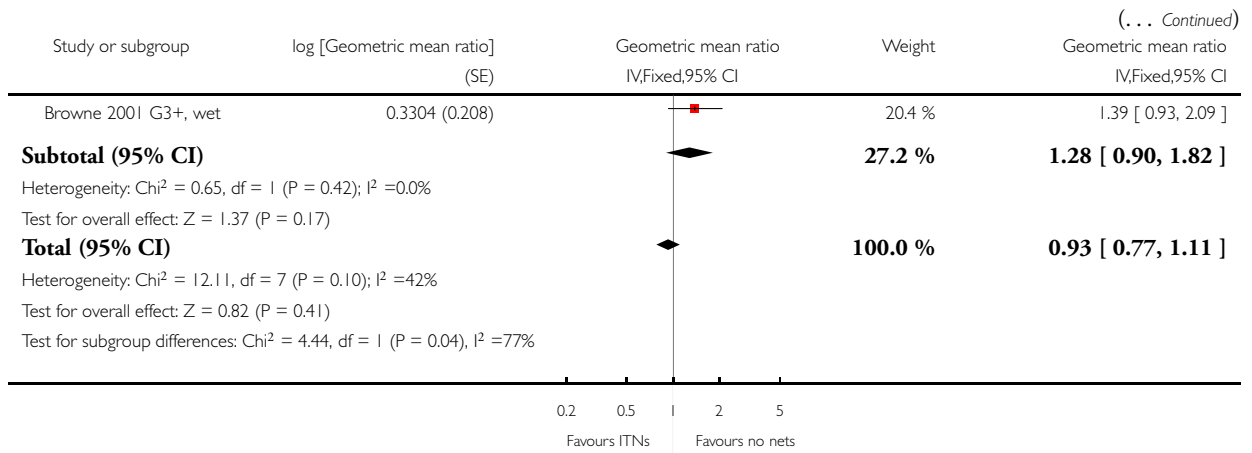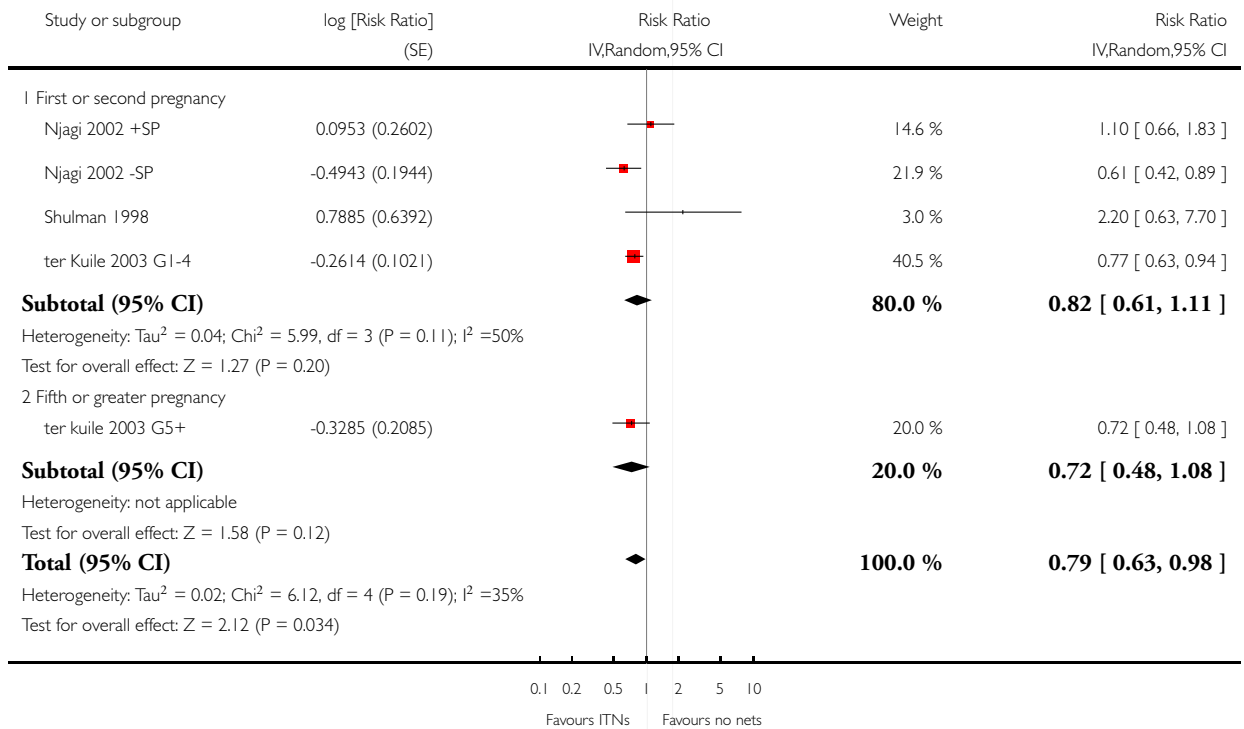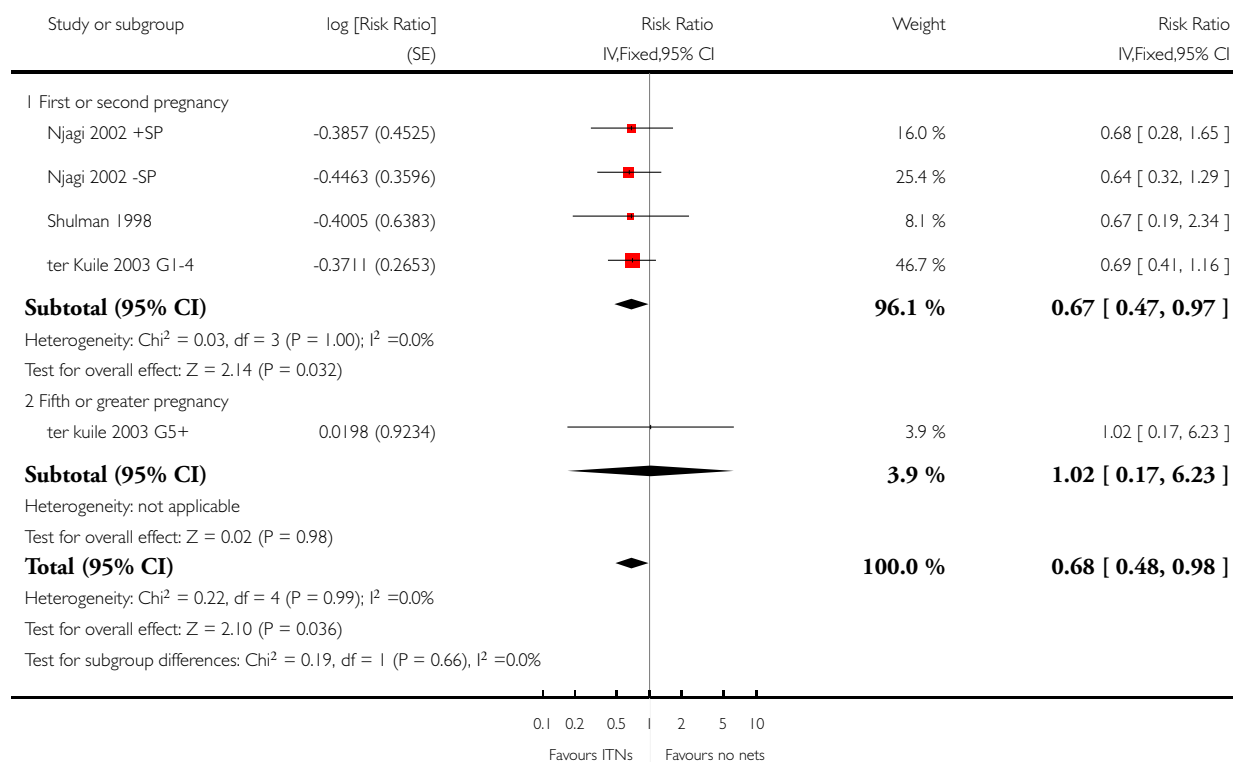**Analysis 1.10.   Comparison 1 Insecticide-treated nets versus no nets, Outcome 10 Fetal loss.**

Review: Insecticide-treated nets for preventing malaria in pregnancy

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 10 Fetal loss

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 First or second pregnancy				
Njagi 2002 +SP	-0.3857 (0.4525)		16.0 %	0.68 [0.28, 1.65]
Njagi 2002 -SP	-0.4463 (0.3596)		25.4 %	0.64 [0.32, 1.29]
Shulman 1998	-0.4005 (0.6383)		8.1 %	0.67 [0.19, 2.34]
ter Kuile 2003 G1-4	-0.3711 (0.2653)		46.7 %	0.69 [0.41, 1.16]
Subtotal (95% CI)			**96.1 %**	**0.67 [0.47, 0.97]**
Heterogeneity: Chi² = 0.03, df = 3 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 2.14 (P = 0.032)				
2 Fifth or greater pregnancy				
ter kuile 2003 G5+	0.0198 (0.9234)		3.9 %	1.02 [0.17, 6.23]
Subtotal (95% CI)			**3.9 %**	**1.02 [0.17, 6.23]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.02 (P = 0.98)				
Total (95% CI)			**100.0 %**	**0.68 [0.48, 0.98]**
Heterogeneity: Chi² = 0.22, df = 4 (P = 0.99); I² =0.0%				
Test for overall effect: Z = 2.10 (P = 0.036)				
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² =0.0%				

0.1   0.2   0.5   1   2   5   10

Favours ITNs   Favours no nets

WHAT'S NEW

Last assessed as up-to-date: 12 February 2009.

11 May 2009	Amended	**Types of intervention** ... Control *Women in both arms must also receive malaria chemoprophylaxis or IPT* **changed to** *Women in both arms may also receive malaria chemoprophylaxis or IPT.*

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 2, 2006

13 February 2009	New search has been performed	Search updated. No new studies were found.
25 July 2008	Amended	Converted to new review format and minor edits.
15 November 2006	Amended	2007, Issue 1: Confidence interval corrected for one analysis of placental parasitaemia.
20 August 2006	Amended	2006, Issue 4: "Abortion or stillbirth" changed to "fetal loss".

CONTRIBUTIONS OF AUTHORS

Carrol Gamble assessed potentially relevant trials for inclusion into the review, assessed the risk of bias in included studies, independently extracted data, entered data into Review Manager, carried out the data analysis, and co-wrote the review. John Paul Ekwaru developed the protocol, scanned the results of literature search for potential relevant trials, assessed potentially relevant trials for inclusion into the review, independently extracted data, and co-wrote the review. Feiko ter Kuile reviewed the protocol and co-wrote the manuscript.

DECLARATIONS OF INTEREST

Feiko ter Kuile was an author of two of the included trials. Carrol Gamble and Paul Ekwaru: none known.

SOURCES OF SUPPORT

Internal sources

- Makerere University, Uganda.
- University of Liverpool, UK.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DfID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Feiko ter Kuile joined the review team, the order of the outcome measures were restructured, and quasi-randomized controlled trials were excluded to reflect changes in Cochrane Infectious Diseases Group guidelines.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bedding and Linens; *Insecticides; Anemia [blood]; Antimalarials; Malaria [*prevention & control]; Mosquito Control [*methods]; Nitriles; Permethrin; Pregnancy Complications, Hematologic [blood]; Pregnancy Complications, Parasitic [*prevention & control]; Pyrethrins; Randomized Controlled Trials as Topic

MeSH check words

Animals; Female; Humans; Pregnancy