The aim of the Column is to highlight Cochrane Reviews of relevance to public health, and to stimulate debate on relevance, feasibility and acceptability. This month, we feature the review on insecticide-treated bednets for the prevention of malaria in pregnancy. Juliana Yartey provided comments on the review relevance and we asked Mike Clarke to outline on the features of cluster randomized trials as these are widely used to evaluate health care interventions. He also expands on the methodology to use when cluster randomized trials are included in systematic reviews.

The Cochrane Collaboration (http://www.cochrane.org) is an international, non-profit organization that prepares and disseminates up-to-date systematic reviews on the effects of healthcare interventions in order to help people make well-informed decisions. Systematic reviews aim to answer focused healthcare questions by systematically identifying and evaluating all relevant research studies and synthesizing their results.

**Insecticide-treated nets for preventing malaria in pregnancy**

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**Background**

Approximately 50 million pregnant women are exposed to malaria each year. In most of sub-Saharan Africa, with stable malaria transmission, malaria in pregnancy is usually characterized by low-grade parasitaemia which can cause maternal anaemia,1 and low birth weight,2,3 thus contributing to early infant mortality.4,5 In areas of low malaria transmission, such as in many regions in Asia and the Americas, women do not acquire substantial anti-malarial immunity and malaria in pregnancy is an acute and sometimes severe disease which can result in fetal and maternal death.6

The WHO recommends a number of strategies for the control of malaria in pregnancy.7 These include the use of insecticide-treated nets (ITNs) and antimalarial drugs, either through prevention (intermittent preventive therapy, IPT) or treatment. Chemoprophylaxis or IPT were found to be beneficial for prevention of malaria in the first two pregnancies by a Cochrane review.8 ITNs are highly effective in reducing mortality and morbidity from malaria in children living in sub-Saharan Africa9 but the evidence about their effect in pregnant women is still inconsistent.

This review summarized the available evidence from randomized controlled trials of the impact of ITNs on the health of pregnant women and on the birth outcome.

**Methods**

**Search strategy**

We searched the Cochrane Infectious Diseases Group Specialized Register (January 2006), CENTRAL (The Cochrane Library 2005, Issue 4), MEDLINE (1966 to January 2006), EMBASE (1974 to January 2006), LILACS (1982 to January 2006) and reference lists. We also contacted researchers working in the field.
Selection criteria
We included individual and cluster randomized controlled trials that investigated the effect of ITNs in women living in malaria endemic areas. The control was no nets or untreated nets; all women also received malaria chemoprophylaxis or IPT.

Data analysis
Three authors independently assessed trials for methodological quality and extracted data. Five studies 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.

All cluster randomized trials reported comparative outcome measures with 95% CI adjusted for clustering, unless otherwise stated. We combined data using the generic inverse variance method.

Because the greatest effect of ITNs was anticipated in women with fewer previous pregnancies, we aimed to stratify the analyses by groups according to parity, whenever details were provided.

Results
In Africa, ITNs, compared with no nets, reduced placental malaria in all pregnancies [relative risk (RR) 0.79, 95% CI 0.63–0.98]. They also reduced low birth weight (RR 0.77, 95% CI 0.61–0.98) and fetal loss in the first to fourth pregnancy (RR 0.67, 95% CI 0.47–0.97). For anaemia and clinical malaria, results tended to favour ITNs, but the effects were not significant. In Thailand, one trial which compared ITNs with untreated nets showed a significant reduction in anaemia and fetal loss in all pregnancies, but no reductions for clinical malaria or low birth weight.

Conclusions
The use of ITNs by communities or by individuals in malaria-endemic regions of Africa has a beneficial impact on pregnancy outcomes. No further trials of ITNs in pregnancy are required in sub-Saharan Africa and research efforts should focus instead on improving strategies for ITN delivery. Further research is required on the potential impact of ITNs in Asia and Latin America.


References

Commentary: Cochrane review on ITNs for preventing malaria in pregnancy
Juliana Yartey

The burden of malaria during pregnancy, not only in the Africa region but also in many areas of the world where malaria remains a public health problem, is immense. In high transmission areas, malaria infection in pregnant women (MIP) is often asymptomatic and therefore not usually detected and treated, resulting in severe anaemia for the mother...
with attendant consequences for the neonate (fetal loss, low birth weight and infant mortality). In areas with low and unstable malaria transmission, the consequences of infection are even more severe for the mother and may be fatal. Hence, prevention of malaria during pregnancy is critical for both mother and child in stable and unstable transmission areas and a key strategy for malaria control.

WHO recommends the use of ITNs for prevention and antimalarial drugs either for IPT or for case management of malaria in pregnant women. With increasing *Plasmodium falciparum* resistance to sulphadoxine–pyrimethamine, the recommended drug for IPT in high transmission areas, and the absence of alternate strategies in low and unstable transmission areas, ITNs are increasingly becoming the mainstay of malaria prevention in both stable and unstable transmission areas. A demonstration of the effectiveness of ITNs in reducing the overall burden and consequences of MIP is therefore of critical importance.

Although ITNs have been shown to be effective in reducing malaria morbidity and mortality in young children, their effect in pregnant women have been less clear. The outcome of this Cochrane review of the available evidence on the effect of ITNs on the health status of pregnant women and birth outcomes is therefore important in ascertaining the beneficial effect of ITN use among pregnant women and justification for further promotion.

This review clearly demonstrates that ITN use reduces placental malaria, fetal loss, low birth weight, and to some degree anaemia and clinical malaria, although the latter effects were not statistically significant. The authors’ conclusion that the use of ITNs in malaria-endemic regions of Africa has a beneficial impact on pregnancy outcomes and that no further trials of ITNs are required in sub-Saharan Africa provides impetus for scaling up ITN delivery to pregnant women to protect their health and pregnancy outcomes. It also enables the scientific and programmatic community to direct resources to other pertinent research questions.

This excellent review is therefore timely in the context of current global efforts by the Roll Back Malaria (RBM) Partnership to scale up effective malaria interventions to achieve RBM goals by 2010 and the Millennium development goals by 2015.

Related questions that remain to be investigated are the usefulness of ITNs in low and unstable transmission areas and the delivery mechanisms that would make them accessible to all pregnant women and render them effective at all times since pregnancy has a perennial occurrence.

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**Commentary: Cluster trials: a few words on why and how to do them**

**Mike Clarke**

Have you heard ‘the whole is greater than the sum of the parts’? If that happens in research it is usually a bonus but there is a type of trial where we expect the whole to be *less* than the sum of the parts. In a *cluster randomized trial*, if we treat the study as though each person in the cluster is independent of the others, we will get an over precise answer. And, an over precise answer, especially if it is precisely wrong, might be the last thing we want from research. On the other hand, if we assume that the results are the equivalent of having just one person in each cluster, we will underestimate the strength of any effect. We need to do something in between. Researchers who do cluster trials need to make the necessary correction and reviewers who include their trials in a meta-analysis need to be sure that these corrections have been made.

In cluster trials, interventions or strategies are compared by randomizing groups of people, such as a class of school children, a general practitioner’s clinic, or the people who live in a village, to the alternative interventions. This is different to the more usual trial in which each person is randomized individually to one or other intervention. If a trial involved just two clusters, you can see how weak the design would be for coping with chance and confounding factors. Imagine if only two people who had dislocated a shoulder were studied and the flip of coin meant that one received physiotherapy and the other did not. Any differences in outcome might be due to the physiotherapy, but they might also be due to the severity of the dislocation, the amount of normal exercise done by the person or their natural propensity to heal.

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The problems would be the same in a trial with just two clusters. Differences in outcome might arise because one class contained a disruptive child, one clinic took place on a cold day or the hierarchy of authority in one village was less rigidly applied. These differences might not affect everyone in a cluster to the same extent but any similarities among people within a cluster weaken the power to detect differences in the effects of interventions between the clusters. We overcome this by randomizing more clusters, to try to balance out the different characteristics. It means that more people have to be studied than would be the case in an individually randomized trial.

So, why use cluster designs, rather than randomizing individuals? Usually for reasons such as efficiency, practicality and concerns that the strategies being tested need to be kept separate to avoid contamination. For example, it might not be efficient to travel to every village, randomizing half the inhabitants to have a HIV test. Instead whole villages could be randomized, with the person administering the test needing to visit only 50% of them. It might not be practical to vary randomly the posters discussing depression in a clinic, and providing sex education to some children in a class and not others will probably breakdown as knowledge is exchanged between them.

The Cochrane review of ITNs for protecting pregnant women against malaria, expected that it might include both cluster trials and individually randomized trials, planned accordingly and did find both. Three of the five trials randomized whole communities to bednets or not, and analysed the pregnant women in these communities as a subgroup. The other trials randomized individual pregnant women to receive bednets or no bednets in Kenya; or treated bednets versus untreated bednets in Thailand. Fortunately, the cluster trials had all been analysed appropriately, allowing the reviewers to combine the results without needing to make the necessary adjustments for themselves.