

Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon

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ABSTRACT

Objective To determine the effectiveness in reducing malaria of combining an insect repellent with insecticide treated bed nets compared with the nets alone in an area where vector mosquitoes feed in the early evening.

Design A double blind, placebo controlled cluster-randomised clinical study.

Setting Rural villages and peri-urban districts in the Bolivian Amazon.

Participants 4008 individuals in 860 households.

Interventions All individuals slept under treated nets; one group also used a plant based insect repellent each evening, a second group used placebo.

Main outcome measure Episodes of *Plasmodium falciparum* or *P vivax* malaria confirmed by rapid diagnostic test or blood slide, respectively.

Results We analysed 15 174 person months at risk and found a highly significant 80% reduction in episodes of *P vivax* in the group that used treated nets and repellent (incidence rate ratio 0.20, 95% confidence interval 0.11 to 0.38, $P<0.001$). Numbers of *P falciparum* cases during the study were small and, after adjustment for age, an 82% protective effect was observed, although this was not significant (0.18, 0.02 to 1.40, $P=0.10$). Reported episodes of fever with any cause were reduced by 58% in the group that used repellent (0.42, 0.31 to 0.56, $P<0.001$).

Conclusions Insect repellents can provide protection against malaria. In areas where vectors feed in the early evening, effectiveness of treated nets can be significantly increased by using repellent between dusk and bedtime. This has important implications in malaria vector control programmes outside Africa and shows that the combined use of treated nets and insect repellents, as advocated for most tourists travelling to high risk areas, is fully justified.

Registration NCT 00144716.

INTRODUCTION

Bed nets impregnated with insecticide are highly effective at reducing morbidity and mortality from malaria.¹ Most successful reports have been from sub-Saharan Africa, where the most important vector species, *Anopheles gambiae*, feeds indoors over night.² Malaria

vectors in other parts of the world, however, are less readily controlled by treated bed nets, particularly those species that prefer to feed outdoors or those that feed in the early evening.^{2,3} About 36% of the population of the Americas live in areas with a risk of malaria.⁴ Of the 1.14 million cases of malaria reported in the Americas during 2000, 87% were recorded in the Amazonian subregion of South America.⁴ The primary malaria vector in the Amazon, *A darlingi*, has a peak biting activity between 8 pm and 10 pm, and more than 80% of feeding occurs before most local people go to bed, where they can be protected by a treated bed net.⁵

As a result, treated nets will probably need to be supplemented in the few hours just after dusk by some other control measure. Field evaluations of several plant-based insect repellents and a N,N-diethyl-*m*-toluamide (DEET) standard in this region found that one particular substance, *Eucalyptus maculata citriodon*, provided a high degree of protection (>98%) against *A darlingi* for up to four hours.³ We selected a plant based repellent as we consider a natural product has the potential for local production, making it a more readily available, cheaper, and thus a more sustainable option for potential large scale use.

We conducted a double blind randomised controlled trial of the combined use of insect repellent and treated bed nets in reducing malaria in an area of evening biting vectors.

METHODS

Recruitment—The study was carried out between March and September 2003 in rural and peri-urban communities in the Bolivian Amazon Region. Each study house was located a minimum of 25 metres from any other in the study to avoid any effect of diversion of insects from treatment to placebo homes. Researchers collected baseline data (age, sex, occupation) for each participant and obtained written informed consent from each individual or carer of those aged under 18. We estimated a need to recruit and follow-up 408 households in each arm with an average of five individuals per household for the full six month transmission season (more details on bmj.com).

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Age specific incidence per 1000 person years (episodes/person months at risk) of different outcomes by treatment group

	Age 10-14 years		Age ≥15 years	
	Repellent	Placebo	Repellent	Placebo
<i>P falciparum</i>	0.0 (0/1641)	40.0 (6/1801)	2.0 (1/6065)	0.0 (0/5667)
<i>P vivax</i>	36.8 (5/1629)	185.7 (27/1745)	17.9 (9/6044)	83.7 (39/5591)
All cause fever	197.4 (27/1641)	719.6 (108/1801)	170.2 (86/6065)	343.0 (162/5667)

Intervention—Field staff followed the strict inclusion criteria to randomise participants at the household level following a basic sequential alternate A/B/A/B regimen. Field staff and study participants were blind to the group allocation. After we recorded baseline parameters, all participants received a freshly impregnated treated bed net (25 mg/m² deltamethrin) plus either the insect repellent (*Eucalyptus maculata citriodon*) with a *p*-menthane 3,8 diol (PMD) concentration of 30% (MASTA, UK) for the treatment group or 0.1% clove oil for the placebo group. Treated nets were also provided to participants in households not enrolled in the study to reduce risks of short range diversion of mosquitoes. Participants applied lotion at dusk each evening. Compliance was monitored by questionnaire and verified by local field staff recording amounts used at monthly follow-up visits and through unannounced evening “sniff checks.”

Assessments—We recorded malaria infection (with or without fever) at baseline early in the malaria season in March and at active monthly follow-up visits between April and July using *P falciparum* specific rapid diagnostic test. As a secondary outcome, the local health district clinic passively detected *P vivax* episodes by microscopic blood slide examination, which was subsequently validated at the central regional health district malaria laboratory. All patients with positive results were referred to the local health centre for prompt treatment. At each visit researchers asked about and recorded any adverse events.

Statistical analysis—To assess the efficacy of the intervention the analysis included all individuals randomised, but only for the period of time that they were compliant with the intervention. We adjusted analyses for age as an a priori covariate because of the effect of age acquired immunity on malaria infection. Full details are on bmj.com.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Insecticide treated bed nets are a highly effective means of reducing morbidity and mortality from malaria in Africa, where local vectors bite indoors late at night
Insect repellents can reduce mosquito bites but protection against insect-borne disease is not clear

WHAT THIS STUDY ADDS

Treated bed nets should not be used as the only means of preventing malaria in areas where vectors feed mainly in the evening
Use of an insect repellent can significantly reduce the risk of malaria
The combined use of a repellent and a treated bed net should be advocated to those travelling to malaria risk areas

RESULTS

Details of the numbers randomised and the flow through the study are on bmj.com. There were no significant differences in most household characteristics (number of household members, roof material, water source, heating source, or possession of electricity, fridge, and radio) between the two groups (data not shown), but households allocated to the repellent group were slightly more likely to own a television than those allocated to the placebo group (P=0.056) (see bmj.com). There were also no significant differences in age or sex between the groups but at baseline more participants in the repellent group were positive for *P falciparum* (P=0.065). No adverse events were reported.

As compliance was high for this type of study, with just 1.5% person months excluded in each group, the results of our per protocol analysis would be similar to an intention to treat analysis. The number of *P falciparum* episodes detected was low, and all episodes in the placebo group were in children (age 10-14), while the single episode in the repellent group was in an adult (56 years old) (table). Univariate regression analysis suggested an effect of borderline significance, with an 84% reduction in incidence of *P falciparum* in the repellent group (P=0.091). The univariate effect of age group, however, was highly significant with a 95% reduction in incidence in adults (≥15 years) compared with children aged 10-14 (P=0.005). After we accounted for age, the effect of the repellent on incidence of *P falciparum* remained but was even less significant (incidence rate ratio 0.18, 95% confidence interval 0.02 to 1.40, P=0.102).

Analysis of first episodes of *P vivax* showed a reduction in those who used repellent, and again there was a significant influence of age, with a 53% lower incidence in adults compared with children (P=0.002). Even after adjustment for the effect of age, the repellent provided 80% protection (0.20, 0.11 to 0.38, P<0.001).

Similarly, for the analysis of all episodes of fever (reported fever in the past month) there was a 59% reduction in the group that used repellent (P<0.001), a 42% lower incidence of fevers in adults compared with children (P<0.001), and a borderline 56% higher incidence of fevers (P=0.061) in those living in larger households (six or more people) compared with those in smaller households (fewer than six). After adjustment for these factors, there was 58% lower incidence of reported fevers in the repellent compared with the placebo group (0.42, 0.31 to 0.56, P<0.001).

DISCUSSION

This randomised controlled trial shows that insect repellent applied to the skin has a significant impact on the incidence of malaria. This difference was detected in people who were also sleeping under insecticide treated nets, highlighting the value of additional methods of protection in areas where malaria transmission occurs mainly in the early evening before treated nets are used.

The large effect of the use of repellent on the incidence of *P falciparum* and *P vivax* suggests that most malaria transmission occurs in the early evening, before people

are protected by sleeping under a treated bed net. Our results on the effect of the repellent on the incidence of *P falciparum*, however, probably reflect insufficient statistical power because of the overall low incidence of falciparum cases during the study. We found clear evidence to support the use of a combination of insect repellent and treated bed nets as personal protection against malaria. This is particularly important to the growing number of tourists and business travellers, who have no immunity to malaria. This trial provides evidence for health professionals and specialist travel health organisations to advocate such combined measures in high risk areas, particularly with early evening or outdoor feeding vectors.

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Competing interests: NH has received minor funding from numerous manufacturers and suppliers of insect repellents in Europe and the US for laboratory evaluation of their products, and from national consumer groups to compare efficacy of repellents on the European market.

Ethical approval: London School of Hygiene and Tropical Medicine (University of London) ethics committee and Ministerio de Salud y Previsión Social, Bolivia.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study

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Objective To assess the risks and benefits associated with caesarean delivery compared with vaginal delivery.

Design Prospective cohort study within the 2005 WHO global survey on maternal and perinatal health.

Setting 410 health facilities in 24 areas in eight randomly selected Latin American countries; 123 were randomly selected and 120 participated and provided data

Participants 106 546 deliveries reported during the three month study period, with data available for 97 095 (91% coverage).

Main outcome measures Maternal, fetal, and neonatal morbidity and mortality associated with intrapartum or elective caesarean delivery, adjusted for clinical, demographic, pregnancy, and institutional characteristics.

Results Women undergoing caesarean delivery had an increased risk of severe maternal morbidity compared with women undergoing vaginal delivery (odds ratio 2.0 (95% confidence interval 1.6 to 2.5) for intrapartum caesarean and 2.3 (1.7 to 3.1) for elective caesarean). The risk of antibiotic treatment after delivery for women having either type of caesarean was five times that of women having vaginal deliveries. With cephalic presentation, there was a trend towards a reduced odds ratio for fetal death with elective caesarean, after adjustment for possible confounding variables and gestational age (0.7, 0.4 to 1.0). With breech presentation, caesarean delivery had a large protective effect for fetal death. With cephalic presentation,

however, independent of possible confounding variables and gestational age, intrapartum and elective caesarean increased the risk for a stay of seven or more days in neonatal intensive care (2.1 (1.8 to 2.6) and 1.9 (1.6 to 2.3), respectively) and the risk of neonatal mortality up to hospital discharge (1.7 (1.3 to 2.2) and 1.9 (1.5 to 2.6), respectively), which remained higher even after exclusion of all caesarean deliveries for fetal distress. Such increased risk was not seen for breech presentation. Lack of labour was a risk factor for a stay of seven or more days in neonatal intensive care and neonatal mortality up to hospital discharge for babies delivered by elective caesarean delivery, but rupturing of membranes may be protective. **Conclusions** Caesarean delivery independently reduces overall risk in breech presentations and risk of intrapartum fetal death in cephalic presentations but increases the risk of severe maternal and neonatal morbidity and mortality in cephalic presentations.

INTRODUCTION

The increase in rates of caesarean delivery at an institutional level is not associated with any clear overall benefit for the baby but is linked with increased morbidity.¹ There is an urgent need to provide women and care providers with information on the potential individual risks and benefits associated with caesarean delivery.