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Malaria: prevention in travellers

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ABSTRACT

INTRODUCTION: Malaria transmission occurs most frequently in environments with humidity over 60% and ambient temperature of 25–30 °C. Risks increase with longer visits and depend on activity. Infection can follow a single mosquito bite. Incubation is usually 10–14 days but can be up to 18 months depending on the strain of parasite. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug preventive interventions in adult travellers? What are the effects of drug prophylaxis in adult travellers? What are the effects of antimalaria vaccines in travellers? What are the effects of antimalaria interventions in child travellers, pregnant travellers, and in airline pilots? We searched: Medline, Embase, The Cochrane Library and other important databases up to February 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 69 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acoustic buzzers, aerosol insecticides, amodiaquine, air conditioning and electric fans, atovaquone-proguanil, biological control measures, chloroquine (alone or with proguanil), diethyltoluamide (DEET), doxycycline, full-length and light-coloured clothing, insecticide-treated clothing/nets, mefloquine, mosquito coils and vaporising mats, primaquine, pyrimethamine–dapsone, pyrimethamine–sulfadoxine, smoke, topical (skin-applied) insect repellents, and vaccines.

QUESTIONS

INTERVENTIONS

NON-DRUG PREVENTION IN ADULT TRAVELLERS

Likely to be beneficial

Unknown effectiveness

DRUG PROPHYLAXIS IN ADULT TRAVELLERS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Likely to be ineffective or harmful

ANTIMALARIA VACCINES IN ADULT AND CHILD TRAVELLERS

Unknown effectiveness

Key points

- Malaria transmission occurs most frequently in environments with a humidity over 60% and ambient temperature of 25–30 °C. Risks increase with longer visits, and depend on activity.

  Infection can follow a single mosquito bite. Incubation is usually 10–14 days, but can be up to 18 months depending on the strain of parasite.

  Complications are usually because of delayed or inappropriate treatment, but up to 88% of previously healthy travellers recover fully with prompt treatment. Older people have a worse prognosis.

- Many of the studies on prevention of malaria have been performed on people other than travellers, such as residents of endemic malaria areas.

- Various non-drug preventive measures may be effective, but some may have adverse effects.

  There is a consensus that skin-applied chemical repellents containing DEET (diethyltoluamide) reduce the risk of insect bites. Picaridin is a newer and possibly more effective repellent than DEET, but it has not yet been evaluated against clinical outcomes.

  Using treated bednets or clothing, may be beneficial.

  We don't know whether insecticide sprays or lifestyle changes such as wearing full-length clothing, dietary supplementation, use of air conditioning or electric fans, mosquito coils or vaporising mats, bath or chemical base oils, skin-applied plant-based repellents, electronic buzzers, outdoor smoke , vaccines, or biological control measures can reduce the risk of malaria infection. Mosquito coils and vaporising mats should not be used indoors.

- Various drug treatments may be effective in preventing malaria, but we cannot be sure which is the most effective drug regimen, and most have adverse effects which can sometimes be serious.

  Atovaquone–proguanil and doxycycline may be beneficial.

  Chloroquine is considered to reduce the risk of malaria in travellers to areas where chloroquine resistance is low, although few studies have been done.

  Mefloquine and chloroquine–proguanil may be beneficial, but their adverse effects must also be considered.

  We don't know whether pyrimethamine–dapsone or pyrimethamine–sulfadoxine are effective.

  Children may be at risk of encephalopathic adverse effects from topical insect repellents containing DEET. There is consensus that chloroquine is effective and safe in preventing malaria in children, but we don't know whether this is the case for any other treatments.

- Insecticide-treated bed nets may be effective in preventing malaria in pregnant women.

  We found no RCT evidence about insecticide-treated clothing in pregnant women, but evidence in non-pregnant adults that it is effective is likely to be generalisable to pregnant women. However, there are attendant risks.

  There is consensus that chloroquine may be beneficial in pregnant women.

- Atovaquone–proguanil may have no more adverse effects than placebo in airline pilots, but we have no direct evidence assessing whether treatments are safe or effective in this occupational group. There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots.

- CAUTION

Adverse effects of primaquine and amodiaquine limit their use in preventing malaria.

DEFINITION

Malaria is an acute parasitic disease of the tropics and subtropics, caused by the invasion and destruction of red blood cells by one or more of four species of the genus *Plasmodium: P falciparum* , *P vivax* , *P ovale*, and *P malariae*. [1] The clinical presentation of malaria varies according to the infecting species, and according to the genetics, immune status, and age of the infected person. [2] The most severe form of human malaria is caused by *P falciparum*, in which variable clinical features include spiking fevers, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea, and abdominal pain; other symptoms related to organ failure may supervene, such as acute renal failure, generalised convulsions, and circulatory collapse, followed by coma and death. [3] [4] *P falciparum* accounts for more than 50% of malaria infections in most East Asian countries, over 90% in sub-Saharan Africa, and almost 100% in Hispaniola. [5] Travellers are defined here as visitors from a malaria-free area to a malaria-endemic area, who stay in the endemic area for less than 1 year.

INCIDENCE/ PREVALENCE

Malaria is the most dangerous parasitic disease of humans, infecting about 5% of the world's population, and causing about one million deaths each year. [6] The disease is strongly resurgent, owing to the effects of war, climate change, large-scale population movements, increased breeding opportunities for vector mosquitoes, rapidly spreading drug and insecticide resistance, and neglect of public health infrastructure. [1] [7] Malaria is currently endemic in more than 100 countries, which are visited by more than 125 million international travellers each year. [4] Cases of malaria acquired by international travellers from industrialised countries probably number 25,000 annually. Of these, about 10,000 are reported and 150 are fatal. [8]

AETIOLOGY/ RISK FACTORS

Humans acquire malaria from sporozoites transmitted by the bite of infected female anopheline mosquitoes. [9] Of about 3200 mosquito species so far described, some 430 belong to the genus *Anopheles* . Of these, about 70 anopheline species are known to transmit malaria, with about 40 species considered important vectors. [10] When foraging, blood-thirsty female mosquitoes fly upwind searching for the scent trail of an attractive host. [11] Female anophelines are attracted to their human hosts over a range of 7–20 m, through a variety of stimuli, including exhaled carbon dioxide, lactic acid, other host odours, warmth, and moisture. [12] Larger people tend to be bitten by mosquitoes more than smaller individuals. [12] [13] Women receive significantly more mosquito bites in trials than men. [14] Children secrete lower levels of chemical attractants than adults, and therefore usually receive fewer mosquito bites than adults. [15] Malaria transmission does not usually occur at temperatures below 16 °C or above 35 °C, or at altitudes greater than 3000 m above sea level at the equator (lower elevations in cooler climates), because sporozoite development in the mosquito cannot take place. [16] The optimal conditions for transmission are a humidity of over 60%, and an ambient temperature of 25–30 °C. [17] Most of the important vectors of malaria breed in small temporary collections of fresh surface water exposed to sunlight and with little predation, and in sites such as residual pools in drying river beds. [18] Although rainfall provides breeding sites for mosquitoes, excessive rainfall may wash away mosquito larvae and pupae. [19] Conversely, prolonged droughts may be associated with increased malaria transmission if they reduce the size and flow rates of large rivers sufficiently to produce suitable *Anopheles* breeding sites. [20] Anopheline mosquitoes vary in their preferred feeding and resting locations, although most bite in the evening and at night. [21] The *Anopheles* mosquito will feed by day only if unusually hungry. [22] *Anopheles* adults usually fly not more than 2–3 km from their breeding sites, although a flight range of up to 7 km has been observed. [23] One cross sectional study of about 7000 children under the age of 10 years found that, during months of peak transmission, living within 3 km of an *Anopheles* breeding site significantly increased the risk of malaria compared with living 8–10 km away (RR 21.00, 95% CI 2.87 to 153.00). [24] Exceptionally, strong winds may carry *Anopheles* up to 30 km or more. [12] In travellers, malaria risk is related to destination, activity, and duration of travel. A retrospective cohort study (5898 confirmed cases) conducted in Italian travellers between 1989 and 1997 found that the malaria incidence was 1.5/1000 for travel to Africa, 0.11/1000 for travel to Asia, and 0.04/1000 for travel to Central and South America. [25] A survey of approximately 170,000 Swedish travellers found that the prevalence of malaria was lowest among travellers to Central America and the Caribbean (0.01/1000), and higher among travellers to East, Central, and West Africa (prevalence among travellers to East Africa 2.4/1000, Central Africa 3.6/1000, and West Africa 3.0/1000). [26] A survey of 2131 German travellers to sub-Saharan Africa found that solo travellers were at almost a ninefold greater risk of infection than those on package tours. [27] A case control study (46 cases, 557 controls) reported that a visit to the tropics for longer than 21 days doubled the malaria risk compared with visits lasting 21 days or less. [28]

PROGNOSIS

Malaria can develop after just one anopheline mosquito bite. [29] Human malaria has a usual incubation period that ranges from 10–14 days (*P falciparum*, *P vivax*, and *P ovale*) to about 28 days (*P malariae*). [30] Certain strains of *P vivax* and *P ovale* can have a much longer incubation period

of 6–18 months. [20] About 90% of malaria attacks in travellers occur at home. [31] About 36% of cases that develop after returning home do so more than 2 months after the traveller's return. [32] People returning from an endemic area with any fever pattern should be considered to have malaria until proved otherwise. [4] [6] [22] [29] [33] Once malaria infection occurs, older travellers are at greater risk of poor clinical outcomes and death. In US travellers between 1966 and 1987, the case fatality rate was 0.4% for people aged 0–19 years, 2.2% for ages 20–39 years, 5.8% for ages 40–69 years, and 30.3% for those aged 70–79 years. [34] Complications and death from malaria are mainly due to inappropriate treatment, or to delayed initiation of treatment. [35] If malaria is diagnosed and treated promptly, about 88% of previously healthy travellers will recover completely. [36]

AIMS OF INTERVENTION

To reduce the risk of infection; to prevent illness and death, with minimal adverse effects of treatment.

OUTCOMES

Rates of clinical malaria and death, and adverse effects of treatment. Proxy measures include numbers of mosquito bites and rates of mosquito catches in indoor areas. One experimental study in rabbits has suggested that *Anopheles stephensi* biting behaviour is not affected by their *P falciparum* infection status. [37] This suggests that numbers of *A stephensi* mosquito bites may be a reasonable measure of *P falciparum* malaria risk in humans. Long-term residents of malaria endemic areas acquire partial immunity to infected mosquito bites, with only a small proportion of such bites progressing to a new infection (in children aged 6 months to 6 years, monitored for 18 months in western Kenya, only 7.5% of infected bites produced a clinical episode of malaria). [38] In non-immune travellers, the likelihood of malaria infection after a single infected bite is much higher (US marines who spent 1–14 nights in Liberia experienced a 44% malaria acquisition rate). [39]

METHODS

BMJ Clinical Evidence search and appraisal February 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2007, Embase 1980 to February 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE) and AMED for studies on bath/body oils and dietary supplementation. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, and prospective and retrospective cohort studies in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We also searched for cohort studies on specific harms of named interventions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Additional hand searches were performed by the contributor of his own files and the *Journal of Travel Medicine*, *Journal of the Royal Army Medical Corps*, and *Transactions of the Royal Society of Tropical Medicine and Hygiene*. As *BMJ Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our overall assessment of the interventions in this review. Evidence from case control and observational studies have been included in some sections where randomised studies did not exist or where they did not address specific questions. In some sections, evidence of harms has been extracted from case series. In the questions on preventive and prophylactic interventions in adults, we have excluded studies in pregnant women or airline pilots, because these populations are covered by separate questions. Where no data were available in travellers, we have included systematic reviews and RCTs in people in malaria-endemic settings, as we believe that the results of these studies are generalisable to travellers.

QUESTION What are the effects of non-drug interventions to prevent malaria in non-pregnant adult travellers?

OPTION AEROSOL INSECTICIDES IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of aerosol insecticides to prevent malaria in travellers. One large questionnaire survey in travellers found insufficient evidence on the effects of aerosol insecticides in preventing malaria. Two community RCTs in residents of malaria-endemic areas found that indoor spraying of aerosol insecticides reduced clinical malaria.

Benefits: We found no systematic review or RCTs in travellers (see comment below). One large questionnaire survey of 89,617 European tourists returning from East Africa measured malaria incidence with a two-stage self-completed questionnaire administered during the return flight and again 12 weeks later. [40] It found that commercially available personal aerosol insecticides did not significantly reduce the incidence of malaria (P = 0.55). Two community RCTs in lifelong residents of malaria-endemic areas found that indoor residual spraying of synthetic pyrethroids reduced clinical malaria. [41] [42]

Harms: The RCTs gave no information on adverse effects. [41] [42]

Comment: **Clinical guide:**
Historically, indoor residual spraying has not been recommended for short-stay travellers, and we found weak evidence from a large observational study that aerosol insecticides did not reduce the risk of malaria in travellers. [40] However, we found evidence from RCTs of benefit from indoor residual spraying of synthetic pyrethroids in preventing malaria in residents of malaria-endemic areas. [41] [42] It is possible that this benefit may also be seen in travellers if the same insecticides are used in the same conditions.

OPTION BIOLOGICAL CONTROL MEASURES IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of biological control measures to prevent malaria in travellers.

Benefits: We found no systematic review or RCTs of biological control measures in preventing malaria in travellers (see comment below).

Harms: We found no RCTs.

Comment: One systematic review (search date 1997) identified two cohort studies based on mosquito counts. [43] It found no evidence that growing the citrosa plant, and encouraging natural predation of insects by erecting bird or bat houses reduced bites to humans from infected anopheline mosquitoes. The only known way to reduce mosquito populations naturally is to eliminate sources of standing water — such as blocked gutters, tree-stump holes, and discarded tyres, cans, and bottles. [43]

Clinical guide:
There is no reliable evidence about the effects of biological control measures in preventing malaria in travellers.

OPTION AIR CONDITIONING AND ELECTRIC FANS IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of air conditioning or electric fans to prevent malaria in travellers. One large questionnaire survey found that air conditioning reduced the incidence of malaria. One small observational study found that electric ceiling fans reduced total catches of culicine mosquitoes in indoor spaces. However, it found no significant difference in total catches of anopheline mosquitoes.

Benefits: We found no systematic review or RCTs (see comment below). One questionnaire survey of 89,617 European tourists returning from East Africa measured malaria incidence with a two-stage self-completed questionnaire administered during the return flight and again 12 weeks later. [40] It found that sleeping in an air-conditioned room significantly reduced the incidence of malaria (P = 0.04).

Harms: We found no RCTs.

Comment: One cohort study (6 experimental huts in villages in Pakistan) of various antimosquito interventions found that an electric ceiling fan run at high speed significantly reduced total catches of blood-fed culicine mosquitoes (P less than 0.05). [44] However, it did not significantly reduce total catches of blood-fed anopheline mosquitoes. These studies support the finding that mosquitoes are reluctant to fly in windy conditions, [45] but suggest that anopheline mosquitoes may be more tolerant than culicine mosquitoes of air turbulence.

Clinical guide:
There is weak evidence of possible benefit from air conditioning in preventing malaria in travellers. There is no reliable evidence about the effects of electric fans in preventing malaria in travellers.

OPTION ELECTRONIC BUZZERS IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of electronic buzzers to prevent malaria in adults.

Benefits: We found no systematic review or RCTs with clinical malaria as an outcome.

Harms: We found no RCTs.

Comment: We found one non-randomised controlled trial (18 houses in Gabon) of a commercially available ultrasound-emitting device. The trial lasted 6 weeks and used total mosquito catches as an outcome. [46] Most mosquitoes were culicine. It found no significant difference in mosquito catches between the ultrasound-emitting device and a sham device (P = 0.48).

Clinical guide:
There is weak evidence suggesting that electronic buzzers may be of no benefit in preventing malaria in travellers.

OPTION MOSQUITO COILS AND VAPORISING MATS IN NON-PREGNANT ADULT TRAVELLERS

We found one systematic review but no RCTs on the effects of coils to prevent malaria in travellers, and no RCTs on the effects of vaporising mats. One case control study of coils in travellers found no evidence of a protective effect against malaria. Two case control studies of coils in residents found no evidence of a protective effect against malaria.

Benefits: We found one systematic review (search date 2003) that evaluated the use of coils to prevent malaria. [47] It identified no RCTs. We found no systematic review and no RCTs examining the effect of vaporising mats on the incidence of clinical malaria. We found three case control studies. [28] [48] [49] The first case control study (603 British travellers to the Gambia between September and December, 48% of whom burnt mosquito coils) found that, when assessing people with and without malaria, there was no significant difference in coil use between groups (OR 0.65, 95% CI 0.32 to 1.34). [28] In the second case control study (457 urban residents in southern India, surveyed during the rainy season), approximately 13% of participants used mosquito coils to prevent malaria, and approximately 43% used vaporising mats; the use of these devices did not significantly reduce malaria rates (OR 0.85, 95% CI 0.57 to 1.28). The use of other repellent methods such as nets, oils, and creams was included in this final figure. [48] The third case control study (406 village residents in a high-transmission area of southern Laos) found that non-use of a mosquito coil did not increase the risk of malaria acquisition (OR 1.35, 95% CI 0.06 to 2.91, P = 0.38). [49]

Harms: The systematic review found one trial, which reported irritation of the eyes and nose after coil use. [47] The studies in the systematic review [47] and the subsequent case control studies [28] [48] [49] did not report on other potential adverse effects of exposure to the substances emitted by coils or vaporising mats. These potential adverse effects need investigation.

Comment: One RCT of coils (residential houses in a squatter area in Malaysia) and one observational study (6 experimental huts in villages in Pakistan) of pyrethroid vaporising mats found that these devices reduced numbers of culicine mosquitoes in indoor spaces. [50] [44]

Clinical guide:
There is evidence that mosquito coils and vaporising mats may be of no benefit in preventing malaria in travellers. Because of their unknown safety profile, these devices should not be used indoors.

OPTION OUTDOOR SMOKE IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of outdoor smoke to prevent malaria. One controlled clinical trial found that outdoor smoke repelled mosquitoes during the evening.

Benefits: We found no systematic review or RCTs of outdoor smoke that assessed effects on malaria acquisition.

Harms: We found no RCTs.

Comment: One controlled clinical trial, in which five small fires were tended on five successive evenings in a village in Papua New Guinea, found a smoke-specific and species-specific effect from different types of outdoor smoke. [51] Catches of one anopheline species were reduced by 84% by burning betelnut (95% CI 62% to 94%), by 69% by burning ginger (95% CI 25% to 87%), and by 66% by burning coconut husks (95% CI 17% to 86%). There may be an irritant and toxic effect of outdoor smoke on the eyes and respiratory system, but this effect was not quantified in the controlled clinical trial. [51]

Clinical guide:
There is weak evidence of benefit from certain types of outdoor smoke in repelling mosquitoes. This may translate into clinical benefit by reducing bites, which is likely to reduce malaria infection. However, there is currently no evidence about the effects of outdoor smoke on malaria risk in travellers.

OPTION INSECTICIDE-TREATED BED NETS IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs in travellers. One systematic review in adult and child residents of malaria-endemic settings found that insecticide-treated bed nets reduced the number of mild episodes of malaria, and reduced child mortality.

Benefits: We found no systematic review or RCTs in travellers. We found one systematic review (search date 2003), which identified 21 RCTs in malaria-endemic settings (stable transmission area greater than 1 infective bite/person/year; non-traveller children and adults). [52] It found that, over 4–29 months, bed nets sprayed or impregnated with a pyrethroid insecticide such as permethrin were associated with lower rates of mild episodes of malaria compared with no or untreated bed nets (insecticide-treated nets *v* no nets: 4 RCTs; RRR 50%; insecticide-treated nets *v* untreated nets: 3 RCTs; RRR 39%, CIs not calculated for either analyis, as the analyses included both cluster and non-cluster randomised trials). It found that bed nets sprayed or impregnated with a pyrethroid insecticide such as permethrin significantly reduced child mortality (impregnated nets *v* no nets: 3 RCTs; RR 0.83, 95% CI 0.76 to 0.90; impregnated nets *v* untreated nets: 1 RCT; RR 0.77, 95% CI 0.86 to 0.95).

Harms: The review gave no information on adverse effects. [52]

Comment: **Clinical guide:**
Permethrin remains active for about 4 months. [29] Mosquitoes are increasingly tolerant of pyrethroid insecticides, and there is some evidence that using a carbamate insecticide (such as carbosulfan) to treat bed nets may deter mosquitoes more effectively than using a pyrethroid insecticide to treat nets. [53] Although the systematic review analysing insecticide-treated bed nets was undertaken in non-traveller children and adults, the results are likely to be generalisable to other groups, such as travellers. Therefore, the evidence suggests that insecticide-treated bed nets are likely to be of benefit in preventing malaria in travellers.

OPTION INSECTICIDE-TREATED CLOTHING IN NON-PREGNANT ADULT TRAVELLERS

Three RCTs in soldiers and refugee householders who were not receiving chemoprophylaxis found that permethrin-treated fabric (clothing or sheets) reduced the incidence of malaria. However, one controlled trial in soldiers receiving chemoprophylaxis found no significant difference in the incidence of malaria between those wearing permethrin-treated uniforms and control soldiers, although the presence of background chemoprophylaxis may have masked the effect of permethrin-treated uniforms.

Benefits: We found no systematic review but found two RCTs [54] [55] [56] and one controlled clinical trial. [57] The first RCT (172 Colombian soldiers patrolling a malaria-endemic area for a mean of 4.2 weeks) found that permethrin-impregnated uniforms significantly reduced the incidence of malaria compared with non-impregnated uniforms (3/86 [3%] with impregnated uniforms *v* 12/86 [13%] with non-impregnated uniforms; RR 0.25, 95% CI 0.07 to 0.85). [54] The second RCT (102 refugee households in northwestern Pakistan) found that permethrin-treated wraps and top sheets significantly reduced the risk of falciparum malaria compared with placebo over 4 months (RR 0.56, 95% CI 0.41 to 0.78). [55] The third RCT (198 Somali refugees) found that permethrin-impregnated clothing significantly reduced malaria infection rates over 3 months compared with placebo (proportion infected: 38% with permethrin-treated clothing *v* 66% with placebo; P = 0.0002; absolute numbers not reported). [56] One non-randomised controlled trial (663 non-immune Thai soldiers patrolling a malaria-endemic area for 6 months) found that permethrin-treated uniforms did not significantly reduce the incidence of malaria compared with placebo-treated uniforms (68/249 [27%] with permethrin treated uniforms *v* 118/414 [29%] with placebo-treated uniforms; RR and CI not reported). [57] All participants were given the same chemoprophylaxis throughout the study.

Harms: The first RCT also included an analysis of permethrin-impregnated uniforms compared with non-impregnated uniforms in 286 soldiers patrolling a leishmaniasis-endemic area for a mean 6.6 weeks. [54] It found that 2/229 (1%) participants wearing permethrin-impregnated uniforms experienced irritation and itching. No comparative information was given for soldiers wearing non-impregnated uniforms. Neither the second RCT [55] nor the non-randomised study [57] reported on adverse effects. The third RCT reported that no adverse effects were observed in any of the participants. [56]

Comment:

In the first RCT, the entire uniform (hat, shirt, undershirt, trousers, and socks) was treated with a single application of permethrin. [54] All participants were instructed to wear the uniform continuously, day and night, with the sleeves rolled down. Each participant washed his own uniform two or three times during the study, using soap and water. Topical (skin-applied) insect repellents were not used. In the second RCT, the chaddar (a veil or wrap) and top sheets of participants were treated with 1 g/m^2 permethrin. In the third study, the uniform shirt and trousers of participants were sprayed evenly at high pressure, until entirely saturated with an emulsion containing 151 mL permethrin in 7.5 L water. [57] Re-treatment was not reported in any of the studies.

Clinical guide:

There is some evidence of benefit from insecticide-treated clothing in preventing malaria. Trials in soldiers may not be generalisable to other travellers, because tourists or business travellers may be less likely than soldiers to wear their impregnated garments continuously.

OPTION LIFESTYLE CHANGES (INCLUDING FULL-LENGTH CLOTHING, LIGHT CLOTHING, BEHAVIOUR MODIFICATION) IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of full-length or light-coloured clothing to prevent malaria in travellers. One case control study in expatriates found that wearing clothes covering arms or legs reduced the incidence of malaria. One controlled trial in military personnel and one large questionnaire survey in travellers reported that wearing long trousers and long-sleeved shirts reduced the incidence of malaria.

Benefits:

Full-length clothing:

We found no systematic review or RCTs. We found one non-randomised controlled trial (two co-located squadrons of US Air Force personnel exposed to malaria for 1 month during World War II, with one squadron wearing long-sleeved shirts and trousers continuously and the other wearing short-sleeved shirts and shorts continuously). [58] The trial found that wearing long-sleeved shirts and trousers significantly reduced the incidence of malaria (2/150 [1%] with long-sleeved shirts *v* 62/150 [41%] with short-sleeved shirts; RR and CI not reported). The trial provided no information on denominators, the design or conduct of the study, statistical analysis, or confounders. We also found one case control study (144 expatriates staying in the Central African Republic for more than 4 months), which found that wearing clothes covering arms or legs in the evening or at night significantly reduced malaria acquisition (OR 0.13, 95% CI 0.02 to 0.65, P = 0.01). [59] We also found one large questionnaire survey (89,617 European tourists returning from East Africa), which found that wearing long-sleeved shirts and trousers significantly reduced the incidence of malaria (P = 0.02). [40]

Other lifestyle changes:

We found no studies (see comment below).

Harms:

None.

Comment:

Other lifestyle changes:

Other lifestyle changes include not travelling to malaria-endemic regions during the rainy season (when most malaria transmission occurs) and not going outdoors in the evening or at night.

Clinical guide:

Travellers who take day trips from a malaria-free city to a malaria-endemic region may be at minimal risk if they return to the city before dusk. [60] Some authors suggest wearing light-coloured rather than dark clothing, as insects prefer landing on dark surfaces. [60] [61] However, we found no reliable evidence about the effects of wearing light-coloured clothing. Full-length clothing may prevent malaria in travellers.

OPTION SKIN-APPLIED CHEMICAL REPELLENTS IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of skin-applied chemical repellents to prevent malaria in travellers. However, two RCTs and one case control study of DEET-containing repellent soap in residents in Asia and South America found that use of soap was associated with reduced malaria incidence. Extensive clinical experience of DEET has led to the consensus that it is likely to be beneficial in preventing malaria. DEET has been reported to cause systemic and skin adverse reactions, particularly with prolonged use. Picaridin is a newer, and possibly safer and more effective, chemical repellent than DEET, but it has not yet been evaluated against clinical outcomes.

Benefits:

We found no systematic review or RCTs on the effects of skin-applied chemical repellents to prevent malaria in travellers. However, we found two RCTs, [62] [63] one case control study, [64] and one

field study [65] of repellent soap (containing 20% DEET and 0.5% permethrin) in residents. The first RCT, which randomised communities in rural Ecuador and Peru (8272 people over 1 year), found no significant difference in the incidence of malaria between repellent soap compared with no soap (protective efficacy of repellent soap 0% in Ecuador and 26% in Peru; reported as non-significant). [62] The RCT reported that continuous soap use was only carried out by 50–70% of participants. The second RCT (127 Afghan refugee village households in Pakistan, 1148 people, over 6 months) found that repellent soap significantly reduced the number of people experiencing one or more episodes of *P falciparum* malaria compared with placebo lotion, (23/618 [4%] using repellent soap *v* 47/530 [9%] using placebo lotion; OR 0.44, 95% CI 0.25 to 0.76). [63] The case control study (96 cases of *P falciparum* and *P vivax* malaria, resident in Nangahar province, eastern Afghanistan) found that recalled use of repellent soap around the likely time of infection (10 days before) significantly reduced malaria infection (OR 0.08, 95% CI 0.01 to 0.61, P less than 0.001). [64] The field study of picaridin in Burkina Faso (more than 49,000 mosquitoes collected, over 96 nights, of which more than 95% were of the *Anopheles gambiae* complex) found that, after 10 hours of exposure, picaridin reduced the number of mosquitoes landing on the test humans compared with DEET (3698 mosquitoes with picaridon *v* 6836 mosquitoes with DEET; significance not reported for this comparison). [65]

Harms: We found one case series of systemic toxic reactions (confusion, irritability, insomnia) in US national park employees after repeated and prolonged use of DEET. [66] We found 14 case reports of contact urticaria and irritant contact dermatitis (mostly in soldiers) as a result of DEET. [40] The risk of absorption is especially high if DEET is left in the antecubital fossa overnight. [67] DEET also damages leather and some synthetic clothing fibres, and degrades plastics, such as eyeglass frames. [68] Unlike DEET, picaridin is odourless and non-sticky, and does not damage plastics or fabrics; it has shown no evidence of carcinogenicity or teratogenicity in animal studies. [69] [70] The first RCT reported that skin irritation was rare. [62] The second RCT reported that one person had skin irritation. [63] The case control study reported that one person described a burning sensation while using the soap. [64] The field study gave no information on adverse effects. [65]

Comment: Larger RCTs are needed to compare DEET versus other topical (skin-applied) repellents and placebo in preventing malaria.

Clinical guide:
Five decades of experience of DEET have led to consensus that it is effective in preventing malaria in travellers. Picaridin may be a more effective repellent than DEET, but it has not yet been evaluated against clinical outcomes.

OPTION SKIN-APPLIED PLANT-BASED REPELLENTS IN NON-PREGNANT ADULT TRAVELLERS

N e w

We found no evidence on the effects of skin-applied plant-based repellents to prevent malaria in travellers. We found one RCT assessing the effects of skin-applied plant-based repellants on mosquito landing catches, providing insufficient evidence to assess whether these substances are effective in preventing malaria.

Benefits: We found no systematic review or RCTs in travellers that assessed the effects of skin-applied plant-based repellants on malaria acquisition rates.

Harms: The studies did not report on the tolerability or potential adverse effects of the plant-based repellents used.

Comment: We found one small RCT [71] and two very small non-randomised studies [72] [73] that assessed mosquito landings. The small RCT (unspecified number of adult volunteers in rural India, 683 anopheline mosquitoes collected over 10 nights) found that neem oil mixed at 2% strength in coconut oil applied at around 1800 hours to face, arms and legs gave better protection against anopheline landing over 12 hours than placebo coconut oil (0 mosquitoes in 2% neem oil *v* 144 mosquitoes in placebo control; percentage protection 100%; P value not reported). [71] The first non-randomised study (5 adult volunteers in rural northeast Bolivia, 8855 mosquitoes collected, more than 80% anopheline, over 25 nights) compared lemon eucalyptus in isopropanol applied at 1830 hours to the legs versus control (baby oil in 10% ethanol). [72] It found that lemon eucalyptus significantly reduced mosquito landing over 4 hours compared with control (97% protection, P value reported as significant). The study also found that 2% neem oil in alcohol did not significantly reduce mosquito landing over 4 hours compared with baby oil in ethanol (2% neem oil 57% protection; reported as non-significant). The second non-randomised study (8 adult volunteers in rural India, unspecified number of mainly culicine mosquitoes collected, over 20 nights) found that, when applied at dusk to hands, face, and feet, both 1 ml of *Cymbopogan martinii martinii* var. *Sofia* (palmarosa oil) and *Cymbopogan citratus* (lemon grass oil) each reduced mosquito landing compared with untreated controls from dusk to dawn (palmarosa oil 97.0% protection, lemon grass oil 96.9% protection; P

value not reported). [73] Using skin-applied plant-based repellents to prevent malaria may be more acceptable to certain travellers than using chemical repellents, and may also be safer. However, there is only weak evidence that these substances are effective for this indication.

Clinical guide:
As with chemical repellents, the duration of protection of plant-based repellents depends on a number of factors, including amount of repellent applied, ambient humidity, rate of sweating, etc. Under study conditions, a duration of protection of 11.0 hours has been recorded for both *Cymbopogan martinii martinii* var. *Sofia* (palmarosa oil) and *Cymbopogan citratus* (lemon grass oil). [73]

OPTION BATH OR CHEMICAL BASE OILS IN NON-PREGNANT ADULT TRAVELLERS New

We found no evidence of sufficient quality on the effects of bath or chemical base oils to prevent malaria in travellers.

Benefits: We found no systematic review or RCTs in travellers, and no studies with clinical outcomes. We found one non-randomised controlled trial using mosquito landing catches as an outcome. The non-randomised study (8 adult volunteers in rural India, unspecified number of mainly culicine mosquitoes collected, over 20 nights) found that 1 ml of mylol, applied to hands, face, and feet, reduced mosquito landing compared with untreated controls from dusk to dawn (96% protection; P value not reported). [73]

Harms: The study did not report on the adverse effects of mylol.

Comment:

Clinical guide:
Bath oils, and possibly chemical base oils, seem to protect against insect biting not by a repellant action, but by forming a physical barrier between the human target and the insect. [74] Using bath or chemical base oils to prevent malaria may be more acceptable to certain travellers than using chemical repellents, and may also be safer. However, there is only weak evidence that these substances are effective for this indication.

OPTION DIETARY SUPPLEMENTATION IN NON-PREGNANT ADULT TRAVELLERS New

We found no evidence on the effects of dietary supplementation in preventing malaria in travellers. We found three non-randomised trials that did not show any repellent effect of vitamin B when mosquito landings were used as the outcome.

Benefits: We found no systematic review or RCTs in travellers that assessed effects of dietary supplementation on malaria acquisition rates.

Harms: We found no RCTs.

Comment: We found three non-randomised controlled trials (reported in two papers) that assessed effects on mosquito landing catches. [75] [76] The first non-randomised trial (18 North American adult volunteers, exposed in a sealed room to 100 female *Aedes aegypti* mosquitoes for 10 minutes) found no significant difference in the proportion of mosquitoes biting between 200 mg of thiamine chloride (vitamin B1) daily for 3 days and placebo (proportion of mosquitoes which bit people: 50% with thiamine chloride *v* 38% with controls; P value reported as not significant). [75] The second non-randomised trial (23 North American adult volunteers, glass vial rolled between hands for 2 minutes then vial exposed to 28–32 female *Anopheles stephensi* mosquitoes for 2 minutes, crossover design) found no significant difference in the number of mosquito landings over 4 weeks after crossover between 1 week's treatment with vitamin B complex multivitamin tablet (that included vitamin C) daily and vitamin C 500 mg control (absolute figures not reported, P greater than 0.9). [76] The second non-randomised trial (17 North American adult volunteers, glass vial rolled between hands for 2 minutes then vial exposed to 28–32 female *Anopheles stephensi* mosquitoes for 2 minutes, crossover design) found no significant difference between vitamin B1 100 mg three times daily for one day and vitamin C 250 mg control in the number of mosquito landings over 4 weeks after crossover (absolute figures not reported, P greater than 0.9 for both interventions *v* control). [76] The studies gave no information on adverse effects. [75] [76]

Clinical guide:
There is evidence that dietary supplementation with vitamin B has no repellent effect on healthy mosquitoes. However, vitamin B1, along with garlic and other dietary and herbal agents, is popularly recommended as malaria prophylaxis. [76] Dietary supplementation to prevent malaria may be more acceptable to some travellers than antimalaria drugs, but there is no evidence that it is effective for this indication.

QUESTION What are the effects of antimalaria drug prophylaxis in non-pregnant adult travellers?

OPTION PRIMAQUINE IN NON-PREGNANT ADULT TRAVELLERS

One RCT found that primaquine had a protective efficacy of 94% for P falciparum and 85% for P vivax malaria in non-immune soldiers. It found that, in some people, primaquine was associated with severe epigastric pain, abdominal pain, or vomiting. Primaquine can cause potentially lethal acute intravascular haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and methaemoglobinaemia in people with normal G6PD activity. The small risk of severe haemolysis outweighs the possible benefit from using primaquine to prevent malaria.

Benefits: We found no systematic review but found one RCT. [77] The RCT (176 non-immune Colombian soldiers, aged 18–42 years) compared primaquine (30 mg/day) versus placebo over a 16-week period. It found that the protective efficacy of primaquine was 94% (95% CI 78% to 99%) for *P falciparum* infection and 85% (95% CI 57% to 95%) for *P vivax* infection.

Harms: The RCT found that primaquine was associated with severe epigastric pain, abdominal pain, or vomiting in 3/122 (2.5%) of participants. [77] There were no severe adverse effects with placebo. Although neither RCT reported any such events, it is important to note that primaquine can cause acute intravascular haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and methaemoglobinaemia in people with normal G6PD activity. [77] [78]

Comment:

Primaquine versus chloroquine:
We found one non-randomised controlled trial (99 non-immune Indonesian males, aged 7–59 years, migrating to a malaria-endemic setting), which compared primaquine (0.5 mg/kg every 2 days) versus chloroquine (5 mg/kg weekly) over 16–19 weeks in an area of chloroquine resistance. [78] It found that, compared with chloroquine, primaquine reduced *P falciparum* malaria (RR 0.25, 95% CI 0.08 to 0.83; P = 0.014) and *P vivax* malaria (RR 0.10, 95% CI 0.005 to 0.71; P = 0.012). It also found that primaquine was associated with significantly fewer adverse effects than chloroquine over 16 weeks (total adverse effects: 17 with primaquine *v* 114 with chloroquine; P less than 0.0001). We also found one systematic review (search date 2005) in Spanish, which is being translated and will be considered for inclusion in when we perform the next update of this review. [79]

Clinical guide:
The small risk of severe and possibly fatal haemolysis makes the risk–benefit ratio unacceptable when using primaquine to prevent malaria. Severe haemolytic events have occasionally occurred in trials of primaquine/primaquine analogues, even when the participants had been carefully prescreened for G6PD deficiency.

OPTION CHLOROQUINE IN NON-PREGNANT ADULT TRAVELLERS

We found no systematic review or RCTs on the effects of chloroquine in travellers. One RCT in Austrian workers residing in Nigeria found no significant difference in the incidence of malaria after 6–22 months between chloroquine and sulfadoxine–pyrimethamine. P falciparum resistance to chloroquine is now established in most malaria-endemic regions. However, clinical experience has led to the consensus that chloroquine is effective for preventing malaria in people travelling to areas where no chloroquine resistance has developed.

Benefits: We found no systematic review or RCTs in travellers. One RCT (173 Austrian industrial workers residing in Nigeria) found no significant difference in the incidence of malaria after 6–22 months between chloroquine and sulfadoxine–pyrimethamine. [80]

Harms: The RCT found that chloroquine was associated with insomnia in 3/87 (3%) of people. [80] Two people withdrew from the study because of adverse effects, one with skin rash and the other with visual disturbance. Retrospective questionnaire surveys have suggested that severe adverse effects from chloroquine are rare at prophylactic dosages. [81]

Comment: Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [82] [83] *P falciparum* resistance to chloroquine is now established in most malaria-endemic regions, although there are countries (principally in Central America and the Near East) where there has been no reported resistance.

Chloroquine versus primaquine:
See comment on primaquine, p 11 .

Clinical guide:
Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria in regions where there is no parasite resistance to the drug have led to the consensus that it is effective in travellers to these regions (chiefly Central America and the Near East). [84]

OPTION CHLOROQUINE–PROGUANIL IN NON-PREGNANT ADULT TRAVELLERS

One RCT found no significant difference in the incidence of P falciparum malaria between chloroquine–proguanil and chloroquine plus pyrimethamine–sulfadoxine. One RCT found no significant difference in the incidence of P falciparum malaria between chloroquine–proguanil and proguanil alone. One RCT found no significant difference between chloroquine–proguanil and atovaquone–proguanil in preventing malaria. RCTs comparing adverse effects of chloroquine–proguanil versus atovaquone–proguanil found different results. One RCT found that chloroquine–proguanil increased adverse effects compared with three other common antimalaria drug regimens (doxycycline, mefloquine, and atovaquone–proguanil). Another RCT found no significant difference in adverse effects between chloroquine–proguanil and atovaquone–proguanil.

Benefits:

Chloroquine–proguanil versus chloroquine plus sulfadoxine–pyrimethamine:
We found one open-label RCT (767 Scandinavian travellers to East Africa; 70% of trips were longer than 4 weeks; duration of follow-up not reported) comparing chloroquine–proguanil versus chloroquine plus sulfadoxine–pyrimethamine. [85] It found no significant difference between treatments in rates of *P falciparum* malaria (4/384 [1.0%] with chloroquine–proguanil *v* 3/383 [0.7%] with chloroquine plus sulfadoxine–pyrimethamine; RR 1.3, 95% CI 0.3 to 5.9).

Chloroquine–proguanil versus proguanil alone:
We found one RCT (1625 Dutch travellers to Africa; 60% spent less than 6 weeks in tropical areas). [86] It found no significant difference in incidence of *P falciparum* malaria 4 weeks after returning to the Netherlands between chloroquine 300 mg weekly plus proguanil 200 mg daily and proguanil alone (risk per 100 person months: 2.8, 95% CI 0.9 to 10.1 with chloroquine–proguanil *v* 6.0, 95% CI 2.6 to 14.0 with proguanil alone).

Chloroquine–proguanil versus atovaquone–proguanil:
See benefits of atovaquone–proguanil in adults, p 15 .

Harms:

Chloroquine–proguanil versus chloroquine plus sulfadoxine–pyrimethamine:
In the RCT conducted in Scandinavian travellers, adverse effects associated with chloroquine–proguanil were nausea (3%), diarrhoea (2%), and dizziness (1%). [85]

Chloroquine–proguanil versus proguanil alone:
One cohort study (470 British soldiers in Belize) found that the risk of mouth ulcers almost doubled with chloroquine–proguanil compared with proguanil alone (P = 0.025). [87]

Chloroquine–proguanil versus atovaquone–proguanil:
See harms of atovaquone–proguanil, p 15 .

Chloroquine–proguanil versus doxycycline:
See harms of doxycycline, p 12 .

Chloroquine–proguanil versus mefloquine:
See harms of mefloquine, p 13 .

Comment:

The incidence of confirmed *P falciparum* malaria in both trials was so low that a clinically important effect cannot be excluded. [85] [86] The RCT that compared adverse effects of four different drug regimens was not powered to assess malaria prevention. [88] It found no cases of malaria with any treatment. The RCT tested the difference in tolerability between all four treatments but did not compare any two interventions versus each other directly.

Clinical guide:
Chloroquine–proguanil is a complex two-drug regimen, and consensus from two decades of use, together with more recent evidence from one RCT, suggests that it may have similar benefits to atovaquone–proguanil for preventing malaria in travellers. However, chloroquine–proguanil is poorly tolerated.

OPTION DOXYCYCLINE IN NON-PREGNANT ADULT TRAVELLERS

One RCT in soldiers and one RCT in migrants with limited immunity found that doxycycline reduced the risk of malaria compared with placebo. The RCT in soldiers found a similarly low incidence of malaria with doxycyline and mefloquine. One of the RCTs found that, over 13 weeks, doxycycline was associated with

nausea and vomiting, diarrhoea, cough, headache, and unspecified dermatological symptoms. We found no evidence on long-term safety. One RCT found that doxycycline had fewer adverse effects than mefloquine or chloroquine–proguanil, and had similar adverse-effect rates compared with atovaquone–proguanil.

Benefits: We found no systematic review but found two RCTs. [89] [90]

Doxycycline versus placebo:
The first RCT (136 Indonesian soldiers) compared doxycycline versus mefloquine versus placebo in a malaria-endemic setting (see comment below). [89] It found that, in an area of drug resistance, doxycycline significantly reduced the risk of malaria compared with placebo after a 13–15 week period of prophylaxis (AR: 1/67 [2%] with doxycycline *v* 53/69 [77%] with placebo; RR 0.02, 95% CI 0.003 to 0.14). The second RCT (300 Indonesian migrants with limited immunity) comparing azithromycin versus doxycycline versus placebo found that doxycycline significantly reduced the incidence of malaria compared with placebo over 20 weeks (2/75 [3%] cases of *P falciparum* malaria with doxycycline *v* 29/77 [38%] with placebo; RR 0.07, 95% CI 0.02 to 0.29; NNT 3, 95% CI 2 to 4; 1/75 [2%] cases of *P vivax* malaria with doxycycline *v* 27/77 [35%] with placebo; RR 0.04, 95% CI 0.01 to 0.28). [90]

Doxycycline versus mefloquine:
The first RCT (136 Indonesian soldiers) found that doxycycline and mefloquine were similarly effective at reducing the risk of malaria after a 13–15 week period of prophylaxis (AR: 1/67 [2%] with doxycycline *v* 0/68 [0%] with mefloquine; significance assessment not performed).

Harms: **Doxycycline versus placebo:**
The first RCT found that doxycycline was associated with gastrointestinal symptoms (including nausea and vomiting, abdominal pain, and diarrhoea) in 16/67 (24%) soldiers, unspecified dermatological problems in 22/67 (33%), cough in 21/67 (31%), and headache in 11/67 (16%) over 13 weeks. [89]

Doxycycline versus mefloquine, chloroquine–proguanil, or atovaquone–proguanil:
The first RCT found that, compared with mefloquine, doxycycline reduced headache (11/67 [16%] with doxycycline *v* 25/68 [37%] with mefloquine; P less than 0.01) and dizziness (6/67 [9%] with doxycycline *v* 18/68 [26%]; P less than 0.01) over 13 weeks. [89] One RCT (623 non-immune travellers to sub-Saharan Africa) compared four chemoprophylaxis regimens (doxycycline, mefloquine, chloroquine–proguanil, and atovaquone–proguanil) started 17 days before travel and continued for 4 weeks after return. [88] It found that doxycycline reduced adverse effects compared with mefloquine and chloroquine–proguanil, and had similar adverse-effect rates compared with atovaquone–proguanil (severe adverse effects: 12% with chloroquine–proguanil *v* 11% with mefloquine *v* 7% with atovaquone–proguanil *v* 6% with doxycycline; P = 0.14; mild to moderate adverse effects: 45% with chloroquine–proguanil *v* 42% with mefloquine *v* 33% with doxycycline *v* 32% with atovaquone–proguanil; P = 0.048 for comparison of all 4 treatments). See comment below.

Observational studies:
One questionnaire survey (383 returned Australian travellers taking doxycycline) found that 15% reported nausea or vomiting, 12% reported diarrhoea, and 9% of female travellers reported vaginitis. [91] Evidence from case reports suggests that, in sunny conditions, up to 50% of travellers using doxycycline may experience photoallergic skin rash. [92]

Comment: Most drug trials in travellers have been conducted in soldiers, and the results may not be generalisable to tourists or business travellers. [93] [94] Both RCTs were three-arm, parallel studies. Only the doxycycline versus placebo comparisons are reported here. [89] [90] The RCT that compared adverse effects of four different drug regimens was not powered to assess malaria prevention. [88] It found no cases of malaria with any treatment. The RCT tested the difference in tolerability between all four treatments but did not compare any two interventions versus each other directly.

Clinical guide:
Doxycycline is a low-cost, once-daily drug regimen for which there is evidence of benefit, but which is contraindicated in children and in pregnancy.

OPTION MEFLOQUINE IN NON-PREGNANT ADULT TRAVELLERS

One systematic review of one RCT in soldiers found that mefloquine reduced cases of malaria compared with placebo, and that mefloquine had a protective efficacy of 100%. Three RCTs in non-military travellers found that mefloquine increased neuropsychiatric adverse effects compared with placebo or alternative chemoprophylaxis.

Benefits:

We found one systematic review [94] and one subsequent RCT. [95]

Mefloquine versus placebo:
We found one systematic review (search date 2002), which identified one RCT (203 Indonesian soldiers) comparing three interventions: mefloquine, doxycycline, and placebo, in a malaria-endemic setting (see comment below). [94] It found that, compared with placebo, mefloquine had a protective efficacy of 100% (95% CI 93% to 100%) after up to 15 weeks of treatment (malaria cases: 0/202 person months of exposure with mefloquine *v* 53/109 person months of exposure with placebo).

Mefloquine versus atovaquone–proguanil:
The subsequent RCT (976 people) compared mefloquine plus placebo versus atovaquone–proguanil. [95] It found no clinical cases of malaria among people included in the trial.

Mefloquine versus doxycycline:
See benefits of doxycycline, p 12 .

Harms:

Mefloquine versus placebo:
The review found significantly more withdrawals with mefloquine than with placebo (4 RCTs, 1382 people; RR 3.38, 95% CI 1.62 to 7.03). [94] We found one additional RCT that exclusively examined adverse effects of a single dose of mefloquine versus placebo. [96] It found that mefloquine increased the risk of neuropsychiatric adverse effects (mainly sleep disturbances, strange dreams, and inability to concentrate) compared with placebo (100 adult travellers; 13/59 [22%] with mefloquine *v* 3/31 [10%] with placebo; RR and CI not reported, see comment below).

Mefloquine versus chloroquine or doxycyline:
The systematic review identified 10 RCTs (275 people) of mefloquine for 2–15 weeks of treatment. [94] It found no significant difference between mefloquine and alternative antimalaria prophylaxis (chloroquine or doxycycline) in withdrawal (29/863 [3%] with mefloquine *v* 20/798 [2%] with alternative prophylaxis; RR 1.32, 95% CI 0.75 to 2.31). Commonly reported adverse effects associated with mefloquine were headache (16%), insomnia (15%), and fatigue (8%). The review found more than 500 case reports of adverse effects of mefloquine, including four reports of death.

Mefloquine versus doxycycline:
See harms of doxycycline, p 12 .

Mefloquine versus chloroquine–proguanil:
One RCT (623 non-immune travellers to sub-Saharan Africa) compared four chemoprophylaxis regimens (chloroquine–proguanil, mefloquine, doxycycline, and atovaquone–proguanil) started 17 days before travel and continued for 4 weeks after return. [88] It found that mefloquine had similar adverse-event rates to chloroquine–proguanil, and more adverse effects than doxycycline or atovaquone–proguanil (severe adverse effects: 12% with chloroquine–proguanil *v* 11% with mefloquine *v* 7% with atovaquone–proguanil *v* 6% with doxycycline; P = 0.14; mild to moderate adverse effects: 45% with chloroquine–proguanil *v* 42% with mefloquine *v* 32% with atovaquone–proguanil *v* 33% with doxycycline; P = 0.048 for comparison of all 4 treatments). Mefloquine was associated with the highest rate of moderate to severe neuropsychological adverse effects (37% with mefloquine *v* 30% with chloroquine–proguanil *v* 24% with doxycycline *v* 20% with atovaquone–proguanil; P = 0.003). See comment below.

Mefloquine versus atovaquone–proguanil:
The subsequent RCT (976 non-immune tourists and business travellers) found no significant difference in the risk of adverse effects between mefloquine plus placebo and atovaquone–proguanil (324/483 [67%] with mefloquine plus placebo *v* 313/493 [63%] with atovaquone–proguanil; ARR +2.6%, 95% CI –3.4% to +8.5%). [95] However, when adverse effects specifically attributable to the study drug were analysed, there were significantly more adverse effects caused by mefloquine plus placebo than by atovaquone–proguanil (204/483 [42%] with mefloquine plus placebo *v* 149/493 [30%] with atovaquone–proguanil; RR 1.40, 95% CI 1.18 to 1.66; NNH 9, 95% CI 6 to 17; see comment below). Specifically, mefloquine plus placebo increased the incidence of "strange or vivid dreams" compared with atovaquone–proguanil (66/483 [14%] with mefloquine plus placebo *v* 33/493 [7%] with atovaquone–proguanil), insomnia (65/483 [13%] *v* 15/493 [3%]), dizziness or vertigo (43/483 [9%] *v* 11/493 [2%]), anxiety (18/483 [4%] *v* 3/493 [1%]), depression (17/483 [4%] *v* 3/493 [1%]), visual difficulties (16/483 [3%] *v* 8/493 [2%]), and headache (32/483 [7%] *v* 19/493 [4%]). Another RCT (623 non-immune travellers to sub-Saharan Africa) compared four chemoprophylaxis regimens: mefloquine; chloroquine–proguanil; doxycycline; and atovaquone–proguanil. [88] It found that mefloquine had more adverse effects than atovaquone–proguanil (see mefloquine versus chloroquine–proguanil, above, for full details of this trial). [88]

Observational studies:
Retrospective questionnaire surveys in tourists and business travellers also found that sleep disturbance and psychosis were common with mefloquine. [97] One review of 74 dermatological case reports found that up to 30% of mefloquine users developed a maculopapular rash, and 4–10% had pruritus. [98] Ten cohort studies in tourists found that more women than men experienced adverse effects (including dizziness, sleep disturbance, headache, diarrhoea, and nausea) with mefloquine. [91] [97] [99] [100] [101] [102] [103] [104] [105] [106] One case control study (564 Dutch travellers between 1997–2000) found that the risk of psychiatric events was significantly higher among people taking mefloquine than in people not taking drug prophylaxis (mefloquine use: 21% in people with psychiatric events *v* 9% in controls; adjusted OR 3.5, 95% CI 1.4 to 8.7). [107] This increase was greater among women (mefloquine use: 22% in women with psychiatric events *v* 7% in controls; adjusted OR 47.1, 95% CI 3.8 to 578.6). One retrospective questionnaire survey of 93,668 European travellers to East Africa found that elderly travellers experienced fewer adverse reactions (not reported) with mefloquine than younger travellers (P less than 0.05). [108] A review of 516 published case reports suggested that many of mefloquine's adverse effects could be explained as a posthepatic syndrome owing to mefloquine use combined with concurrent insults to the liver (such as from alcohol, dehydration, oral contraceptive pills, recreational drugs, and other liver-damaging drugs), and that in some users mefloquine may also cause a symptomatic thyroid disturbance. [109]

Comment:

The RCT in Indonesian soldiers was a three-arm parallel RCT. It compared mefloquine (68 people) versus doxycycline (67 people) versus placebo (69 people). Only the comparison of mefloquine versus placebo is included here. [94] Early RCTs of mefloquine prophylaxis were carried out in soldiers and suggested good tolerability, but military drug trials cannot be generalised owing to higher rates of co-medications and co-morbidities in non-military groups. [94] RCTs in mefloquine prophylaxis in non-military travellers found an excess of neuropsychiatric adverse effects in the mefloquine arm. [88] [95] [96] The second RCT had two mefloquine arms, with different formulations of the drug. [96] The RCT comparing mefloquine versus atovaquone–proguanil suggested a higher rate of adverse effects with mefloquine than in previous studies, but this RCT only reported adverse effects occurring after starting active treatment, which was 3 weeks earlier in the mefloquine group than in the atovaquone–proguanil group. [95]

Clinical guide:
Mefloquine is useful to treat malaria, but there is strong evidence of harm with its use at current dosages to prevent malaria, especially in women.

OPTION ATOVAQUONE–PROGUANIL IN NON-PREGNANT ADULT TRAVELLERS

One RCT in migrants with limited immunity and one RCT in non-immune soldiers found that atovaquone–proguanil reduced the proportion of people with malaria compared with placebo. Another RCT found no significant difference between atovaquone–proguanil and chloroquine–proguanil in preventing malaria. A third RCT comparing atovaquone–proguanil versus mefloquine found no cases of clinical malaria throughout the trial, but found a higher rate of neuropsychiatric harm with mefloquine than with atovaquone–proguanil. One RCT found that atovaquone–proguanil reduced adverse effects compared with mefloquine and chloroquine–proguanil, and had similar adverse-effect rates compared with doxycycline. Another RCT found no significant difference in adverse effects between atovaquone–proguanil and chloroquine–proguanil.

Benefits:

We found no systematic review, but found four RCTs. [95] [110] [111] [112]

Atovaquone–proguanil versus placebo:
We found two RCTs. [112] [110] The first RCT (299 Indonesian migrants with limited immunity) found that atovaquone–proguanil significantly decreased the proportion of people with malaria at 24 weeks compared with placebo (AR 3/150 [2%] with atovaquone–proguanil *v* 37/149 [25%] with placebo; P less than 0.001). [110] The second RCT (180 non-immune Colombian soldiers) found lower rates of malaria with atovaquone–proguanil, used for the duration and for one week, after a 10–16 week residence in an endemic area, than with placebo (9/120 [8%] with atovaquone–proguanil *v* 19/60 [32%] with placebo; P value not reported). [112]

Atovaquone–proguanil versus chloroquine–proguanil:
One multicentre RCT (1083 travellers) comparing atovaquone–proguanil versus chloroquine–proguanil found no significant difference in the incidence of malaria after 9 weeks (1/511 [0.2%] case of *P ovale* malaria with atovaquone–proguanil *v* 3/511 [0.6%] cases of *P falciparum* malaria with chloroquine–proguanil; ARR 0.4%; RR 0.33, 95% CI 0.03 to 3.16). [111]

Atovaquone–proguanil versus mefloquine:
See benefits of mefloquine in adults, p 13 .

Harms:

Atovaquone–proguanil versus placebo:
The RCT found that stomatitis (P less than 0.001) and back pain (P = 0.009) occurred significantly more frequently in the atovaquone–proguanil group, whereas abdominal pain (P = 0.02) and malaise (P = 0.01) occurred significantly more frequently with placebo (absolute numbers not reported). [110] Four people had severe adverse effects that were possibly drug-related (3 people with abdominal pain and 1 with skin rash). [110] In the second RCT, headache was more commonly reported with atovaquone–proguanil (7% with atovaquone–proguanil *v* 3% with placebo; absolute numbers and P values not reported), as was fever (5% with atovaquone–proguanil *v* 0% with placebo; absolute numbers and P values not reported) . [112] I

Atovaquone–proguanil versus chloroquine–proguanil:
The multicentre RCT in travellers found no significant difference between atovaquone–proguanil and chloroquine–proguanil in the proportion of people who one or more adverse effect (311/511 [61%] with atovaquone–proguanil *v* 329/511 [64%] with chloroquine–proguanil; RR 0.95, 95% CI 0.85 to 1.04). [111] Common adverse effects were mainly gastrointestinal (diarrhoea: 5% with atovaquone–proguanil *v* 7% with chloroquine–proguanil; mouth ulcers: 4% *v* 5%; abdominal pain: 3% *v* 6%; and nausea: 2% *v* 7%), neuropsychiatric (strange/vivid dreams: 4% with atovaquone–proguanil *v* 3% with chloroquine–proguanil; dizziness: 3% *v* 4%; insomnia: 2% *v* 2%), and visual difficulties (2% with atovaquone–proguanil *v* 2% with chloroquine–proguanil). [111] Another RCT (623 non-immune travellers to sub-Saharan Africa) compared four chemoprophylaxis regimens (atovaquone–proguanil, chloroquine–proguanil, mefloquine, and doxycycline) started 17 days before travel and continued for 4 weeks after return. [88] It found that atovaquone–proguanil reduced severe (requiring medical advice) adverse effects compared with chloroquine–proguanil, but did not report the significance of the difference between groups (11/164 [7%] with atovaquone–proguanil *v* 19/153 [12%] with chloroquine–proguanil; significance of between-group difference not reported). It also found lower rates of mild to moderate adverse effects with atovaquone–proguanil than with chloroquine–proguanil (32% with atovaquone–proguanil *v* 45% with chloroquine–proguanil; significance of between-group difference not reported).

Atovaquone–proguanil versus doxycycline:
See harms of doxycycline, p 12 .

Atovaquone–proguanil versus mefloquine:
See harms of mefloquine in adults, p 13 .

Comment:

Clinical guide:
Atovaquone–proguanil is a high-cost, once-daily drug regimen for which there is evidence of benefit.

OPTION AMODIAQUINE IN NON-PREGNANT ADULT TRAVELLERS

We found no RCTs on the effects of amodiaquine in preventing malaria in travellers. We found limited observational evidence that amodiaquine may cause neutropenia, liver damage, and hepatitis. Amodiaquine use is now restricted to treatment rather than prevention of malaria in resource-rich countries because of concern about adverse effects.

Benefits:

We found no systematic review and no RCTs in travellers.

Harms:

One retrospective cohort study in 10,000 British travellers taking prophylactic amodiaquine for 6–13 weeks reported severe neutropenia in about 1/2000 users. [113] We found 28 case reports describing liver damage or hepatitis in travellers who had taken amodiaquine for about 2 months to treat or prevent malaria. [114] [115] [116] [117] [118] [119]

Comment:

Clinical guide:
Amodiaquine is useful to treat malaria, but there is evidence of harm with its use at current dosages to prevent malaria. Amodiaquine use is now restricted to treatment rather than prevention of malaria in resource-rich countries because of concern about adverse effects.

OPTION PYRIMETHAMINE–DAPSONE IN NON-PREGNANT ADULT TRAVELLERS

We found no RCTs in travellers. One RCT in Thai soldiers found insufficient evidence to compare pyrimethamine–dapsone versus proguanil-dapsone. We found limited observational evidence that pyrimethamine–dapsone may cause agranulocytosis.

Benefits:

We found no systematic review or RCTs in travellers. One RCT in Thai soldiers comparing pyrimethamine–dapsone versus proguanil-dapsone found no significant difference in *P falciparum*

infection rates over 40 days (10% with proguanil-dapsone *v* 11% with pyrimethamine–dapsone; results presented graphically, P value not reported). It found a significantly lower *P vivax* infection rate with proguanil-dapsone than with pyrimethamine–dapsone (2% with proguanil-dapsone *v* 12% with pyrimethamine–dapsone; results presented graphically, P less than 0.001). [120]

Harms: The RCT in Thai soldiers found that less than 2% reported any drug-related symptoms from pyrimethamine–dapsone. [120] One retrospective cohort study in 15,000 Swedish travellers taking pyrimethamine–dapsone reported agranulocytosis in about 1/2000 users. [121]

Comment: **Clinical guide:**
Pyrimethamine–dapsone is not currently licensed to prevent malaria.

OPTION PYRIMETHAMINE–SULFADOXINE IN NON-PREGNANT ADULT TRAVELLERS

We found no RCTs of pyrimethamine–sulfadoxine alone. One RCT found no significant difference between chloroquine–proguanil and chloroquine plus pyrimethamine–sulfadoxine in the incidence of P falciparum malaria. One retrospective observational study suggested that pyrimethamine–sulfadoxine was associated with severe cutaneous reactions. Pyrimethamine–sulfadoxine is not currently licensed in the UK for the prevention of malaria.

Benefits: We found no systematic review or RCTs of pyrimethamine–sulfadoxine alone.

Sulfadoxine–pyrimethamine plus chloroquine versus chloroquine–proguanil:
See benefits of chloroquine–proguanil in adults, p 12 .

Harms: One retrospective observational study in 182,300 US travellers taking weekly prophylactic pyrimethamine–sulfadoxine reported severe cutaneous reactions (erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis) in 24 people (1/5000–1/8000) after a mean of 3.4 weeks of use. The associated mortality was about 1/11,000–1/25,000 users. [121]

Comment: **Clinical guide:**
Pyrimethamine–sulfadoxine is not currently licensed in the UK for the prevention of malaria.

QUESTION What are the effects of antimalaria vaccines in adult and child travellers?

OPTION VACCINES IN ADULT AND CHILD TRAVELLERS

We found no systematic review or RCTs on antimalarial vaccines in travellers. One systematic review in residents found no significant difference in episodes of clinical malaria between blood-stage vaccines and placebo. Another review in residents found that one pre-erythrocytic vaccine (RTS,S) reduced clinical episodes of malaria compared with placebo, but found no significant difference between three other pre-erythrocytic stage vaccines (CS-NANP, CS102 peptide, ME-TRAP) and placebo. A third review of antimalaria vaccines in residents of malaria-endemic areas found that the SPf66 vaccine reduced first attacks of P falciparum malaria compared with placebo.

Benefits: We found no systematic review or RCTs of antimalaria vaccines in travellers. We found three systematic reviews assessing antimalaria vaccines in residents. [122] [123] [124] The first review (search date 2006) identified two RCTs (137 people) assessed the effects of blood-stage vaccines on clinical malaria in residents of malaria-endemic regions. [122] The largest RCT (120 children aged 5–9 years) identified by the review assessed participants exposed to natural challenge. It found no significant difference in episodes of clinical malaria between MSP/RESA (a blood-stage vaccine) and placebo (RR 1.64, 95% CI 0.94 to 2.85 in non-pre-treated participants; RR 1.25, 95% CI 0.71 to 2.20 in those pre-treated with sulfadoxine–pyrimethamine). The second review (search date 2006, 11 RCTs, more than 3000 people) found that one pre-erythrocytic vaccine (RTS,S) significantly reduced clinical episodes of malaria compared with placebo (2 RCTs, 1911 participants, RR 0.76 95% CI 0.66 to 0.88). [123] However, the review found no significant difference in clinical episodes of malaria between three other pre-erythrocytic stage vaccines (CS-NANP, CS102 peptide, ME-TRAP) and placebo (RRs non-significant for all vaccines *v* placebo). The third review (search date 2005, 10 RCTs, 9698 people) found that SPf66 vaccine significantly reduced new episodes of clinical *P falciparum* malaria compared with placebo (9 RCTs, 7399 people, RR 0.90, 95% CI 0.84 to 0.96). However, when examined geographically, subgroup analyses found no significant difference in new episodes of clinical malaria in Africa between SPf66 and placebo (4 RCTs, 2371 people, RR 0.98, 95% CI 0.90 to 1.07) or in Asia (1 RCT, 1221 people, RR 1.06, 95% CI 0.90 to 1.25). The review found that SPf66 significantly reduced new episodes of clinical malaria in South America (4 RCTs, 3087 people, RR 0.72, 95% CI 0.63 to 0.82). [124]

Harms: Vaccine-related adverse effects with the blood-stage and pre-erythrocytic vaccines were mainly increased rates of local reactions (mainly injection-site pain, swelling, arm motion limitation, headache, and malaise). [122] [123] RCTs assessing SPf66 vaccine identifed by the third review also reported increases in local reactions, and also found systemic reactions (whole-body reactions including fever, headache, gastric symptoms, and dizziness) in as many as 67% of participants receiving the vaccine. [124]

Comment: **Clinical guide:**
There is currently no licensed vaccine to prevent malaria.

QUESTION What are the effects of antimalaria interventions in child travellers?

OPTION TOPICAL (SKIN-APPLIED) INSECT REPELLENTS CONTAINING DEET (DIETHYL-3-METHYL-BENZAMIDE) IN CHILD TRAVELLERS

We found no RCTs on the effects of DEET in preventing malaria in child travellers. However, many years of clinical experience have led to the consensus that using the topical insect repellent DEET is likely to beneficial in preventing malaria. Case reports in young children found serious adverse effects with DEET.

Benefits: We found no systematic review or RCTs.

Harms: We found 13 case reports of encephalopathic toxicity in children aged under 8 years after excessive use (not clearly defined) of topical (skin-applied) insect repellents containing DEET (diethyl-3-methyl-benzamide). [125] [126]

Comment: **Clinical guide:**
Infants and young children have thinner skin and greater surface area to mass ratio. [127] Decades of experience of using DEET to prevent malaria in children have led to consensus that it is effective, but needs to be used with caution. Some authors advise that ethylhexanediol should be issued as a topical (skin-applied) insect repellent in preference to DEET in children aged 1–8 years. [128]

OPTION ANTIMALARIA DRUGS IN CHILD TRAVELLERS

Decades of experience of using chloroquine to prevent malaria, in areas where there is no parasite resistance to the drug, have led to the consensus that it is effective in this setting. We found insufficient evidence about the effects of other antimalaria drugs in preventing malaria in child travellers.

Benefits: We found one RCT (multicentre study; 221 non-immune travellers aged 2–17 years), which compared atovaquone–proguanil versus chloroquine–proguanil. [129] It found no cases of malaria in either arm (see comment below). We found no RCTs on the effects of other antimalaria drugs on preventing malaria in child travellers.

Harms: The RCT found no significant difference between atovaquone–proguanil and chloroquine–proguanil in one or more adverse events after about 20–50 days of use (most commonly diarrhoea, abdominal pain, vomiting, nausea, or oral ulceration; 39/110 [35%] with atovaquone–proguanil *v* 41/111 [37%] with chloroquine–proguanil, RR and CI not reported). [129]

Comment: The RCT was not powered to detect clinically important differences in drug efficacy. [129] Doxycycline is contraindicated in children under 12, as it may cause staining in growing teeth. [130]

Clinical guide:
Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria, in areas where there is no parasite resistance to the drug, have led to the consensus that it is effective in travellers to these areas, and is safe in children. [84]

QUESTION What are the effects of antimalaria interventions in pregnant travellers?

OPTION INSECTICIDE-TREATED BED NETS IN PREGNANT TRAVELLERS

We found no RCTs on the effects of insecticide-treated bed nets in preventing malaria in pregnant travellers. One RCT of pregnant residents of a malaria-endemic area found insufficient evidence on the effects of permethrin-treated bed nets in preventing malaria. Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated bed nets in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers.

Benefits: We found no systematic review or RCTs in pregnant travellers. We found one systematic review (search date 2006), which identified five RCTs, four conducted in Africa comparing insecticide-treated bed nets versus no nets, and one conducted in Thailand comparing insecticide-treated bed nets versus untreated nets. [131] The review did not perform a meta-analysis for the outcome of incidence of malaria, which was assessed in three RCTs. The first RCT (503 pregnant women living in Kenya) found no significant difference in the incidence of clinical malaria during pregnancy between insecticide-treated bed nets and no nets (OR 0.85, 95% CI 0.47 to 1.54; absolute numbers not reported). The second RCT (2991 pregnant women living in Kenya) also found no significant difference in the incidence of clinical malaria during pregnancy between insecticide-treated bed nets and no nets (HR 0.72, 95% CI 0.19 to 2.75; absolute numbers not reported). The third RCT (341 pregnant women living in Thailand, followed for a mean of 16.6 weeks, at 3 sites in a malaria-endemic area) found that, at one study site (but not at the other two), permethrin-impregnated bed nets significantly reduced the incidence of malaria in pregnancy compared with untreated nets (RR 0.39, 95% CI 0.37 to 0.82; absolute numbers not reported). The review also found no significant difference in parasite densities between insecticide treated-bed nets and no nets (2 RCTs in Africa, OR 0.93, 95% CI 0.77 to 1.11; absolute numbers not reported). The review did not present results for the outcome of parasite density from the RCT conducted in Thailand comparing insecticide-treated nets versus untreated nets.

Harms: The review gave no information on adverse effects. [131]

Comment: One non-randomised controlled trial (36 pregnant and 36 non-pregnant Gambian women sleeping alone under a bed net in 6 identical huts, for 3 consecutive nights) found that pregnant women were twice as likely as non-pregnant women to be bitten by anopheline mosquitoes (mean bites/night: 6.3 for pregnant women *v* 3.1 for non-pregnant women; P = 0.0002). [132]

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated bed nets in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers (see bed nets in non-pregnant adults, p 7). Pregnant travellers are specified as a different group because malaria is more common and more severe in pregnant women, and because antimalaria drugs may have toxic effects on the fetus. [133] Contracting malaria significantly increases the likelihood of miscarriage.

OPTION INSECTICIDE-TREATED CLOTHING IN PREGNANT TRAVELLERS

We found no RCTs in pregnant travellers of the effects of insecticide-treated clothing. However, it is likely that the evidence of benefit from insecticide-treated clothing in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers.

Benefits: We found no systematic review or RCTs.

Harms: We found no evidence relating to pregnant travellers.

DEET (diethyl-3-methyl- benzamide):
See harms of topical (skin-applied) insect repellents in pregnant travellers, p 19 .

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 18 .

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated bed nets in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers (see insecticide-treated clothing in non-pregnant adults, p 7).

OPTION SKIN-APPLIED INSECT REPELLENTS IN PREGNANT TRAVELLERS

We found no RCTs in pregnant travellers. It is unclear which skin-applied chemical repellents are safe in pregnancy. However, it is likely that the evidence of benefit from skin-applied insect repellants in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers.

Benefits: We found no systematic review or RCTs.

Harms: We found little evidence in pregnant travellers.

DEET:
We found one case report indicating an adverse fetal outcome (mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphology) in a child whose mother had applied DEET daily throughout her pregnancy. [134] One RCT in pregnant women (897 refugees in a Thai forest area of low malaria endemicity) comparing DEET (median dose 214.2 g/pregnancy) versus a cosmetic cream found no differences in weekly reporting of headache, dizziness, or nausea and vomiting over 2–6 months. [135] It also found no adverse effects on infant survival, growth, or development at either birth or 1 year (survival: 95.2% with DEET *v* 94.0% with cosmetic cream; P = 0.57; mean weight at 1 year 7983 g with DEET *v* 7984 g with cosmetic cream). Some animal studies have found that DEET crosses the placental barrier. [136] Animal studies of reproductive effects of DEET are inconclusive. [137] [138]

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 18 . The RCT in refugees reported that DEET significantly increased the proportion of women reporting skin warmth (359/449 [80%] with DEET *v* 258/448 [58%] with cosmetic cream; RR 1.39, 95% CI 1.27 to 1.52), although the clinical significance of this is unclear. [135]

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated bed nets in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers (see skin-applied insect repellants in non-pregnant adults, p 8). However, there is inconclusive evidence regarding the safety of DEET in pregnant travellers. Some authors advise that only plant-derived skin-applied insect repellents are safe in pregnancy because of a potential risk of mutagenicity from DEET. [128] However, we found no evidence on the effects of other repellents.

OPTION ANTIMALARIA DRUGS IN PREGNANT TRAVELLERS

One systematic review identified no RCTs on the effects of antimalaria drugs in pregnant travellers. It found that, in pregnant residents of malaria-endemic settings, antimalaria drugs reduced malaria and episodes of fever compared with no prophylaxis. It found no significant difference in perinatal deaths or preterm births. We found insufficient evidence on the safety of chloroquine, doxycycline, and mefloquine in pregnancy. Decades of experience of using chloroquine to prevent malaria, in areas where there is no parasite resistance to the drug, have led to the consensus that it is effective in this setting.

Benefits: We found no systematic review or RCTs in pregnant travellers. We found one systematic review (search date 2006) of antimalaria drugs in pregnant women living in malaria-endemic settings. [139] It found that antimalaria prophylaxis significantly reduced the proportion of women infected at least once compared with no prophylaxis (1 RCT, 337 women; AR 5/167 [3%] with prophylaxis *v* 37/170 [22%] with no prophylaxis; RR 0.14, 95% CI 0.06 to 0.34), and significantly reduced the number of episodes of fever (1 RCT, 227 women; 21/119 [18%] with prophylaxis *v* 45/108 [42%] with no prophylaxis; RR 0.42, 95% CI 0.27 to 0.66). It found no significant difference between antimalaria prophylaxis and no prophylaxis in the number of perinatal deaths (4 RCTs, 2890 women; 66/1464 [4%] with prophylaxis *v* 64/1426 [4%] with no prophylaxis; RR 1.02, 95% CI 0.73 to 1.43), in the number of preterm births (1 RCT, 199 women; 4/102 [4%] with prophylaxis *v* 8/97 [8%] with no prophylaxis; RR 0.48, 95% CI 0.15 to 1.53), or in mean birth weight (4 RCTs, 2671 women; WMD +24 g, 95% CI –55 g to +105 g; random effects analysis).

Harms: The review gave no information about adverse effects. [139]

Chloroquine:
One RCT (1464 pregnant long-term residents of Burkina Faso) gave no information on adverse effects. [140]

Doxycycline:
Case reports found that doxycycline taken in pregnancy or while breast feeding may damage fetal or infant bones or teeth. [81]

Mefloquine:
One RCT (339 long-term Thai residents) found that mefloquine significantly increased the proportion of women reporting dizziness compared with placebo (28% with mefloquine *v* 14% with placebo; P less than 0.005). However, it found no other significant adverse effects on the mother, the pregnancy, or on infant survival or development over 2 years' follow-up. [141]

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 18 . Mefloquine is secreted in small quantities in breast milk, but it is believed that levels are too low to harm infants. [81] Because

of the potential for damage to fetal or infant bones or teeth, doxycycline is contraindicated in pregnant or breastfeeding women. [130]

Clinical guide:
Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria, in areas where there is no parasite resistance to the drug, have led to the consensus that it is effective in travellers to these areas, and safe in pregnant women. [84]

QUESTION What are the effects of antimalaria interventions in airline pilots?

OPTION ANTIMALARIA DRUGS IN AIRLINE PILOTS

There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots. We found one small RCT reporting on the adverse effects of atovaquone–proguanil in non-travelling volunteers, under aircraft cabin-pressure conditions. It found no significant difference in adverse effects between atovaquone–proguanil and placebo. Another RCT of adverse effects found no evidence that mefloquine affected flying performance after 3 weeks of treatment.

Benefits:

We found no systematic review or RCTs (see comment below). One retrospective questionnaire survey (28 Israeli pilots taking doxycycline and 15 non-aviator crew taking mefloquine) found no cases of malaria at 4 weeks. [142]

Harms:

Atovaquone–proguanil:
One small crossover RCT reporting on adverse effects (24 male and female non-travelling Dutch volunteers, assessed in a hypobaric chamber) found that atovaquone–proguanil did not significantly affect vigilance, sustained attention, complex information processing, sleepiness, sleep quality, or sleep time compared with placebo. [143] No serious adverse effects were reported. There were 12 mild adverse events (including diarrhoea) with atovaquone–proguanil, and 17 adverse events with placebo (significance assessment not performed). There was one case of nosebleeding during the trial period, and one of night sweating.

Doxycycline:
One retrospective questionnaire survey (28 Israeli pilots) found that 39% experienced adverse effects from up to 2 months of doxycycline treatment (abdominal pain: 7/28 [25%]; fatigue: 5/28 [18%]; see comment below). [142]

Mefloquine:
One placebo-controlled RCT of adverse effects (23 trainee commercial pilots) found no evidence that mefloquine significantly affected flying performance after 3 weeks of treatment (mean total number of errors recorded by the instrument coordination analyser: 12.6 with mefloquine *v* 11.7 with placebo). [144] One retrospective questionnaire survey (15 Israeli non-aviator aircrew) found that 13% of respondants experienced adverse effects from mefloquine after up to 2 months of treatment (dizziness, nausea, and abdominal pain: 2/15 [13%]; abdominal discomfort: 1/15 [7%]; see comment below). [142]

Comment:

Clinical guide:
There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots (see question on drug prophylaxis in adults). There is evidence that atovaquone–proguanil does not harm airline pilots compared with placebo. Airline pilots are specified as a different population because, as an occupational group, they are subject to health and safety legislation that is highly prescriptive about certain drugs.

GLOSSARY

Aedes Genus of day-biting mosquitoes which transmit various infections (dengue fever, yellow fever), but not malaria.
Anopheles Genus of evening- and night-biting mosquitoes which transmit malaria.
Carbamate Class of synthetic insecticides (for example, carbosulfan) used to treat bed nets.
Electronic buzzers Commercial devices which emit high-frequency sound waves, commonly marketed as insect repellents.
Plasmodium falciparum infection The most severe and life-threatening form of human malaria.
Plasmodium vivax infection A less severe form of human malaria, sometimes with a long incubation period of 6 to 18 months.
Biological control measures Antimosquito interventions based on modifying the local flora or fauna.
Protective efficacy $((R_1 - R_2)/R_1) \times 100$ where R_1 is the incidence of the event in the control population and R_2 is the incidence of the event in the immunised population. [145] This is the same as the relative risk reduction.

SUBSTANTIVE CHANGES

Skin-applied plant-based repellents in non-pregnant adult travellers New option added; no RCT evidence assessing malaria acquisition identified; categorised as Unknown effectiveness.

Bath or chemical base oils in non-pregnant adult travellers New option added; no RCT evidence identified; categorised as Unknown effectiveness.

Dietary supplementation in non-pregnant adult travellers New option added. No RCT evidence identified. Categorised as Unknown effectiveness.

Atovaquone–proguanil in non-pregnant adult travellers One RCT added. [112] Categorisation unchanged (Likely to be beneficial).

Coils and vaporising mats in non-pregnant adult travellers Two case control studies added. [48] [49] Categorisation unchanged (Unknown effectiveness)

Insecticide-treated clothing in non-pregnant adult travellers One RCT added, which found that permethrin-treated clothing reduced malaria incidence in non-pregnant refugees. [56] Categorisation of insecticide-treated clothing in travellers unchanged (Likely to be beneficial).

Lifestyle changes (including full-length clothing, light clothing, behaviour modification) in non-pregnant adult travellers One case control study added; [59] categorisation unchanged (Unknown effectiveness).

Skin applied chemical repellents in non-pregnant adult travellers Two RCTs, [62] [63] one case control study, [64] and one field study [65] added. Categorisation unchanged (Likely to be beneficial).

Vaccines against malaria Three systematic reviews assessing antimalaria vaccines in residents added. [122] [123] [124] Categorisation unchanged for vaccines in travellers (Unknown effectiveness)

Insecticide-treated bed nets in pregnant travellers One systematic review added; [131] recategorised as Likely to be beneficial.

Antimalaria drugs (atovaquone–proguanil, doxycycline) in airline pilots Evidence re-evaluated. Recategorised as Likely to be beneficial.

Insecticide-treated clothing in pregnant travellers Evidence re-evaluated. Recategorised as Likely to be beneficial.

Skin-applied insect repellents in pregnant travellers Evidence re-evaluated. Recategorised as Trade-off between benefits and harms.

REFERENCES

1. Weller PF. Protozoan infections. In: Dale DC, ed. *Infectious diseases*. New York: WebMD, 2003:651–675.
2. Pasvol V. Malaria. In: Cohen J, Powderly WG, eds. *Infectious diseases*. 2nd ed. London: Mosby, 2004:1579–1591.
3. Jong EC, McMullen R. *The travel and tropical medicine manual*. Philadelphia: Saunders, 2003.
4. World Health Organization. *International travel and health*. Geneva: WHO, 2003:30–148.
5. Funk-Baumann M. Geographic distribution of malaria at traveler destinations. In: Schlagenhauf P, ed. *Traveler's malaria*. Hamilton, Ontario: BC Decker, 2001:56–93.
6. White NJ. Malaria. In: Cook GC, Zumla AI, eds. *Manson's tropical diseases*. 21st ed. London: Saunders, 2003:1205–1295.
7. Martens P, Hall L. Malaria on the move: human population movement and malaria transmission. *Emerg Infect Dis* 2000;6:103–109.[PubMed]
8. Wellems TE, Miller LH. Two worlds of malaria. *N Engl J Med* 2003;349:1496–1498.[PubMed]
9. Krogstad DJ. *Plasmodium* species (malaria). In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 5th ed. New York: Churchill Livingstone, 2000:2817–2831.
10. Renshaw M, Silver JB. Malaria, human. In: Service MW, ed. *Encyclopedia of arthropod-transmitted infections of man and domesticated animals*. New York: CABI Publishing, 2001:314–327.
11. White GB. Medical acarology and entomology. In: Cook GC, Zumla AI, eds. *Manson's tropical diseases*. 21st ed. London: Saunders, 2003:1717–1805.
12. Service MW, Townson H. The Anopheles vector. In: Warrell DA, Gilles HM, eds. *Essential malariology*. 4th ed. London: Arnold, 2002:59–84.
13. Goodyer LI. *Travel medicine for health professionals*. London: Pharmaceutical Press, 2004.
14. Golenda CF, Solberg VB, Burge R, et al. Gender-related efficacy difference to an extended duration formulation of topical *N*,*N*-diethyl-*m*-toluamide (DEET). *Am J Trop Med Hyg* 1999;60:654–657.
15. Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV. Insect avoidance and malaria prevention. *J Travel Med* 2003;10:225–240.[PubMed]
16. Burkot TR, Graves PM. Malaria, babesiosis, theileriosis and related diseases. In: Eldridge BF, Edman JD, eds. *Medical entomology*. Dordrecht: Kluwer Academic Publishers, 2004:187–230.
17. Snow RS, Gilles HM. The epidemiology of malaria. In: Warrell DA, Gilles HM, eds. *Essential malariology*. 4th ed. London: Arnold, 2002:85–106.
18. Peters W, Pasvol G. *Tropical medicine and parasitology*. 5th ed. London: 2002.
19. Gillies MT. Anopheline mosquitos: vector behaviour and bionomics. In: Wernsdorfer WH, McGregor I, eds. *Malaria: principles and practice of malariology*. Edinburgh: Churchill Livingstone, 1988:453–485.
20. Taylor TE, Strickland GT. Malaria. In: Strickland GT, ed. *Hunter's tropical medicine and emerging infectious diseases*. 8th ed. Philadelphia: WB Saunders, 2000:614–663.
21. Bradley DJ, Warrell DA. Malaria. In: Warrell DA, Cox TM, Firth JD, et al, eds. *Oxford textbook of medicine*. 4th ed. Oxford: Oxford University Press, 2003:721–748.
22. Kassianos GC. *Immunization: childhood and travel health*. 4th ed. Oxford: Blackwell Science, 2001.
23. Charlwood JD, Alecrim WA. Capture-recapture studies with the South American malaria vector Anopheles darlingi, Root. *Ann Trop Med Parasitol* 1989;83:569–576.[PubMed]
24. Ghebreyesus TA, Haile M, Witten KH, et al. Incidence of malaria among children living near dams in northern Ethiopia: community based incidence survey. *BMJ* 1999;319:663–666.[PubMed]
25. Romi R, Sabatinelli G, Majori G. Malaria epidemiological situation in Italy and evaluation of malaria incidence in Italian travelers. *J Travel Med* 2001;8:6–11.[PubMed]
26. Askling HH, Nilsson J, Tegnell A, et al. Malaria risk in travellers. *Emerg Infect Dis* 2005;1:436–441.
27. Jelinek T, Loscher T, Nothdurft HD. High prevalence of antibodies against circumsporozoite antigen of *Plasmodium falciparum* without development of symptomatic malaria in travellers returning from sub-Saharan Africa. *J Infect Dis* 1996;174:1376–1379.[PubMed]
28. Moore DAJ, Grant AD, Armstrong M, et al. Risk factors for malaria in UK travellers. *Trans R Soc Trop Med Hygiene* 2004;98:55–63.
29. Winstanley P. Malaria: treatment. *J R Coll Physicians Lond* 1998;32:203–207.[PubMed]
30. Sturchler D. Global epidemiology of malaria. In: Schlagenhauf P, ed. *Traveler's malaria*. Hamilton, Ontario: BC Decker, 2001:14–55.
31. Kain KC, Keystone JS. Malaria in travelers. Epidemiology, disease and prevention. *Infect Dis Clin North Am* 1998;12:267–284.[PubMed]
32. Schwartz E, Parise M, Kozarsky P, et al. Delayed onset of malaria implications for chemoprophylaxis in travelers. *N Engl J Med* 2003;349:1510–1516.[PubMed]
33. Hellgren U. Approach to the patient with malaria. In: Keystone JS, Kozarsky PE, Freedman DO, Nothdurft HD, Connor BA, eds. *Travel medicine*. London: Mosby, 2004:169–274.
34. Greenberg AE, Lobel HO. Mortality from *Plasmodium falciparum* malaria in travelers from the United States, 1959 to 1987. *Ann Intern Med* 1990;113:326–327.[PubMed]
35. Grobusch MP. Self-diagnosis and self-treatment of malaria by the traveler. In: Keystone JS, Kozarsky PE, Freedman DO, et al, eds. *Travel medicine*. London: Mosby, 2004:157–167.
36. Miller SA, Bergman BP, Croft AM. Epidemiology of malaria in the British Army from 1982 1996. *J R Army Med Corps* 1999;145:20–22.[PubMed]
37. Robert LL, Schneider L, Wirtz RA. Deet and permethrin as protectants against malaria-infected and unifected *Anopheles stephensi* mosquitoes. *J Am Mosq Control Assoc* 1991;7:304–306.
38. Beier JC, Oster CN, Onyango FK, et al. *Plasmodium falciparum* incidence relative to entomological inoculation rates at a site proposed for testing malaria vaccines in western Kenya. *Am J Trop Med Hyg* 1994;50:529–536.[PubMed]
39. McCarthy JS. Malaria chemoprophylaxis: in war and peace. *Med J Aust* 2005;182:148–149.[PubMed]
40. Schoepke A, Steffen R, Gratz N. Effectiveness of personal protection measures against mosquito bites for malaria prophylaxis in travellers. *J Travel Med* 1998;5:188–192.[PubMed]

41. Misra SP, Webber R, Lines J, et al. Spray versus treated nets using deltamethrin a community randomized trial in India. *Trans R Soc Trop Med Hyg* 1999;93:456–457.[PubMed]
42. Rowland M, Mahmood P, Iqbal J, et al. Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomized trial. *Trop Med Int Health* 2000;5:472–481.[PubMed]
43. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. *Ann Intern Med* 1998;128:931–940. Search date 1997; primary sources Medline, the Internet, the Extension Toxicology Network database, hand searches of reference lists, and contact with distributors of natural insect repellents.[PubMed]
44. Hewitt SE, Farhan M, Urhaman H, et al. Self-protection from malaria vectors in Pakistan: an evaluation of popular existing methods and appropriate new techniques in Afghan refugee communities. *Ann Trop Med Parasitol* 1996;90:337–344.[PubMed]
45. Service MW. *Mosquito ecology: field sampling methods*. 2nd ed. London: Chapman and Hall, 1993.
46. Sylla el-HK, Lell B, Kremsner PG. A blinded, controlled trial of an ultrasound device as mosquito repellent. *Wein Klin Wochenschr* 2000;112:448–450.
47. Lawrance CE, Croft AM. Do mosquito coils prevent malaria? A systematic review of trials. *J Travel Med* 2004;11:92 96. Search date 2003; primary sources Cochrane Central Register of Controlled Trials, Medline, Embase, Lilacs, Cinahl, the Internet, hand searches of reference lists, and personal contact with manufacturers and researchers.[PubMed]
48. Srinivas G, Amalraj RE, Dhanraj B. The use of personal protection measures against malaria in an urban population. *Public Health* 2005;119:415–417.[PubMed]
49. Vythilingam I, Sidavong B, Chan ST, et al. Epidemiology of malaria in Attapeu Province, Lao PDR in relation to entomological parameters. *Trans R Soc Trop Med Hyg* 2005;99:833–839.
50. Yap HH, Tan HT, Yahaya AM, et al. Field efficacy of mosquito coil formulations containing d-allethrin and d-transallethrin against indoor mosquitoes especially *Culex quinquefasciatus*. *Southeast Asian J Trop Med Public Health* 1990;21:558–563.[PubMed]
51. Vernede R, van Meer MMM, Aplers MP. Smoke as a form of personal protection against mosquitoes, a field study in Papua New Guinea. *Southeast Asian J Trop Med Public Health* 1994;25:771–775.
52. Lengeler C. Insecticide treated bednets and curtains for preventing malaria. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003.
53. Guillet P, N'Guessan R, Darriet F, et al. Combined pyrethroid and carbamate 'two-in-one' treated mosquito nets: field efficacy against pyrethroid-resistant Anopheles gambiae and Culex quinquefasciatus. *Med Vet Entomol* 2001;15:105–112.
54. Soto J, Medina F, Dember N, et al. Efficacy of permethrin-impregnated uniforms in the prevention of malaria and leishmaniasis in Colombian soldiers. *Clin Infect Dis* 1995;21:599–602.[PubMed]
55. Rowland M, Durrani N, Hewitt S, et al. Permethrin-treated chaddars and topsheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. *Trans R Soc Trop Med Hyg* 1999;93:465–472.[PubMed]
56. Kimani EW, Vulule JM, Kuria IW, et al. Use of insecticide-treated clothes for personal protection against malaria: A community trial. *Malar J* 2006;5:63.
57. Eamsila C, Frances SP, Strickman D. Evaluation of permethrin-treated military uniforms for personal protection against malaria in northeastern Thailand. *J Am Mosq Control Assoc* 1994;10:515–521.[PubMed]
58. Joy RJ. Malaria in American troops in the South and Southwest Pacific in World War II. *Med Hist* 1999;43:192–207.[PubMed]
59. Matsika-Claquin MD, Menard D, Fontanet AL, et al. Efficacy of chloroquine-proguanil malaria prophylaxis in a non-immune population in Bangui, Central African Republic: a case-control study. *Trans R Soc Trop Med Hyg* 2006;100:381–386.
60. Juckett G. Malaria prevention in travelers. *Am Fam Physician* 1999;59:2523–2530.[PubMed]
61. Bradley DJ, Warhurst DC. Guidelines for the prevention of malaria in travellers from the United Kingdom. *Commun Dis Rep CDR Rev* 1997;7:R137–R152.[PubMed]
62. Kroeger A, Gerhardus A, Kruger G, et al. The contribution of repellent soap to malaria control. *Am J Trop Med Hygiene* 1997;56:580–584.
63. Rowland M, Downey G, Rab A, et al. DEET mosquito repellent provides personal protection against malaria: a household randomized trial in an Afghan refugee camp in Pakistan. *Trop Med Int Health* 2004;9:335–3420.
64. Rowland M, Freeman T, Downey G, et al. DEET mosquito repellent sold through social marketing provides personal protection against malaria in an area of all-night mosquito biting and partial coverage of insecticide-treated nets: a case-control study of effectiveness. *Trop Med Int Health* 2004;9:343–350.
65. Costantini C, Badolo A, Ilboudo-Sanogo E. Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against Anopheles gambiae complex and other Afrotropical vector mosquitoes. *Trans R Soc Trop Med Hyg* 2004;98:644–652.
66. McConnell R, Fidler AT, Chrislip D. Everglades National Park health hazard evaluation report. Cincinatti, Ohio: US Department of Health and Human Services, Public Health Service, 1986. NIOSH Health Hazard Evaluation Report No. HETA-83-085-1757.
67. Lamberg SI, Mulrennan JA. Bullous reaction to diethyl toluamide (DEET) resembling a blistering insect eruption. *Arch Dermatol* 1969;100:582–586.[PubMed]
68. Curtis CF, Townson H. Malaria: existing methods of vector control and molecular entomology. *Br Med Bull* 1998;54:311–325.[PubMed]
69. Astroff AB, Young AD, Holzum B, et al. Conduct and interpretation of a dermal developmental toxicity study with KBR 3023 (a prospective insect repellent) in the Sprague-Dawley rat and Himalayan rabbit. *Teratology* 2000;61:222–230.
70. Wahle BS, Sangha GK, Lake SG, et al. Chronic toxicity and carcinogenicity testing in the Sprague-Dawley rat of a prospective insect repellant (KBR 3023) using the dermal route of exposure. *Toxicology* 1999;142:41–56.
71. Sharma VP, Ansari MA, Razdan RK. Mosquito repellent action of neem (Azadirachta indica) oil. *J Am Mosq Control Assoc* 1993;9:359–360.
72. Moore SJ, Lenglet A, Hill N. Field evaluation of three plant-based insect repellents against malaria vectors in Vaca Diez Province, the Bolivian Amazon. *J Am Mosq Control Assoc* 2002;18:107–110.
73. Ansari MA, Razdan RK. Relative efficacy of various oils in repelling mosquitoes. *Indian J Malariol* 1995;32:104–111.
74. Magnon GJ, Robert LL, Kline DL, et al. Repellency of two deet formulations and Avon Skin-So-Soft against biting midges (Diptera: Ceratopogonidae) in Honduras. *J Am Mosq Control Assoc* 1991;7:80–82.
75. Khan AA, Maibach HI, Strauss WG, et al. Vitamin B1 is not a systemic mosquito repellent in man. *Trans St Johns Hosp Dermatol Soc* 1969;55:99–102.
76. Ives AR, Paskewitz SM. Testing vitamin B as a home remedy against mosquitoes. *J Am Mosq Control Assoc* 2005;21:213–217.
77. Soto J, Toledo J, Rodriquez M, et al. Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann Intern Med* 1998;129:241–244.[PubMed]
78. Baird JK, Fryauff DJ, Basri H, et al. Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. *Am J Trop Med Hyg* 1995;52:479–484.[PubMed]
79. Carmona-Fonseca J. High efficacy of primary chemoprophylaxis with primaquine. Metanalysis. *Iatreia* 2006;19:244–260.
80. Stemberger H, Leimer R, Wiedermann G. Tolerability of long-term prophylaxis with Fansidar: a randomized double-blind study in Nigeria. *Acta Trop* 1984;41:391–399.[PubMed]
81. Petersen E. Malaria prophylaxis. Effects and side-effects of drugs used for prevention of malaria. *Ugeskr Laeger* 1997;159:2723–2730. [In Danish]
82. Gherardin T. Mefloquine as malaria prophylaxis. *Aust Fam Physician* 1999;28:310.
83. Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992 1998: a review. *J Travel Med* 1999;6:122–133.[PubMed]
84. Croft AM, Geary KG. Chloroquine and combinations. In: Schlagenhauf P, ed. *Traveler's malaria*. Hamilton, Ontario: BC Decker, 2001:163–182.
85. Fogh S, Schapira A, Bygbjerg IC, et al. Malaria chemoprophylaxis in travellers to east Africa: a comparative prospective study of chloroquine plus proguanil with chloroquine plus sulfadoxine-pyrimethamine. *BMJ* 1988;296:820–822.[PubMed]
86. Wetsteyn JCFM, de Geus A. Comparison of three regimens for malaria prophylaxis in travellers to east, central, and southern Africa. *BMJ* 1993;307:1041–1043.[PubMed]
87. Drysdale SF, Phillips-Howard PA, Behrens RH. Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990;335:164.
88. Schlagenhauf P, Tschopp A, Johnson R, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *BMJ* 2003;327:1078–1081.[PubMed]
89. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997;126:963–972.[PubMed]
90. Taylor WR, Richie TL, Fryauff DJ, et al. Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis* 1999;28:74–81.[PubMed]
91. Phillips MA, Kass RB. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. *J Travel Med* 1996;3:40–45.[PubMed]
92. Leutscher PDC. Malaria prophylaxis. *Ugeskr Laeger* 1997;159:4866–4867. [In Danish]
93. Anonymous. Mefloquine and malaria prophylaxis. *Drug Ther Bull* 1998;36:20–22. [Letter][PubMed]
94. Croft AMJ, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. c
95. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized double-blind study. *Clin Infect Dis* 2001;33:1015–1021.[PubMed]
96. Potasman I, Juven Y, Weller B, et al. Does mefloquine prophylaxis affect electroencephalographic patterns? *Am J Med* 2002;112:147–149.[PubMed]
97. Barrett PJ, Emmins PD, Clarke PD, et al. Comparison of adverse events associated with use of mefloquine and combinations of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;313:525–528.[PubMed]
98. Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clin Exp Dermatol* 1999;24:249–254.[PubMed]
99. Weinke T, Trautmann M, Held T, et al. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991;45:86–91.[PubMed]
100. Bem L, Kerr L, Stuerchler D. Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions. *J Trop Med Hyg* 1992;95:167–169.[PubMed]
101. Huzly D, Schonfeld C, Beurle W, et al. Malaria chemoprophylaxis in German tourists: a prospective study on compliance and adverse reactions. *J Travel Med* 1996;3:148–155.
102. Schlagenhauf P, Steffen R, Lobel H, et al. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. *Trop Med Int Health* 1996;1:485–494.[PubMed]
103. Handschin JC, Wall M, Steffen R, et al. Tolerability and effectiveness of malaria chemoprophylaxis with mefloquine or chloroquine with or without co-medication. *J Travel Med* 1997;4:121–127.[PubMed]
104. Van Riemsdijk MM, van der Klauw MM, van Heest JAC, et al. Neuro-psychiatric effects of antimalarials. *Eur J Clin Pharmacol* 1997;52:1–6.[PubMed]
105. Micheo C, Arias C, Rovira A. Adverse effects and compliance with mefloquine or chloroquine + proguanil malaria chemoprophylaxis. *Proc Second Eur Conf Travel Med*, Venice, Italy, 2000:29–31.

106. van Riemsdijk MM, Ditters JM, Sturkenboom MCJM, et al. Neuropsychiatric events during prophylactic use of mefloquine before travelling. *Eur J Clin Pharmacol* 2002;58:441–445.[PubMed]
107. Van Riemsdijk MM, Sturkenboom MC, Pepplinkhuizen L, et al. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. *J Clin Psychiatry* 2005;66:199–204.[PubMed]
108. Mittelholzer ML, Wall M, Steffen R, et al. Malaria prophylaxis in different age groups. *J Travel Med* 1996;4:219–223.
109. Croft AM, Herxheimer A. Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement? *BMC Public Health* 2002;2:6.[PubMed]
110. Ling J, Baird JK, Fryauff DJ, et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria among migrants to Papua, Indonesia. *Clin Infect Dis* 2002;35:825–833.[PubMed]
111. Hogh B, Clarke PD, Camus D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. *Lancet* 2000;356:1888–1894.[PubMed]
112. Soto J, Toledo J, Luzz M, et al. Randomized, double-blind, placebo-controlled study of Malarone for malaria prophylaxis in non-immune Colombian soldiers. *Am J Trop Med Hygiene* 2006;75:430–433.
113. Hatton CSR, Peto TEA, Bunch C, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986;1:411–414.[PubMed]
114. Neftel K, Woodtly W, Schmid M, et al. Amodiaquine induced agranulocytosis and liver damage. *BMJ* 1986;292:721–723.[PubMed]
115. Larrey D, Castot A, Pessayre D, et al. Amodiaquine-induced hepatitis. A report of seven cases. *Ann Intern Med* 1986;104:801–803.[PubMed]
116. Woodtli W, Vonmoos P, Siegrist P, et al. Amodiaquine-induced hepatitis with leukopenia. *Schweiz Med Wochenschr* 1986;116:966–968. [In German][PubMed]
117. Bernuau J, Larrey D, Campillo B, et al. Amodiaquine-induced fulminant hepatitis. *J Hepatol* 1988;6:109–112.[PubMed]
118. Charmot G, Goujon C. Minor hepatitis probably caused by amodiaquine. *Bull Soc Pathol Exot* 1987;80:266–270. [In French]
119. Raymond JM, Dumas F, Baldit C, et al. Fatal acute hepatitis due to amodiaquine. *J Clin Gastroenterol* 1989;11:602–603.[PubMed]
120. Shanks GD, Edstein MD, Suriyamongkol V, et al. Malaria chemoprophylaxis using proguanil/dapsone combinations on the Thai-Cambodian border. *Am J Trop Med Hyg* 1992;46:643–648.[PubMed]
121. Miller KD, Lobel HO, Satriale RF, et al. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine for malaria prophylaxis. *Am J Trop Med Hyg* 1986;35:451–458.[PubMed]
122. Graves P, Gelband H. Vaccines for preventing malaria (blood-stage). [Review] [30 refs]. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
123. Graves P, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). [Review] [45 refs]. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
124. Graves P, Gelband H. Vaccines for preventing malaria (SPf66). [Review] [30 refs]. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
125. Osimitz TG, Murphy JV. Neurological effects associated with use of the insect repellent *N*,*N*-diethyl-*m*-toluamide (DEET). *J Toxicol Clin Toxicol* 1997;35:435–441.
126. De Garbino JP, Laborde A. Toxicity of an insect repellent: *N*,*N*-diethyl-*m*-toluamide. *Vet Hum Toxicol* 1983;25:422–423.
127. Are insect repellents safe? *Lancet* 1988;ii:610–611. [Editorial]
128. Bouchaud O, Longuet C, Coulaud JP. Malaria prophylaxis. *Rev Prat* 1998;48:279– 286. [In French][PubMed]
129. Camus D, Djossou F, Schilthuis HJ, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. *Clin Infect Dis* 2004;38:1716–1723.[PubMed]
130. British National Formulary. BNF 53, March 2007. London: British Medical Association/Royal Pharmaceutical Society of Great Britain.
131. Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy.
132. Lindsay S, Ansell J, Selman C, et al. Effects of pregnancy on exposure to malaria mosquitoes. *Lancet* 2000;355:1972.[PubMed]
133. Suh KN, Keystone JS. Malaria prophylaxis in pregnancy and children. *Infect Dis Clin Pract* 1996;5:541–546.
134. Schaefer C, Peters PW. Intrauterine diethyltoluamide exposure and fetal outcome. *Reprod Toxicol* 1992;6:175–176.[PubMed]
135. McGready R, Hamilton KA, Simpson JA, et al. Safety of the insect repellent *N*,*N*-diethyl-*m*-toluamide (DEET) in pregnancy. *Am J Trop Med Hyg* 2001;65:285–289.
136. Blomquist L, Thorsell W. Distribution and fate of the insect repellent 14C-*N*,*N*-diethyl-*m*-toluamide in the animal body. II. Distribution and excretion after cutaneous application. *Acta Pharmacol Toxicol (Copenh)* 1977;41:235–243.[PubMed]
137. Osimitz TG, Grothaus RH. The present safety assessment of DEET. *J Am Mosq Control Assoc* 1995;11:274–278.[PubMed]
138. Samuel BU, Barry M. The pregnant traveler. *Infect Dis Clin North Am* 1998;12:325–354.[PubMed]
139. Garner P, Gulmezoglu AM. Drugs for preventing malaria in pregnant women. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
140. Cot M, Roisin A, Barro D, et al. Effect of chloroquine chemoprophylaxis during pregnancy on birth weight: results of a randomized trial. *Am J Trop Med Hyg* 1992;46:21–27.[PubMed]
141. Nosten F, ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. *J Infect Dis* 1994;169:595–603.[PubMed]
142. Shamiss A, Atar E, Zohar L, et al. Mefloquine versus doxycycline for malaria prophylaxis in intermittent exposure of Israeli Air Force aircrew in Rwanda. *Aviat Space Environ Med* 1996;67:872–873.[PubMed]
143. Simons R, Valk PJ, Krul AJ. Malaria prophylaxis for aircrew: safety of atovaquone/proguanil in healthy volunteers under aircraft cabin pressure conditions. *J Travel Med* 2005;12:210–216.[PubMed]
144. Schlagenhauf P, Lobel H, Steffen R, et al. Tolerance of mefloquine by Swissair trainee pilots. *Am J Trop Med Hyg* 1997;56:235–240.[PubMed]
145. Halliday ML, Kang LY, Rankin JG, et al. An efficacy trial of a mammalian cell-derived recombinant DNA hepatitis B vaccine in infants born to mothers positive for HBsAg, in Shanghai, China. *Int J Epidemiol* 1992;21:564–573.[PubMed]

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