



PRACTICE

THERAPEUTICS

Mosquito repellents for travellers

Nina M Stanczyk *research fellow*¹, Ron H Behrens *senior lecturer*^{1,2}, Vanessa Chen-Hussey *research scientist and clinical trials manager*^{1,3}, Sophie A Stewart *senior research scientist and clinical trials coordinator*³, James G Logan *senior lecturer*^{1,3}

¹Department of Disease Control, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK; ²Hospital for Tropical Diseases, London, UK; ³Arthropod Control Product Test Centre, London School of Hygiene and Tropical Medicine, London, UK

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com.

Case scenario

A pregnant woman visits you as her general practitioner (GP) because she and her children will be visiting a country with mosquito borne disease. You recommend using repellents to protect against mosquitoes, as well as vaccinations and other relevant disease prevention measures. She asks which repellents would be best.

What are the active ingredients?

The key factors to consider when choosing a repellent are the active chemical ingredients and the strength (concentration (%) of active ingredient) because these influence the efficacy and duration of protection.^{1,2} There are four active ingredients with sufficient published scientific evidence to warrant recommendation. Repellents are useful in areas of low risk of mosquito borne disease to prevent nuisance biting (which may lead to problems such as allergies) and are essential in moderate to high risk areas (figure 1) to prevent disease transmission (such as malaria and dengue fever) through bites. Repellents work on mosquitoes by directly stimulating avoidance behaviour or by blocking the mosquito's receptors for attractive odours, not through toxicity.³

DEET—*N,N*-Diethyl-*meta*-toluamide has been in use since 1946 and is the “gold standard” repellent recommended by the World Health Organization Pesticide Evaluation Scheme.⁴

PMD—Many people prefer the idea of a “natural” repellent to a synthetic one. *p*-Menthane-3,8-diol (PMD) was first

isolated as a byproduct of *Eucalyptus citriodora* (lemon eucalyptus).

Icaridin—Icaridin (hydroxyethyl isobutyl piperidine carboxylate) is also known by the trade names Bayrepel, Picaridin, and Saltidin.

Insect Repellent 3535—IR3535 (ethyl butylacetylaminopropionate) is a synthetic repellent that has been less comprehensively studied.

How well do repellents work?

Although this article focuses on mosquitoes, the four recommended active ingredients may also protect against other arthropod vectors, such as sand flies and ticks. The recommended active ingredients should repel up to 100% of mosquitoes of the genera *Aedes*, *Anopheles*, and *Culex* for a specified duration. Although some repellents can last up to 12 hours, the average is 4-8 hours, depending on the active agent, application type, and the local mosquito species.²

DEET—For disease endemic countries DEET should be present at 20-50% concentration, because several large well conducted randomised control trials have shown that this concentration offers complete protection by repelling 100% of *Aedes*, *Culex*, and *Anopheles* mosquitoes for 6-13 hours.^{1,2}

PMD—Repellents with 30% PMD provided complete protection for 4-6 hours against *Aedes*, *Culex*, and *Anopheles* mosquitoes in randomised controlled trials.^{1,2} Apart from its shorter duration of action, efficacy is similar to DEET.

Icaridin—Like DEET, in randomised controlled trials in the field, at concentrations greater than 20%, Icaridin offered complete protection for up to six hours against *Anopheles*, *Aedes*, and *Culex* species.¹

IR3535—This has shown complete protection, comparable to DEET, at 20% concentration against several mosquito species including *Aedes* and *Culex* for 7-10 hours in well

The bottom line

- Always recommend a topically applied repellent with a proven active ingredient such as DEET (20-50%), PMD (30%), or Icaridin (20-50%). IR3535 (20%) is recommended only for areas that are not malaria endemic
- Reapply repellents at least every six to eight hours if using DEET or IR3535, or every four to six hours for PMD and Icaridin, and sooner if they wear off while swimming or sweating in warm weather
- DEET can be used on children over 8 weeks old, PMD on children over 3 years
- DEET is safe for use from the second trimester onwards and while breast feeding

replicated laboratory longevity studies and non-randomised field trials in Thailand. However, protection time is shorter (~3 h) against *Anopheles* species, so it should not be recommended for malaria endemic regions.¹

How safe are repellents?

During the 1980s and 1990s there were several reports of encephalopathy following DEET exposure in children.¹ However, risk assessments by both the US Environmental Protection Agency (USEPA) and independent publications, as well as a clinical trial, found no association between encephalopathy and DEET use, and no toxicological risk or severe effects except after inappropriate use (ingestion, direct inhalation, or eye exposure).⁵ PMD, Icaridin, and IR3535 have also been registered for safe use as repellents by the USEPA⁶ and WHO,^{7,8} but have not been extensively studied in humans.

What are the precautions?

Pregnancy and breast feeding—No trials have assessed the safety of PMD, Icaridin, or IR3535 in human pregnancy or during breast feeding, so these drugs cannot be recommended. A large, well conducted, double blind randomised controlled trial (RCT) in Thailand of 897 pregnant women showed no adverse effects of topically applied DEET in women or their infants when followed for one year after birth, including while breast feeding.⁹ Participants were all in the second or third trimester, however, and no human trials provide safety data for earlier in pregnancy. Nonetheless, studies in rats and rabbits showed no effects on offspring, suggesting that DEET is safe when used as recommended.¹⁰

Children—Topical repellents are recommended for children of all ages unless the label specifically states an age restriction.¹¹ Products containing DEET are considered safe for use in children over 2 months of age.¹⁰ Products containing PMD are not advised in children under 3 years because of the lack of safety data for this age range.¹¹ The repellent should be applied by an adult who has thoroughly read the directions. A third to a half of parents apply repellent incorrectly to children—for example, by applying it to the children's clothing as well as their skin or by not removing it before putting children to bed.¹²

Sunscreen—Limited early laboratory research suggested that applying 33.5% DEET after sunscreen significantly reduces the sun protection factor (SPF) of the sunscreen.¹³ Randomised controlled trials with *Aedes* and *Anopheles* mosquitoes found that applying repellent concurrently with or before sunscreen did not lessen the effect of the repellent,^{14,15} but that reapplication of the sunscreen over the repellent reduced the mean repellent protection time by one hour.¹⁵ Thus advise travellers to apply repellent first or use a combined repellent and sunscreen product and be aware that repellent may wear off more quickly if reapplying only

sunscreen on top. If using a combination product, ensure that the concentration of repellent is sufficient.

How are they used?

Recommend topical repellents, such as lotions and sprays, because they are the most studied and have the greatest efficacy.¹ The repellent should be effective against the vector species present at the destination. Thus, although all four repellents are effective, do not recommend IR3535 for malaria endemic regions, given its shorter duration of action against *Anopheles* spp. Apply evenly to all exposed skin except the face (to avoid accidental eye exposure or ingestion) during times of risk (at dawn, dusk, and evening for most regions, but also during the day, particularly in South East Asia, South America, and in forested areas). Although every product is different, as a general rule, re-apply DEET and IR3535 every six to eight hours, and PMD and Icaridin every four to six hours.^{1,2} The tips for travellers box provides more detail on appropriate use.

How do they compare with alternatives?

An RCT compared common commercial products containing essential oils, vitamin B₁, or the insecticide metofluthrin, in different delivery systems, including wristbands, stickers, patches, sonic devices, and diffusers.¹⁶ It found that only the personal diffusers containing metofluthrin or a mix of essential oils had any repellent effect, reducing localised biting by 87-95%. There is no evidence that any of these devices provide adequate protection for areas with mosquito borne disease.

Other active ingredients include essential oils such as citronella, neem, thyme, geraniol, peppermint, patchouli, and clove. Because these compounds are volatile, efficacy is variable. They may provide 20-100% protection for about two hours, but a recent systematic review of laboratory and field trials found no evidence that they can protect against disease transmission.¹⁷

There is anecdotal evidence that a change in diet and vitamin supplements can protect against mosquito bites. Although this has not been looked at extensively, an RCT of the effect of vitamin B₁₂ on human odour showed that it has no effect on mosquito biting rates.¹⁸ A double blinded RCT that tested the effect of garlic supplements as mosquito repellents found no protective effect.¹⁹ Intake of supplements like vitamin B or garlic should not be recommended for protection against mosquitoes.

Outcome

You recommend a topical repellent with DEET (20-50%) because it is effective and safe for pregnant women and children and provide advice on how to apply it (see tips for travellers box).

Contributors: All authors helped design and plan the manuscript; NMS, VC-H, SAS, and JGL co-wrote the manuscript; and RHB critically revised it. All authors were involved in subsequent revisions. JGL is guarantor.

Tips for travellers

Use a repellent containing 20-50% DEET or Icaridin, or 30% PMD. Use IR3535 (20%) only if travelling to a country without malaria. Higher concentrations of DEET will repel mosquitoes for longer than lower concentrations. However, products with greater than 50% DEET are not recommended

Essential oils such as citronella, repellent wristbands, garlic supplements, and vitamin B₁₂ do not provide adequate protection against biting and disease transmission

Apply repellent evenly to all exposed skin except the face, particularly when there are lots of mosquitoes, such as in the early morning and the evening, but also during the day if mosquitoes are present

DEET and IR3535 should be reapplied every six to eight hours, and PMD and Icaridin every four to six hours, unless stated otherwise on the label. If swimming or sweating in warm weather, they may wear off sooner and will need to be reapplied

Apply repellent and sunscreen simultaneously or repellent first; if using a combination product, check that it contains the right concentration of repellent (20-50% DEET)

You can safely use DEET when pregnant (from the second trimester onwards), when breast feeding, and on children over 2 months old. Thoroughly cover the child's exposed skin (except the face), not clothing, and ensure that you wash it off before bed

Additional resources: www2.epa.gov/insect-repellents; wwwnc.cdc.gov/travel/page/avoid-bug-bites

Competing interests: We have read and understood BMJ policy on declaration on interests and declare the following interests: JGL, VC-H, and SAS are employees of the Arthropod Control Product Test Centre, a wholly owned subsidiary of the London School of Hygiene and Tropical Medicine that performs independent efficacy testing of repellents for commercial companies. The other authors have no competing interests.

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

Patient consent not required (patient anonymised, dead, or hypothetical).

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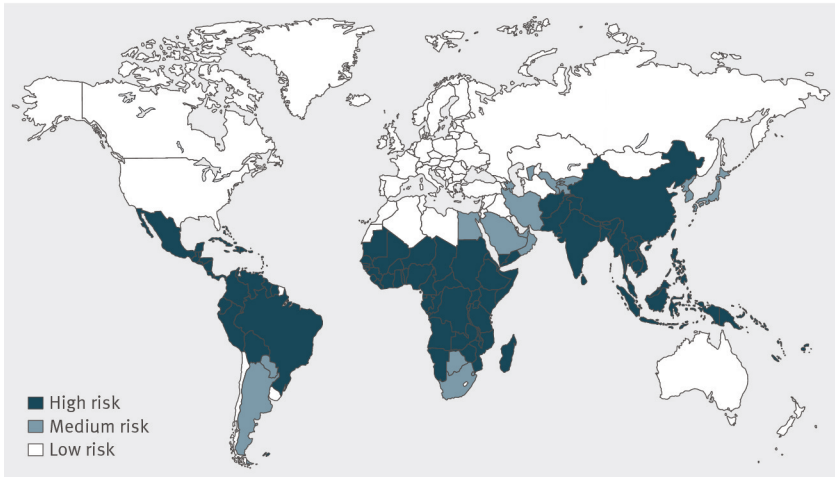
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Accepted: 23 December 2014

Cite this as: *BMJ* 2015;350:h99

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Figure



Areas of low, moderate, and high risk of mosquito borne disease worldwide