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THERAPEUTICS

Mosquito repellents for travellers

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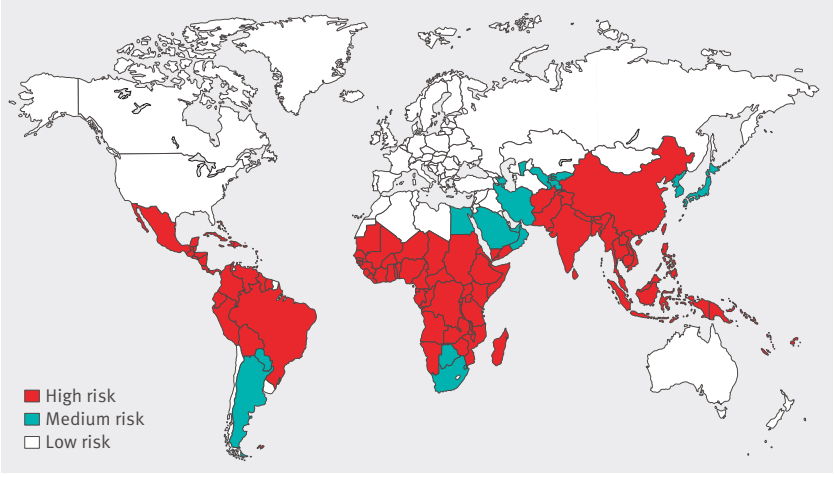
This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City 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) 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 though toxicity.[3]



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

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

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 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 toxological risk or severe effects except after inappropriate use (ingestion,

WHAT YOUR PATIENT IS THINKING

"How can I help you hear?" The transforming power of six little words

In the latest of a monthly series in which patients and carers set the learning outcomes for readers, **Sarah Chapman** offers practical advice when talking to people with hearing loss. For more information about the series, contact Rosamund Snow, patient editor, rsnow@bmj.com

I'm waiting to be called for a smear and I have a couple of concerns to discuss. I'm on high alert. Not for me a browse of last year's magazines; I need to be sure that I know when I'm called, and that means keeping my eyes peeled for the nurse. Having made it to the consulting room, the next obstacle is the "confidential tone"—the enemy of every patient with hearing loss. We stumble our way through a series of questions, half heard, on intimate matters (plenty of scope here for misunderstanding and embarrassment), and I ready myself for the next bit of the ordeal.

Now an internal examination is not likely to gladden the heart, but because I rely on seeing lip movements to aid my hearing, being flat on my back threatens more than just my dignity. I'm grateful that the nurse offers me privacy to get undressed but miss what she's saying from the other side of the curtain. I'm prepared for the business of trying to keep my head raised off the trolley, to increase my chances of keeping my eyes on her face, but of course I can't sustain it and sometimes she talks with her back turned, her head down, or from behind the curtain. Worse is to come. I'm still on the trolley as she gives me a short lesson on my physiology using the curtain and her hand as explanatory props, her face half hidden behind. I can't fault her ingenuity but leave no wiser than when I arrived.

A desire to be polite and not risk irritating the person in whose hands I quite literally found myself meant that on this, as on other occasions, I acted as if I had heard and understood, thanked her, and left her to get on with the next patient. A letter would be sent, I told myself, and I got a sense there was nothing to worry about, so I'd just wait.

If you don't have hearing loss, it must be hard to see why I can't just say that I do, problem solved. It's not quite that simple, not least because hearing loss threatens our communication all the time that we're talking. It's hard to keep interrupting a consultation to say, again, that I didn't hear. Everyone misses bits of conversation sometimes, and as someone with hearing loss I accept that I will miss more than most. I have to try to get the balance right between interrupting to clarify something half heard and letting some things go, hoping the words I lose aren't crucial. Then there are the times that really trip me up—when I'm unaware that I've misheard until an odd look or long pause from the person talking to me gives me a clue that I've got it wrong. Being a patient is potentially stressful, and difficulties with communication add to this. It's very tempting, when I'm struggling to hear, to end the conversation quickly rather than stick at it.

When I go into your consulting room, as your patient or perhaps accompanying someone else, I'm always a person with hearing loss, whatever else might ail me. I might rail against you seeing me primarily as a middle aged white woman, or the other things that might colour your impression when I walk through the door, but I need you to remember this thing and work with me to accommodate it, all the time, every time.

"I've no idea if patient records are marked to flag up when a person has hearing loss, but I'd like them to be"

Without this, we're not going to be able to have a helpful dialogue; little chance of you being able to share your expertise and me my values and concerns, little chance of us making decisions together. You'll be left having only partly reached me and I'll walk away wondering quite how much I missed, perhaps unsure about what will happen next and why.

I've no idea if patient records are marked to flag up when a person has hearing loss, but I'd like them to be. I'd like my healthcare provider to be ready for that, but I must be ready to tell you, to be sure you know that from the start.

I arrive in a café for a first meeting with someone with shared professional interests, whom I know only through Twitter. She knows I'm hard of hearing and when I immediately eject her from her seat in front of a window, offering an awkward explanation that I need to sit where I can best see her face, she asks me "how can I help you hear?" There might as well be fireworks and a full orchestral accompaniment, so great is my surprise at being asked this for the first time ever in three decades as a hearing aid wearer, and so powerful is its effect.

KEY MESSAGES:

1. Please don't ignore my hearing loss. Acknowledge it and ask "how can I help you hear?" This empowers us both. It's a respectful, empathetic, and practical opening question, inviting specific instructions that you can follow, knowing that you are doing the right things to enable a helpful dialogue. I'm immediately made to feel that you're on my side, that we're partners in this business of managing my health, and I'm able to tell you what I need you to do. For me, that's making sure you're not sitting with a window behind you, and that you speak clearly and only when I can see your face. It's not much to ask and it won't take any longer; in fact it will save time. Others may have different needs and they'll be able to tell you what they are.
2. It's easy to start well but soon forget to do the things that help me hear, so keep checking that you're still doing them.
3. Consider supporting your verbal communication with visual information, such as diagrams. Unfamiliar terms can be hard to hear correctly, so I might like them written down.

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direct inhalation, or eye exposure).[5] PMD, Icaridin, and IR3535 have also been registered for safe use as repellents by the USEPA[6] 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.[1 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, reapply 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.

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 B_{12} 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

How do they compare with alternatives?

An RCT compared common commercial products containing essential oils, vitamin B_1, 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 B_{12} 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).