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REVIEW ARTICLE

Chemical and Plant-Based Insect Repellents: Efficacy, Safety, and Toxicity

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Most emerging infectious diseases today are arthropod-borne and cannot be prevented by vaccinations. Because insect repellents offer important topical barriers of personal protection from arthropod-borne infectious diseases, the main objectives of this article were to describe the growing threats to public health from emerging arthropod-borne infectious diseases, to define the differences between insect repellents and insecticides, and to compare the efficacies and toxicities of chemical and plant-derived insect repellents. Internet search engines were queried with key words to identify scientific articles on the efficacy, safety, and toxicity of chemical and plant-derived topical insect repellants and insecticides to meet these objectives. Data sources reviewed included case reports; case series; observational, longitudinal, and surveillance studies; and entomological and toxicological studies. Descriptive analysis of the data sources identified the most effective application of insect repellents as a combination of topical chemical repellents, either N-diethyl-3-methylbenzamide (formerly N, N-diethyl-m-toluamide, or DEET) or picaridin, and permethrin-impregnated or other pyrethroid-impregnated clothing over topically treated skin. The insecticide-treated clothing would provide contact-level insecticidal effects and provide better, longer lasting protection against malaria-transmitting mosquitoes and ticks than topical DEET or picaridin alone. In special cases, where environmental exposures to disease-transmitting ticks, biting midges, sandflies, or blackflies are anticipated, topical insect repellents containing IR3535, picaridin, or oil of lemon eucalyptus (p-menthane-3, 8-diol or PMD) would offer better topical protection than topical DEET alone.

Key words: repellents, insect, insecticides, infectious diseases, arthropod-borne, mosquito-borne, tick-borne

Introduction

Most emerging infectious diseases today are arthropod-borne by ticks or mosquitoes and, with few exceptions, cannot be prevented by vaccinations. Lyme disease, transmitted by ixodid tick bites, is now the most common arthropod-borne infectious disease in the United States and Europe.[1] Recently, 3 new tick-borne diseases have been described in the United States: heartland virus disease, *Borrelia miyamotoi* borreliosis, and 364D rickettsiosis.[2–6] An introduced species of mosquito in the United States and Europe, *Aedes albopictus*, has proven itself to be as competent a new vector of dengue and chikungunya viruses as *Aedes aegypti*, the yellow fever vector, has been in the tropics.[7,8] Because insect repellents offer important topical barriers of personal protection from arthropod-borne infectious diseases, the objectives of this article were to 1) describe the growing threats to public health from emerging arthropod-borne infectious diseases; 2) define the differences between insect repellents and insecticides; 3) compare the efficacies and toxicities of chemical and plant-derived insect repellents; 4) recommend the best combinations of insect repellents and insecticides for personal protection; and 5) describe the most effective nonchemical methods of personal protection from insect bites.

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Methods

To meet the objectives of this article, Internet search engines including PubMed, Medline, Ovid, Google, Google Scholar, and Cochrane were queried with key words as medical subject headings to identify

peer-reviewed scientific articles and governmental publications on the efficacy, safety, and toxicity of synthetic chemical and plant-derived topical insect repellants and insecticides. The key words included repellants, insect; insecticides; and infectious diseases, arthropod-borne, mosquito-borne, and tick-borne.

The articles selected to meet the first objective of describing the burden of arthropod-borne diseases included case reports and case series of newly described infectious diseases and observational, longitudinal, and surveillance studies. The articles selected to meet the second and third objectives of differentiating insecticides from repellents and comparing their efficacies and toxicities included entomological and toxicological studies and field and laboratory evaluations of different repellent and insecticidal formulations. The articles selected to meet the last 2 objectives to recommend the best combinations of chemical and nonchemical methods of personal protection from insect bites included both randomized controlled trials and U.S. governmental publications by the Centers for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). Because this investigation was review of prior published scientific articles, Institutional Review Board approval was waived.

Results

DEFINITIONS

An insect repellant is defined as a chemical or organic agent that makes the atmosphere within 4 centimeters of human skin so noxious to insects as to discourage contact and biting.[9] On the other hand, an insecticide is a chemical or organic agent, often plant-derived, that kills insects, typically with a neurotoxin.[9] Some insect repellents are also insecticides, such as plant-derived permethrin and all other synthetic pyrethroids.[9]

In the United States, the FDA tests and approves topical insect repellants, such as N, N-diethyl-3-methylbenzamide (formerly N, N-diethyl-m-toluamide or DEET) for use and safety in pregnant women; and the EPA approves insecticides for use under the Federal Insecticide, Fungicide, and Rodenticide Act. Many insecticides, such as the carbamates and organophosphates, are EPA-approved for outdoor use but not for indoor use. The only insecticides approved for indoor use are the pyrethroids, which are laboratory-made extracts derived from crushed, dried *Chrysanthemum* flowers.

WHY USE INSECT REPELLENTS?

The 3 major reasons to use insect repellents are: 1) new threats to human health posed by emerging and imported arthropod-borne infectious diseases; 2) the dominance of new, competent insect vectors of infectious diseases; and 3) the inability to primarily prevent the transmission of most arthropod-borne infection diseases by vaccinations with the exceptions of yellow fever vaccine in South America and Africa, Japanese encephalitis vaccine in Southeast Asia, and several regional tick-borne virus vaccines in Eastern Europe.

THE THREATS FROM EMERGING AND IMPORTED ARTHROPOD-BORNE INFECTIOUS DISEASES

Arthropod-borne infectious diseases are primarily transmitted to humans from extensive zoonotic reservoirs in birds and mammals via the bites of infected mosquitoes, midges, flies, fleas, and ticks. The most common arthropod-borne disease in the United States and Europe today is tick-transmitted Lyme disease caused by the spirochete, *Borrelia burgdorferi*.[1] The most common mosquito-borne infectious disease in the United States today is West Nile virus (WNV), an arbovirus transmitted to humans by bites from Culicine mosquitoes.[10] Although most cases of WNV infection remain asymptomatic, WNV neuroinvasive disease causes meningoencephalitis that often results in permanent neurological impairment.[11] After WNV, the next most commonly reported arboviral encephalitides in the United States include mosquito-borne LaCrosse virus, Jamestown Canyon virus, eastern equine encephalitis virus, and tick-borne Powassan virus, which has the highest case fatality rate among the arboviruses.[10]

Unlike mosquitoes, ticks are versatile insect vectors that can transmit a variety of pathogens, including bacteria, viruses, and parasites. In addition, ticks may be asymptomatically coinfected with different pathogens concurrently and pass these pathogens on to their progeny (transovarian transmission) for maintenance throughout all stages of their development (transstadial transmission). The *Borrelia* spirochetes, arboviruses, and tick-transmitted viruses all have large animal reservoirs that are an integral part of the ecosystem and cannot be culled or effectively controlled. With the exception of the live-virus yellow fever vaccine and a few others, there are currently no vaccines to prevent mosquito and tick-borne infectious diseases; and disease transmission to humans can only be prevented by arthropod avoidance, insect repellents, and insecticides.

Emerging competent arthropod vectors: mosquitoes and ticks

Mosquitoes are responsible for the transmission of most arthropod-borne infectious diseases worldwide, with