Mosquito-borne Infections

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Mosquitoes are ubiquitous worldwide, found even in the Arctic. There are more than 3,000 species. The *Aedes* (Zika virus [ZIKV], dengue virus, Chikungunya virus [CHKV]), *Anopheles* (malaria), and *Culex* (West Nile virus) are the primary genera involved in human disease. *Aedes aegypti*, an aggressive daytime biting mosquito, is a particularly effective vector because it inhabits urban areas, feeds preferentially on human blood, and feeds multiple times in a breeding cycle. *Aedes albopictus* (Asian tiger mosquito) has spread worldwide through larva in recycled tires in the 1980s. This mosquito is more widely distributed than *A aegypti*, thrives in rural habitats, and can feed on other animals besides humans. Interestingly, this mosquito now vectors CHKV more efficiently due to a new adaptive mutation that occurred in the virus in 2005 or 2006, leading to reemergence of disease.

After a resoundingly successful mosquito control program in the 1940s and the decline of yellow fever in the 1960s, funding for mosquito control was cut. This has contributed to the dramatic resurgence of dengue, CHKV, and now ZIKV. Children are vulnerable to morbidity and mortality from these diseases.

ZIKV is a flavivirus that first was identified in Uganda in 1947. It emerged in Brazil in early 2015 and rapidly spread to most South American countries, with recent local transmission in the United States territories and the United States mainland. The most devastating effects have been neurotropic, with microcephaly in the newborns of infected mothers. This is the first time that a mosquito-borne disease has been linked with severe congenital malformation. Other neurologic complications such as Guillain-Barré syndrome can occur. Most infected children are either asymptomatic or have a mild illness, which makes the diagnosis challenging. Furthermore, ZIKV has similar clinical features and geographic distribution to dengue virus and CHKV. ZIKV should be suspected in children who have travelled to or lived in an affected area in the past 2 weeks and have 2 or more of the following: acute onset of fever, pruritic maculopapular rash, arthralgia, or nonpurulent conjunctivitis. The infection is diagnosed through flavivirus serologic assays, and molecular testing is available through the Centers for Disease Control and Prevention (CDC). Ongoing research is pursuing the most sensitive and specific testing methodology to decrease the rate of cross-reactivity and false-positive results in suspected cases.

DENV, a flavivirus, accounts for ~100 million infections annually worldwide, 500,000 cases of dengue hemorrhagic fever (DHF), and 22,000 deaths, which occur primarily among children. There was a recent outbreak in Hawaii. The classic dengue presentation is high temperature (104°F [40°C]) accompanied by any 2 of the following: severe headache, retro-orbital pain, muscle and joint pain, nausea, vomiting, swollen glands, or rash. Severe dengue (DHF) is a potentially fatal complication that occurs after 3 to 7 days of illness, with plasma leakage, hemorrhage, and shock. Intensive fluid and electrolyte management in DHF is crucial. In contrast, CHKV infection, caused by an alphavirus, is rarely fatal, does
not cause retro-orbital pain, and characteristically is associated with persistent arthralgia. Management is supportive. The first live recombinant tetravalent dengue vaccine was licensed in December 2015 for individuals ages 9 to 45 years living in endemic areas. Several other vaccines are in phase 3 trials.

Malaria is a protozoal infection transmitted by the bite of the female Anopheles mosquito. The World Health Organization (WHO) estimated 214 million cases worldwide and 438,000 deaths, mostly in children, in 2015. About 1,500 imported cases are diagnosed in the United States each year. Malaria should be considered in all febrile travelers returning from endemic areas within the past year, regardless of a history of malaria prophylaxis. The 5 viral species that commonly infect humans are Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi. The clinical manifestations depend on the infecting species and the immune status of the infected individual. P falciparum most commonly causes severe disease. Classic symptoms are high fever with chills, rigor, sweats, and headache. Early diagnosis is important due to the potential for rapid fatality. Peripheral thick and thin blood smears are the gold standard for diagnosis. Rapid diagnostic test kits available in resource-limited settings can detect malarial antigens within minutes but cannot determine the species or quantify parasitemia.

Neuroinvasive arboviruses are a significant cause of pediatric disease, with more than 1,200 cases of central nervous system infection and 22 deaths in the past decade. La Crosse virus (65%) and West Nile virus (41%) are the leading causes of pediatric neuroinvasive arboviral disease. Eastern equine encephalitis has the highest case fatality rate. La Crosse virus is a California serogroup bunyavirus found in the central and eastern United States. The incidence of infection in endemic areas (20-30 cases per 100,000 per year) exceeds that of bacterial meningitis. Aedes triseriatus is the primary vector. La Crosse virus encephalitis primarily affects children younger than age 15 years. Most infected cases (80%-90%) involve a mild course with headache, fever, and vomiting. The infection can progress to severe disease with seizures and coma in 10% to 20% of cases. West Nile virus is a flavivirus that is vectored through the Culex mosquito, with birds as the natural reservoir. It is present throughout the United States. Although 86% of infected individuals are asymptomatic, those who are symptomatic present with mild flu-like illness and rash. Fewer than 1% develop neuroinvasive disease, with the highest incidence in older adults. Infection with these neuroinvasive arboviruses can be diagnosed by testing serum or cerebrospinal fluid to detect virus-specific immunoglobulin (Ig)M and neutralizing antibodies.

Education of families and caregivers plays an important role in prevention of mosquito-borne infection. Specific measures include eliminating mosquito breeding sites by drainage and removal of receptacles for standing water around the home. Among the large-scale public health measures during outbreaks are drainage of standing water, use of larvicides in waters that are sources of mosquitoes, and use of pesticides to control adult mosquitoes. The use of window and door screens and limiting outdoor activities at dusk and dawn can reduce exposure. Barriers such as mosquito nets and screens for baby strollers and clothing to cover areas of exposed skin are protective. The United States Environmental Protection Agency has approved the use of DEET (N,N-diethyl-meta-toluamide) in children as an effective repellent.

The American Academy of Pediatrics recommends that insect repellants not be used in children younger than age 2 months and that DEET at maximum concentration of up to 30% be used in those older than age 2 months. These repellants should not be applied over cuts or sunburned skin. Permethrin (a synthetic pyrethroid) is an effective repellent that can be sprayed on clothing but should not be sprayed on the skin. In spite of all control measures, mosquitoes and mosquito-borne infections remain a significant public health challenge even today.

COMMENT: The recent Zika outbreaks in South America and subsequent transmission to the Caribbean and United States have put mosquito-borne infections back in the news. These outbreaks led to a designation of a WHO Public Health Emergency of International Concern, influenced attendance at the Rio de Janeiro Olympics, and altered travel plans to affected areas. As of November 23, 2016, the CDC website noted that travel-related cases of ZIKV have been reported throughout the United States, with the highest rates in New York, Florida, and California. This outbreak was especially concerning because of the vertical transmission associated with microcephaly and the worrisome sexual transmission. This outbreak also called to attention the decrease in public health interventions of prevention, including environmental, biologic, and chemical control for mosquito-borne infections, since the 1950s. The range of manifestations of mosquito-borne infections from
infected children being asymptomatic to exhibiting serious infection reminds me of questions that Barton Childs, a famous geneticist and role model at Johns Hopkins, would ask. He would encourage all of us to contemplate these questions when considering an illness in a child: Why this child, why this disease, and why now? Factors that are probably at play with mosquito-borne infections include prior exposure; individual health status, such as malnutrition, chronic illness, and immunodeficiency status; and genetic factors and predisposition that currently are being identified. Prevention remains the key, and we as pediatricians must make sure we reinforce the preventive strategies that Drs Rajagopalan and Ilboudo have outlined in this In Brief. Vaccine development continues and may prove helpful in the future.

– Janet R. Serwint, MD, FAAP
Associate Editor, In Brief

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition
• Chapter 308: Parasitic Infections - https://pediatriccare.solutions.aap.org/chapter.aspx?sectionId=124421438&bookId=1626&resultClick=1#160113746

Parent Resources from the AAP at HealthyChildren.org
• Zika Virus: What Parents Need to Know: https://www.healthychildren.org/English/ages-stages/prenatal/Pages/Zika-Virus.aspx
• Diseases Spread by Insects: https://www.healthychildren.org/English/health-issues/conditions/from-insects-animals/Pages/Diseases-Spread-by-Insects.aspx
• Tularemia: An Infection Caused by Insects: https://www.healthychildren.org/English/health-issues/conditions/from-insects-animals/Pages/Tularemia-An-Infection-Caused-by-Insects.aspx

For a comprehensive library of AAP parent handouts, please go to the Pediatric Patient Education site at http://patiented.aap.org.

ANSWER KEY FOR JULY 2017 PEDIATRICS IN REVIEW
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