

From Hot Topics in Internal Medicine 2016: The Latest Knowledge to Impact Your Practice, presented by the University of Wisconsin School of Medicine and Public Health, Department of Medicine, and University of Wisconsin-Madison School of Nursing

Emerging Infectious Diseases: Zika Virus

Dennis G. Maki, MD, Ovid O. Meyer Professor of Medicine, Divisions of Infectious Disease and Pulmonary/Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, and Attending Physician, Center for Trauma and Life Support, Madison

Conditions leading to emerging infectious diseases (EIDs):

definition of EID—could be infection caused by entirely new microorganism starting to spread, re-emergence of pathogen poorly controlled, or antibiotic resistance on major scale; *societal disruption*—caused by, eg, massive famine or flooding, war; can result in re-emergence of diseases; *changes in health care*—hospital-acquired infections leading cause of complications within health care system; although significant progress made in control, risk still increasing due to number of invasive procedures performed; widespread use of implanted medical devices has led to more infection (although devices increasingly becoming safer); *changes in food production*—risk for food-borne diseases higher now than in previous generation, but progress has been made in controlling them; *changes in human behavior*—sexual revolution of 1960s resulted in pandemic of sexually acquired infections; *environmental changes*—urbanization of Africa has resulted in massive spread of AIDS, Lassa virus, and Ebola virus throughout continent; in North America, living closer to nature results in proximity to animals that carry pathogenic agents; risk for tick-borne diseases significantly increased; almost two-thirds of EIDs have animal reservoir (zoonosis); *changes in public health infrastructure*—in Soviet Union, implosion of economy resulted in widespread failure to immunize children; *changes in microorganisms*—influenza viruses changes structure and cause pandemic disease with new strains every 10 to 30 yr; *international travel*—increases capacity for spread of diseases

Preparing for EIDs: plans must be implementable nationally and locally; terrorist attack of September 2001 led to major commitment of resources; preparing for bioterrorism synonymous with preparing for EIDs

History of Zika virus (ZIKV): outbreak of febrile illness occurred in northeastern Brazil in August 2014; quickly determined that it was not dengue, but ZIKV; ZIKV is flavivirus (RNA virus), same class of virus that causes hepatitis C, yellow fever, Japanese B encephalitis, St. Louis encephalitis, tick-borne encephalitis, and dengue; first identified in 1947 in Uganda (isolated from primate); at first uncertain whether able to cause human disease; until 2000, only few well-documented cases; serologic screening in Asia determined that virus spread to Asia; thought that virus caused only mild illness in most instances; in 2007, large outbreak occurred in Micronesia, particularly Yap Island; quickly determined that virus mosquito-borne; from 2013 outbreak in French Polynesia, important observations made about capacity to cause Guillain-Barré syndrome (GBS) and neuroteratogeny; sequencing of virus in outbreak in Brazil

determined that virus French Polynesian strain with additional mutations; within 10 mo of introduction to Brazil, massive epidemic underway

Epidemiology: seen throughout South and Central America; 31 countries in Western hemisphere have had documented cases, most caused by mosquito transmission; *microcephaly*—in Brazil, 10-fold increase in newborns with severe microcephaly seen coincident with ZIKV outbreak; children with microcephaly severely developmentally delayed, and most require total care for rest of lives; estimated 5000 cases of microcephaly in Brazil; *study in New England Journal of Medicine*—found 72 pregnant Brazilian women with active polymerase chain reaction (PCR)-positive ZIKV infection; serial ultrasonography (US) throughout pregnancy and examination of infant at birth performed; found that 29% of women had abnormal fetal US; 2 infants died in pregnancy, 5 had severe growth retardation, and 7 had major neurologic abnormalities (5 cases of microcephaly); evidence of placental ischemia seen; *study*—showed that ZIKV triggers toll-like receptor 3 (TLR3; TLRs inform body that “invader” coming and turn on immune system); if TLR3 turned on at high level in pregnancy, causes apoptosis of neural progenitor cells in developing fetus (probable mechanism of neuroteratogeny); number of women were infected late in pregnancy (6th to 7th mo of gestation) and had severely impaired children; also noted marked upsurge in GBS; almost all GBS cases in Brazil immunoglobulin (Ig)M-positive for ZIKV; estimated incidence ranges from 1 in 500 to 1 in 10,000; deemed international public health emergency by World Health Organization in February 2016; by May 2016, 61 countries had documented ZIKV, and >500 introduced cases seen in United States, all sexually transmitted

Pathophysiology: *reservoir*—infected humans and primates (primates probably major reservoir); transmitted in nature by bites from infected *Aedes* mosquitoes (classically *Aedes aegypti*); *Aedes mosquitoes*—daytime feeders that also transmit dengue and Chikungunya virus; *A aegypti* found throughout southern part of United States, while *A albopictus* found as far north as Great Lakes areas; widely disseminated throughout southern, eastern, and central part of United States; *other transmission*—transfusion of blood and blood products, organ transplantation, sexual (particularly man to woman), and vertical (to fetus)

Clinical features: 80% of infections asymptomatic; of those asymptomatic, often have mild rash, low-grade fever, slight headache, and characteristic conjunctivitis

Management: no special precautions needed, unless potential exposure to blood present; standard precautions indicated; aspirin not recommended for treatment (infection possibly dengue and could precipitate hemorrhagic dengue); symptomatic treatment; if woman infected, determine whether pregnant; if not pregnant, should have contraception for ≥ 3 mo (ideally, 6 mo); women clear virus more rapidly than men (can carry ZIKV in semen for ≤ 2 mo); if pregnant woman infected, immediately perform US and consider

amniocentesis (decision about whether to terminate pregnancy needed if infection with teratogenic effects present); infected men should use condoms for ≥ 2 mo after infection if sexual partner attempting to become pregnant, and if partner pregnant, should use condoms throughout pregnancy

Diagnosis: easy to diagnose with PCR; serologic test has significant cross-reactivity with other flaviviruses; plaque-reduction neutralization test needed to confirm that infection true ZIKV, not other flavivirus; serum positive by PCR first (usually within 3-4 days); urine positive longer (after 7 days); cerebrospinal fluid positive if headache and neurologic symptoms present; amniotic fluid likely positive if infant infected

Controlling ZIKV globally: avoiding travel to hyperendemic countries; mosquito eradication (priority in Central and South America); in Puerto Rico, limited spraying being done with pyrethrin; protection against mosquito bites (wearing long-sleeved clothing when outside, sleeping under screens and nettings with air conditioning or fan; impregnating clothing with permethrin); study found that full-strength 25% N,N-Diethyl-meta-toluamide (DEET)

resulted in almost total protection for 5 hr; natural agents ineffective or unreliable; picaridin safe and effective repellent; Puerto Rican study showed that mosquito traps markedly reduced incidence of Chikungunya; screening pregnant women in endemic areas; delaying pregnancy until epidemic controlled; screening blood and organ donors; experimental dengue vaccine recently approved, and similar vaccine effective for ZIKV “desperately” needed

Suggested Reading

Balm MN et al: A diagnostic polymerase chain reaction assay for Zika virus. *J Med Virol*, 2012 Sep;84(9):1501-5; **Brasil P et al:** Guillain-Barré syndrome associated with Zika virus infection. *Lancet*, 2016 Apr 2;387(10026):1482; **D’Ortenzio E et al:** Evidence of Sexual Transmission of Zika Virus. *N Engl J Med*, 2016 Jun 2;374(22):2195-8; **Ioos S et al:** Current Zika virus epidemiology and recent epidemics. *Med Mal Infect*, 2014 Jul;44(7):302-7; **Mlakar J et al:** Zika Virus Associated with Microcephaly. *N Engl J Med*, 2016 Mar 10;374(10):951-8; **Musso D et al:** Potential sexual transmission of Zika virus. *Emerg Infect Dis*, 2015 Feb;21(2):359-61; **Torjesen I:** Zika virus outbreaks prompt warnings to pregnant women. *BMJ*, 2016 Jan 26;352:i500.