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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

# Zika!

*By Philip R. Fischer, MD, DTM&H*

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**Dr. Fischer reports no financial relationships relevant to this field of study.**

SYNOPSIS: Zika virus infection has prompted international emergency responses due to its rapid spread in the Americas and its potential to alter brain development in pre-born children. Even as research progresses, prevention of infection depends on avoiding bites from *Aedes* mosquitoes.

SOURCE: Chen LH, Hamer DH. Zika virus: Rapid spread in the Western Hemisphere. *Ann Intern Med.* Published online Feb. 2, 2016. doi: 10.7326/M16-0150.

During recent months, an outbreak of Zika virus infection has been spreading through the Americas. Drs. Chen and Hamer provide a timely and practical update on this infection.

## HISTORY

The virus was first isolated from a monkey being used for yellow fever surveillance in the Zika Forest of Uganda in 1947. Subsequent serologic surveys suggested that the virus was present in both Africa and Asia, but reports of human infection were uncommon until 2007. Then, the virus was associated with an outbreak of a febrile illness on Yap Island in Micronesia. (*See the September 2007 issue of* Infectious Disease Alert.) In late 2013, the virus was identified in French Polynesia and accounted for approximately 19,000 cases. In early 2015, the virus was identified in patients with a dengue-like illness in Brazil. The Brazilian outbreak has subsequently spread and is circulating in more than 20 countries/territories within the Americas and is being carried by travelers to other parts of the world.

## VIRUS

Zika is an RNA flavivirus related to the viruses responsible for dengue, yellow fever, West Nile, and Japanese encephalitis. There are two major lineages of the virus: African and Asian. Outbreaks in the Pacific and in the Americas are due to the Asian lineage of Zika virus.

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## VECTORS

Zika is transmitted by *Aedes* mosquitoes. Different *Aedes* species have been involved in different outbreaks. *Aedes aegypti* and *Aedes albopictus* are present in much of the Americas, including areas in the southern United States. *Aedes* mosquitoes also transmit dengue and chikungunya, so the geographical distribution of these infections overlaps. The mosquitoes usually bite during the daytime.

## CLINICAL PRESENTATIONS

Up to 80% of infected individuals have no clinical manifestations of Zika. Those who are symptomatic have clinical presentations approximately 2-7 days after a bite from an infected mosquito. They have a maculopapular rash for 2-14 days (median duration of rash: 6 days), arthralgia for 1-14 days (median duration of arthralgia: 3.5 days), and conjunctivitis. Myalgia, headache, retro-orbital pain, joint swelling, vertigo, and vomiting are also sometimes reported. The illness is self-limited and usually resolves within a week. (Conversely, the arthralgia of chikungunya can begin similarly but can persist for many months.) Neurologic and autoimmune complications (Guillain-Barre syndrome) were identified during the outbreak of Zika in French Polynesia. Microcephaly was frequently reported in the current Brazilian outbreak.

## DIAGNOSIS

Serological tests for dengue and Zika cross-react, so false-positive results for either infection are possible with infection by the other virus. Viremia occurs for up to 11 days following the onset of symptoms, and RT-PCR tests can confirm the diagnosis during the first week of infection. Zika RNA can be detected in saliva and urine for longer than it can be detected in blood.

## MANAGEMENT

Supportive care should be provided for patients with Zika infection. Ibuprofen and other non-steroidal agents are usually avoided since they might diminish platelet function in patients who are already thrombocytopenic due to the infection. Acetaminophen may be used.

## PREVENTION

There is no vaccine to prevent Zika infection. Prevention of Zika infection is based on mosquito avoidance. Pregnant women should avoid travel to areas where Zika is active. Repellents containing DEET or picaridin are effective. Insecticides and drainage of mosquito breeding areas are similarly appropriate.

## ■ COMMENTARY

The spread of Zika beyond Africa prompted concern for Zika as an "emerging infection" in 2009.[1] Now, news media have popularized dramatic concerns about Zika infection. International organizations are publicizing the "global emergency" status of Zika virus.[2] Countries are seeking billions of dollars of funding to counter the spread of Zika. Meanwhile, the Centers for Disease Control and Prevention (CDC) website is frequently updated with current scientifically sound information.[3]

As viruses spread geographically, the vectors and clinical manifestations can change. This has been seen with yellow fever, West Nile virus, and chikungunya, so it is not surprising that different mosquito vectors and different clinical situations are seen as Zika spreads.[4] If Zika gets established in U.S. populations of *Aedes aegypti*, it could potentially spread west from Florida and Georgia to Texas, and even to parts of New Mexico, Arizona, and California. If the virus spreads in American populations of *Aedes albopictus*, it could spread up the eastern half of the United States as far north as Iowa, Illinois, Indiana, Ohio, and Pennsylvania. (CDC maps show more detail of *Aedes* distribution.[5])

Zika infection is usually asymptomatic, and symptomatic patients usually have a mild illness that resolves within a week. However, risks of two serious complications have heightened concern for spreading Zika infection. First, Guillain-Barre syndrome was reported during the Polynesia outbreak of Zika in 2013. Ongoing surveillance will help determine whether the current American outbreak of Zika is also associated with autoimmune neurologic consequences. Second, there is a possible (not yet definitively proven to be causal) association between Zika and microcephaly. Among the first 35 cases

of microcephaly reported from areas of actively circulating Zika virus to a new registry in Brazil, 74% of mothers reported having a rash during pregnancy.[6] Two patients who died in the immediate neonatal period and two miscarried babies had Zika virus RNA isolated from multiple body tissues; mothers were from Zika-active areas of Brazil and reported febrile illnesses with rash during pregnancy.[6] Brazilian infants with Zika-related microcephaly have had eye changes, including mottling of macular pigment and chorioretinal atrophy, as well as optic nerve changes, including hypoplasia, pallor, and increased cup-to-disk ratio.[7]

So far, the risk to developing fetuses does not seem to be specific to a particular period of pregnancy. Thus, to prevent microcephaly with its attendant neurologic and ocular problems, pregnant women should avoid bites from mosquitoes that might be carrying Zika virus. How should this be done? Most everyone agrees that insect repellents should be used and mosquito populations should be reduced in Zika-active areas through environmental control and/or the use of insecticides. The CDC advises pregnant women (and women who might soon become pregnant) to avoid travel to areas where Zika is circulating.[3] Some countries (including Brazil, Colombia, Ecuador, El Salvador, and Jamaica) have recommended that women residing there avoid becoming pregnant — with El Salvador suggesting women not get pregnant until at least 2018.[4] Whether families choose such extreme measures or not, attention to mosquito control is essential.

Transmission of Zika virus is also possible via blood transfusions and, potentially, through sexual contact. Pregnant women requiring transfusions should, when possible, receive blood from donors who were not recently in Zika-active areas. Even without clear evidence available yet, Public Health England has advised male travelers to Zika-active areas to use condoms for 28 days following travel if their partner is at risk of pregnancy and to use condoms for 6 months if they become ill with Zika infection.[2] If and as Zika virus becomes established in parts of the Americas, and as preventive and therapeutic interventions develop, practical adjustments in travel plans and risk avoidance will need to be updated. ■

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ABSTRACT & COMMENTARY

# Human Paraechovirus Encephalitis in Children


***By Dean L. Winslow, MD, FACP, FIDSA***

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**Dr. Winslow reports no financial relationships relevant to this field of study.**



SYNOPSIS: Human paraechovirus (HPeV) causes encephalitis and is more common in very young or premature female infants. Affected children commonly present with seizures. Diffusion restriction on MRI in the absence of CSF pleocytosis is seen. Neurodevelopmental sequelae are common after long-term follow up.


SOURCE: Britton PN, et al. Paraechovirus encephalitis and neurodevelopmental outcomes. *Pediatrics* 2016;137:1-11.

Children 14 years of age and younger hospitalized with suspected encephalitis in five Australian pediatric tertiary care hospitals were prospectively enrolled in the Australian Childhood Encephalitis (ACE) study between May 2013 and November 2014. Molecular testing for various pathogens was performed on clinical samples including cerebrospinal fluid (CSF).

Thirteen infants with suspected encephalitis and confirmed HPeV infection were identified out of a total of 133 encephalitis cases of all causes. After expert panel review, nine of the 13 infants were determined to have encephalitis. Seven of the nine infants were female, five were born prematurely, all cases occurred in infants younger than 2 months of age (median age 13 days). All presented as outpatients with fever, lethargy, or irritability. Seizure occurred in eight of nine patients. Rash was present in five patients; four had multi-organ dysfunction. HPeV RNA was detected in CSF in all nine patients. Subtyping was performed in four, and all of these were genotype 3. Cranial ultrasound was abnormal in only two children. MRI was performed in seven children, and all of these studies were abnormal with T2 hyperintensity with corresponding diffusion restriction involving periventricular and subcortical white matter and thalamus. Electroencephalogram (EEG) was performed on seven children and was abnormal in six. CSF pleocytosis was absent in all. Eight children required intensive care unit admission, and five patients required mechanical ventilation. All patients received empirical antibiotics for variable periods of time, and seven of nine children received acyclovir. Neurologic outcome at hospital discharge was consistent with none or minor neurologic damage in six children, but longer-term follow-up of eight children at about 12 months after discharge demonstrated that five of eight had significant developmental problems, including cerebral palsy in two and central visual impairment in one. Seven of the eight children had gross motor subscale abnormalities, and this appeared to correlate with the degree of MRI abnormalities.

## ■ COMMENTARY

This prospective study demonstrates that approximately 10% of childhood encephalitis cases during the study period were caused by HPeV. Young age and prematurity were risk factors for development of HPeV encephalitis. All presumably acquired infection in the home during their first weeks of life. While short-term outcomes seemed reassuring, longer-term follow-up demonstrated significant neurodevelopmental sequelae, and these effects were correlated with severity of white matter changes seen on MRI during the acute illness. These MRI findings are not specific for HPeV infection and can be seen in other neonatal encephalitides[1,2] and from other causes.[3,4] Unfortunately, no specific therapy exists for HPeV infection or most of the other viral infections, which can contribute to devastating CNS damage in neonates. ■

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ABSTRACT & COMMENTARY

# Oral Fluconazole During Pregnancy Increases Risk for Spontaneous Abortion


***By Richard R. Watkins, MD, MS, FACP***

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**Dr. Watkins reports that he has received research support from Actavis.**



SYNOPSIS: A nationwide cohort study from Denmark found a significantly increased risk of spontaneous abortion associated with oral fluconazole usage. Caution with this medication during pregnancy is advised.


SOURCE: Molgaard-Nielsen D, et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA* 2016;315:58-67.

Approximately 10% of women in the United States develop vaginal candidiasis during pregnancy. Most are treated with intravaginal topical azoles, although oral fluconazole is sometimes prescribed for severe or recurrent symptoms. Previous studies suggested that high-dose fluconazole may lead to birth defects. Therefore, investigators in Denmark sought to determine whether fluconazole use in pregnancy is associated with spontaneous abortion and stillbirth.

The study used national health registries to identify all pregnancies that ended with a singleton live birth, stillbirth, spontaneous abortion, and other abortive outcomes in Denmark between January 1997 and December 2013. Prescription data for oral fluconazole was also obtained from a national prescription register. Dosing was divided into two categories: 150 mg to 300 mg and 350 mg to 5600 mg. The lower doses were based on the standard treatment for vaginal candidiasis, and the higher doses were for more complicated fungal infections such as recurrent vaginal candidiasis. Each fluconazole-exposed pregnancy was matched to up to four non-exposed control pregnancies to avoid potential confounding. Spontaneous abortion was defined as pregnancy loss from 7 through 22 gestational weeks, and stillbirth was defined as pregnancy loss from 23 weeks. Itraconazole exposure during pregnancy was also investigated to determine a class effect for the azoles.

More than 1.4 million pregnancies were included in the cohort. A total of 147 out of 3315 women exposed to oral fluconazole during weeks 7 through 22 of gestation experienced a spontaneous abortion compared to 563 of the 13,246 unexposed matched women. Fluconazole exposure was associated with a significantly increased risk of spontaneous abortion (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.23-1.77). Twenty-one stillbirths occurred in the 5382 pregnancies exposed to fluconazole from week 7 through birth compared to 77 in the 21,506 unexposed matched women. The risk for stillbirth was increased in the fluconazole-exposed women (HR, 1.32; 95% CI, 0.82-2.14) but did not reach statistical significance. Regarding higher-dose vs lower-dose fluconazole, the differences between the HRs of 1.55 (95% CI, 0.94-2.58) and 1.47 (95% CI, 1.22-1.77), respectfully, did not reach statistical significance for spontaneous abortion ($P = 0.84$). However, the HRs for stillbirth were different between low dose (0.99; 95% CI, 0.56-1.74) and high dose (4.10; 95% CI, 1.89-8.90), which was statistically significant ($P = 0.002$). Compared to topical azole-exposed pregnancies, there was a significantly increased risk of spontaneous abortion in the oral fluconazole-associated pregnancies (HR, 1.62; 95% CI, 1.26-2.07). Finally, seven of 131 women exposed to itraconazole during pregnancy experienced spontaneous abortions, compared to 34 of 524 matched controls (HR, 1.16; 95% CI, 0.51-2.60).

## ■ COMMENTARY

The Infectious Diseases Society of America (IDSA) guidelines on the management of candidiasis state, "Fluconazole, itraconazole, posaconazole, and isavuconazole should be avoided in pregnant women, especially those in the first trimester, because of the possibility of birth defects associated with their use."[1] The study by Molgaard-Nielsen and colleagues lends further support to this recommendation. While miscarriages are often stochastic events, the finding that oral fluconazole significantly increased the risk of spontaneous abortion should make clinicians carefully reflect on the pros and cons of this drug during pregnancy. As the authors note, one possible mechanism of action for the adverse association is that fluconazole can interfere with human CYP450 enzymes, which are expressed during in utero development. Another interesting finding of the study is that higher doses of fluconazole were associated with more stillbirths but not spontaneous abortions. The explanation for this is unclear and could be an undetermined biological mechanism or perhaps statistical imprecision. No clear determination could be made from the data about a class effect of the azoles on pregnancy outcomes, which was not surprising given the small number of pregnancies exposed to itraconazole. Although a larger study might provide an answer to this question, it seems unethical for such an investigation to be conducted given the known risks to the developing fetus. However, a retrospective analysis could be feasible.

Although this was a large cohort, the retrospective design raises the possibility of biases and confounding factors that may have impacted the results. For example, if fluconazole-exposed women sought medical attention for spontaneous abortions more often than the women who were not exposed, this would bias the results toward an increased risk with fluconazole exposure.

Until further safety data emerge, it seems reasonable for clinicians to be very cautious in prescribing oral fluconazole during pregnancy. Topical intravaginal azoles should remain first-line therapy for vaginal candidiasis. For recurrent or refractory cases, longer courses, i.e., 14 days, may be effective; topical nystatin is another option. ■

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ment of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62:e1-e50.

ABSTRACT & COMMENTARY

# Leprosy (Hansen's Disease) in the United States — The Role of Armadillos and the Increasing Incidence in Florida

***By Stan Deresinski, MD, FACP, FIDSA***

*Dr. Deresinski is Clinical Professor of Medicine, Stanford University.*

**Dr. Deresinski reports no financial relationships relevant to this field of study.**

SYNOPSIS: The evidence linking armadillos to human Hansen's disease is increasing and the range of infected armadillos and potentially related human cases has expanded into Florida where the incidence of this infection is increasing.

SOURCES: Leprosy — USA: (FL) increased cases, susp. armadillo transmission, RFI http://www.promedmail.org. Published Date: 2016-02-10. Archive Number: 20160210.4009277; Sharma R, Singh P, Loughry WJ, et al. Zoonotic leprosy in the southeastern United States. *Emerg Infect Dis.* 2015;21:2127-2134.

Hansen's disease is believed to have been introduced into the Western Hemisphere during or shortly after the period of early colonization and became established in areas around the Gulf of Mexico by the middle of the 18th century. In 2010, the last year for which data are available from the National Hansen's Disease Program, 294 new cases were reported from 34 U.S. jurisdictions (including Puerto Rico), with approximately two-thirds from seven states: California, Florida, Hawaii, Louisiana, Massachusetts, New York, and Texas. The infections were multibacillary in 56.8%.

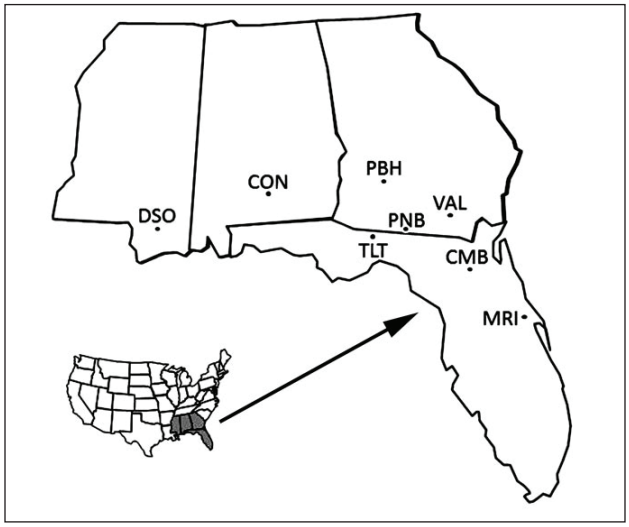
Florida accounted for 10.2% of U.S. cases in 2010, but this proportion has likely increased since then. During the 10 years from 2004 to 2014, Florida reported a total of 92 cases of Hansen's disease — an average of fewer than 10 each year. However, starting with five cases in the first 5 weeks of 2015, the total number of confirmed cases for the entire year reached 27 — almost three times the previous annual average. Unfortunately, 2016 has started on a similar upward path, with six confirmed cases from three counties in the first 5 weeks of the year.

While the majority of cases in the United States were acquired in endemic countries, approximately one-third of patients reported that they had not resided in areas of endemicity and, in addition, had no known contact with an individual with Hansen's disease. Evidence indicates that nine-banded armadillos, which have been epidemiologically associated with Hansen's disease in the United States and Brazil, may have been the source of infection in at least some of those cases. Armadillos are, to greater or lesser extents, common in the southern United States, and their range extends to Central America and northern Argentina. Beginning in 1975, *Mycobacterium leprae* infection was identified in armadillos in Texas and Louisiana, but not in Georgia, Alabama, or Florida, although the range of infection appears to have increased.

To further investigate the epidemiology and zoonotic nature of Hansen's disease, Sharma and colleagues, using serological tests and PCR, found that 106 (15.44%) of 645 armadillos captured in eight separate locations in the southeastern United States not previously known to have enzootic infection were infected. (*See Figure.*) Animals with evidence of *M. leprae* infection were detected at all eight of these locations. The armadillos were infected with one of two genotypes (3I-2-v1 and 3I-2-v5) and, of 52 patients evaluated, 22 (42.3%) were infected with one or the other of these. All patients infected with type 3I-2-v1 reported residing in areas of the southern United States where armadillos are present. All 10 patients infected with 3I-2-v15 resided in the only region where armadillos with this same *M. leprae* genotype strain type also had been found — southern Florida. None of the patients interviewed, however, reported contact with armadillos, but, in addition, none reported contact with known Hansen's disease cases. All patients harboring type 3I-2-v1 had histories of residence in areas of the southern United States where they may have been exposed to *M. leprae* through armadillos.

Armadillos are highly susceptible to infection with

**Figure. Eight Locations in 4 States in the Southeastern United States Where Armadillos Were Sampled and Tested for Infection with *Mycobacterium leprae***




*Mycobacterium leprae* (in contrast to humans, in whom there is a strong genetic component that accounts for the fact that approximately 95% appear resistant to infection), with tissue bacterial loads reaching 1010-1011 organisms per gram. The work of Sharma et al strengthens the link between human infection and armadillos. The fact that infected armadillos had not been detected previously in the southeastern United States suggests that the range of zoonotic Hansen's disease is expanding and may continue to do so. It can be speculated that the reported increase in human infections in Florida may be a reflection of the expansion of this range. ■

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ABSTRACT & COMMENTARY

# Some Professions Are More Dangerous Than Others: HIV Transmission in the Adult Film Industry

***By Stan Deresinski, MD, FACP, FIDSA***

*Dr. Deresinski is Clinical Professor of Medicine, Stanford University.*

**Dr. Deresinski reports no financial relationships relevant to this field of study.**

SYNOPSIS: Routine HIV testing failed to prevent HIV transmission, with an attack rate of 29% in male adult film performers.

SOURCE: Wilken JA, Ried C, Rickett P, et al. Occupational HIV transmission among male adult film performers — multiple states, 2014. *MMWR Morb Mortal Wkly Rep* 2016;65:110-114.

Despite requirements for periodic testing for HIV infection, work-related transmission between heterosexual adult film performers was documented in 2004. Periodic testing alone, nonetheless, remains the primary attempted means of prevention of HIV transmission by many adult film production companies. The failure of this approach has again been highlighted by the case of a 25-year-old male performer who transmitted the infection despite having had a routine negative nucleic acid amplification test (NAAT) shortly before, with the following overall timeline:

- Day 0: Negative NAAT
- Day 10: Onset acute retroviral syndrome
- Day 22: Patient informed of positive HIV test.

In the 22-day interval between the negative NAAT and the patient learning of the subsequent positive test, he had work-related "condomless" sex with a total of 12 male performers while working for two production companies, as well as more than five male non-work-related encounters in the month before and after his symptom onset.

Contact tracing was complicated by the fact that the contacts, both professional and non-professional, lived in seven U.S. states and four foreign countries, while the production companies were based in two other states and filming occurred in yet another state. Ultimately, contact tracing and viral sequence analysis indicated that, after being infected by a

non-performer, the patient subsequently infected both a co-worker and a non-work-related partner in the interval between his negative NAAT and his learning of the subsequent positive test. Of note is that six of the 17 contacts (none of whom used HIV PrEP) had already been chronically HIV-infected prior to exposure to patient A, and one had been exposed prior to patient A being infected. Of the remaining 10, seven had engaged in condomless anal sex with the patient, and two (29%) became infected, an attack rate similar to the 23% rate observed in the 2004 episode.

■ COMMENTARY

Safety in the work place is regulated by the Federal Occupational Safety and Health Administration (OSHA) and parallel state OSHAs. Much of the adult film industry is based in southern California, and voters in Los Angeles County passed a law in 2012 requiring that adult film performers wear condoms during vaginal and anal sex. It also required adult film production companies to obtain a permit from the Los Angeles County Department of Public Health, which, in turn, included requirements that adult film directors complete a training course about bloodborne pathogens and that producers submit an exposure control plan. The California Occupational Safety and Health Standards Board proposed further requirements in 2015.

Adult film production companies and their performers, medical providers, and all persons at risk for HIV should be aware that testing alone is not sufficient to prevent HIV transmission and, thus, does not preclude the necessity of condom use, which also provides protection against other sexually transmitted infections. PrEP provides additional protection and should be considered. ■

ABSTRACT & COMMENTARY

# Dengue in Paradise

***By Stan Deresinski, MD, FACP, FIDSA***

*Dr. Deresinski is Clinical Professor of Medicine, Stanford University.*

**Dr. Deresinski reports no financial relationships relevant to this field of study.**

SYNOPSIS: Dengue virus has infected more than 250 individuals on the island of Hawaii since September 2015.

SOURCES: Dengue outbreak 2015–2016. Available at: http://health.hawaii.gov/docd/dengue-outbreak-2015/. Petersen LR. Interim Assessment of the Response by the Hawaii State Department of Health to the Dengue Outbreak on the Island of Hawaii. Available at: http://health.hawaii.gov/docd/files/2015/12/CDC-Hawaii-assessment_final.pdf.

On Jan. 14, 2016, Hawaii's Civil Defense Agency closed all traffic to the Waipio Valley Access Road on the island of Hawaii and limited access to residents in the valley area in response to an ongoing dengue fever epidemic. This followed previous similar actions at other sites on the island.

On Feb. 8, 2015, Billy Kenoi, the mayor of Hawaii County (coterminous with the island of Hawaii — the "Big Island"), declared a state of emergency in response to the largest outbreak of dengue fever in Hawaii in seven decades. Four days later, David Ige, the governor of the state of Hawaii, followed suit, declaring a state of emergency to fight mosquito-borne illnesses, including dengue fever and the Zika virus. While there had been no locally transmitted cases of Zika virus, there had been a total of 255 confirmed cases of dengue fever in 231 Hawaii residents and 24 travelers to the state. Adults older than 18 years of age accounted for 209 of the total. The first case had onset of illness on Sept. 11, 2015.

*Aedes aegypti*, the dominant vector of human dengue virus infection, has limited geographic distribution in Hawaii, while a second dengue virus vector, *Aedes albopictus* — the Asian tiger mosquito — is present throughout the islands. Both mosquitoes bite during daytime hours and breed in small pools of water, both natural and man-made. The size and location of these pools, as well as other factors, account for the fact that mosquito control measures have apparently never been demonstrated to abort outbreaks.

Dengue is not endemic in Hawaii, but outbreaks have occurred previously, such as the most recent one in 2001-2002 when the virus was introduced by travelers from Tahiti, resulting in 122 laboratory-confirmed cases in Maui, Oahu, and Kauai. The current large outbreak is obviously worrisome with regard to the health of residents and visitors (approximately 12,000 visitors spend the night on

the island of Hawaii each day). While almost 10% (24/255) of cases in the current outbreak occurred in visitors, an analysis after the 2001-2002 occurrence concluded that there was little risk to visitors.

The outbreak can be explained, in part, by the shortsightedness of funding decisions by state government, which, in response to the "Great Recession," reduced the size of the state's mosquito control and entomology staff from 56 in 2009 to 25 in 2016. Somehow they never noticed that the economic downturn had ended. At the invitation of the governor, CDC performed an extensive evaluation of the outbreak and the response to it. The evaluation concluded that the state's responses had been excellent but that the outbreak had "revealed critical deficiencies in communications and medical entomologic capacities within the Department of Health that should be urgently addressed." ■

Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## Put a Lid on It

SOURCE: www.nanosafe1.com/blog/uncategorized/hospitals-miss-opportunity-to-help-put-a-lid-on-spread-of-hai/. Jan. 1, 2016.

This blogger suggests that hospitals, by using lidless toilets, have missed an opportunity to help control the spread of enteric organisms within their facilities. Numerous articles through the years have demonstrated the frequency of bacteria and viruses that may colonize toilet bowls, even after flushing. Bacteria literally adsorb to the porcelain surface of the bowl, with gradual reduction in colony counts with each flush. But even repeated flushing does not eliminate all bacteria. Recent data found that sustained spread of *Salmonella* in a number of households may have been the result of persistence of the organism in the biofilms under the recess of the toilet bowl — an impossible place to clean, if you've tried.

Further, aerosolization of bacteria and viruses from flushing is well recognized. Observations made of standard toilets found that 78% of adjacent surfaces and 81% of air samples were contaminated by enteric viruses after flushing. One investigator simulated fecal samples containing *C. difficile*, and measured aerosols and splashes following a simple flush from two different types of toilets in hospital. *C. difficile* organisms were detected in air samples immediately following a flush — and could be found in air samples up to 60 to 90 minutes later.[1] These were largely found as the result of aerosolization of large droplets. A mean number of 15-47 large droplets were released when flushing a lidless toilet, depending on the design. *C. difficile* organisms could be found in air samples up to 25 cm above the toilet seat.

Even toilets with a lid may not solve the problem. How many times have I seen patients too weak to use the toilet, and instead take advantage of the commode, which is then emptied and flushed directly by a staff person without dropping the lid?

**REFERENCE**


1. Best EL, et al. Potential for aerosolization of *Clostridium difficile* after flushing toilets: The role of toilet lids in reducing environmental contamination risk. *J Hosp Infect* 2012;80: 1-5.


## ESBL Is Blasé Compared with this Superbug

SOURCES: A ProMED-mail post, Jan. 6, 2016. Antibiotic resistance – Canada: Colistin MCR-1, *E coli*, grd. beef, human, 2010. www.promedmail.org.

Liu Y-Y, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. *Lancet Infect Dis* 2016;16; 161-168.

A plasmid-based colistin resistance gene (mcr-1), described in *The Lancet* in November 2015, has now also been found in Canada for the first time, in both meat samples and a human.[1]

Liu and colleagues have been tracking the prevalence of mcr-1 in *E. coli* and *K. pneumoniae* strains collected from five different provinces in China between 2011 and 2014.[2] They found the mcr-1 plasmid-based colistin resistance gene in 78 of 523 samples of raw meat (15%) and 166 of 804 animals (21%) during this period. In addition, they found evidence of the organism in 16 hospitalized patients. The plasmid could be transferred to another *E. coli* at a frequency of 10-1 to 10-3 cells per recipient cell by conjugation, and was maintained in both *K. pneumoniae* and *Pseudomonas aeruginosa*.

This gene has been spotted elsewhere at much lower levels than described by the Chinese. In Denmark, the mcr-1 gene was

found in 5 of 3000 *E. coli* samples (0.16%) from imported chicken meat, as well as in one Danish patient, who died of sepsis. In the United Kingdom, the mcr-1 gene was observed in 15 of 24,000 *E. coli* isolates between 2014 and 2015. For the first time, the gene has now been observed on the North American continent. During an investigation conducted in December 2015, using samples collected from earlier research, Canadian health authorities found the gene in *E. coli* isolates from two samples of ground beef sold in Ontario, as well as from a 62-year-old patient who died in Ottawa. It is believed this patient, who required hospitalization just 3 days after returning to Canada, acquired the organism while living in Egypt.

Colistin is considered the "last-ditch" antibiotic for many multi-drug-resistant organisms, and is often the only agent with activity against some of these bacteria. Colistin acts by binding to a lipid A moiety in the bacterial cell wall, which then precipitates disintegration of the cell membrane. Gram-negative bacteria employ a number of different strategies to protect themselves from polymixins, including a variety of lipopolysaccharide modifications. The mcr-1 gene is a member of the phosphoethanolamine transferase enzyme family, whose expression allows the organism to add phosphoethanolamine to lipid A, negating the efficacy of colistin. While previous mechanisms of colistin resistance were considered intrinsic and not directly transferable, it's the presence of the mcr-1 gene on a plasmid that makes this finding so hair-raising.

This finding should prompt some kind of global response to the use of colistin in animal feed and therapeutics. While countries in Europe restrict the use of colistin to veterinarians, other countries (e.g., China) use colistin as a growth promotor, and at dosages lower than that used for therapeutic purposes. No wonder colistin resistance in gram-negative isolates from China is so unexpectedly common.

**REFERENCES**


1. A ProMED-mail post, Jan. 6, 2016. Antibiotic resistance – Canada: Colistin MCR-1, *E coli*, grd. beef, human, 2010. www.promedmail.org.

2. Liu Y-Y, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. *Lancet Infect Dis* 2016;16;161-168.


## Cleaner Data on Cleaning Needed

SOURCE: Han JH, et al. Cleaning hospital room surfaces to prevent health care-associated infections. A technical brief. *Ann Intern Med* 2015;163:598-607.

I often find articles describing disinfectants and cleaning procedures not only dry but hard to compare with other similar literature. And for good reason, apparently. These authors provide a systematic review of clinical studies examining environmental cleaning procedures, disinfectants, as well as the methods for monitoring such cleaning procedures to prevent health-care-associated infections in hospital. They identified 80 clinical publications in English, 76 of which were primary studies and four of which were other systematic reviews. Only five were randomized, controlled clinical trials. Of the 80 clinical studies, 49 (61%) focused on cleaning and disinfecting, while a smaller number focused on methods for monitoring or implementation of cleaning or monitoring strategies. Various outcomes were reported, most of which focused on surface contamination (measured in a variety of ways), but few used patient-centered outcomes, such as the reduction in colonization or infection. Even when studies examining the efficacy of a certain product reported favorable results, the results often were provided for only one pathogen.

The authors identified some important gaps in this literature that they believe hinder the development of better cleaning techniques and products, as well as our ability to monitor cleanliness. They suggest that future studies provide more comparative data. They also suggest developing a standardized definition of "cleanliness," defining a standardized checklist for what are considered high-touch items in a hospital room, proposing a list of specific equipment requiring testing and monitoring, and deciding how that testing should be done.

For example, while the use of fluorescent UV surface markers and adenosine triphosphate (ATP) bioluminescence were the most commonly reported monitoring methods — and gave useful and direct feedback to staff (as opposed to direct visualization, which was poor) — these methods are not properly standardized, nor do they have good clinical correlates. We've been using an ATP device to monitor our environmental staff's performance, and have found it exceedingly useful in both monitoring cleanliness and providing ongoing education to the staff. But we still don't have any idea what those cut-off values mean in terms of viable bacteria. For example, for a patient infected with an NDM-containing organism, what ATP cut-off for their tray table or toilet is acceptable? If we use ATP to monitor our ERCP/duodenal scopes, is the recent recommendation for a cut-off value of 200 RLU (recently

proposed by our 3M Company representative) significantly safer than a cut-off of 250 RLU? I wish we had better data.

## All Those Fake Knees and Hips

SOURCE: Tande AJ, et al. Clinical presentation, risk factors, and outcomes of hematogenous prosthetic joint infection in patients with *Staphylococcus aureus* bacteremia. *Am J Med*. 2016;129:221.e11-20.

A friend's 85-year-old father recently was hospitalized with community-acquired methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia. He had developed sudden onset of left groin pain and progressive weakness 5 days earlier. He had multiple medical problems, including a prior CVA with residual left-sided weakness, as well as bilateral hip prostheses. Blood cultures quickly cleared with treatment, but he continued to complain of left groin and left hip pain. Studies of the hip were unrevealing, including plain films, a CT scan, and nuclear medicine white blood cell scan. An initial arthrogram failed to aspirate fluid, but a sample of sterile saline injected into the joint yielded six colonies of MSSA, with a somewhat similar antibiogram to the blood isolate (but the aspirate contained only 561 WBC cells/mm$^3$). A second attempted aspiration was dry. The patient was clinically improving, and his fever resolved.

What is the likelihood the hip is infected? Certainly everyone was reluctant to take this fragile elderly man to the operating room for a wash-out or a hip explantation. It wasn't until a PET-CT scan, ordered for the purposes of evaluating a lung nodule, lit up the left hip like a pinball machine was the decision made to proceed with surgery (the operative cultures were positive for scant MSSA).

These authors at the Mayo Clinic provide good answers to this question. They conducted a chart review of all cases of *S. aureus* bacteremia in adults admitted to their facility between 2006-2011, who also had at least one prosthetic joint (knee, hip, shoulder, or elbow) existing at the time of bacteremia. Patients with post-surgical prosthetic joint infection were excluded. Clinical features and outcomes were examined.

A total of 678 patients with *S. aureus* bacteremia were admitted during the study period, 97 (14.3%) of whom had 166 existing joint arthroplasties. Of these, 50 (51.6%) had no prosthetic joint infection, 35 (36.1%) had hematogenous seeding of at least one joint prosthesis, and 12 (12.4%) were either primary post-surgical infections or indeterminate and were excluded. Of the 85 remaining patients, their prosthetic joints included 73 knees, 59 hips, 10 shoulders, and one elbow.

Thirty-four (97%) of the joint infections presented with at least one clinical sign or symptom. The most common symptoms of joint infection were pain (97%), peri-articular swelling or effusion (61%), and peri-articular warmth (46%). The exception was a patient with a septic prosthetic knee joint, and aspiration of the asymptomatic contra-lateral prosthetic knee joint also demonstrated infection.

All 35 of the prosthetic joint infections were associated with community-onset *S. aureus* bacteremia. None of the cases of nosocomial bacteremia were associated with prosthetic joint infection. Seven patients had catheter-associated line infections — none of whom developed prosthetic joint infection.

Community-acquired *S. aureus* bacteremia was associated with an 18-fold increased odds of prosthetic joint infection compared with those patients with nosocomial *S. aureus* bacteremia (odds ratio, 18.07, $P = 0.001$). In multivariate analysis, the presence of three or more prosthetic joints also significantly increased the risk of hematogenous seeding of at least one joint by at least nine-fold compared with those patients with two or fewer prosthetic joints. In patients with hematogenous seeding of a joint, infection occurred in about one-third of the knees and shoulders, and nearly one-fifth of the hips.

Surgical I&D or explantation was performed in 32 patients. Three patients were managed with comfort care measures and, in total, four patients died (11.4%). Overall, treatment was considered successful in 26 patients (74%) and in 29 of 43 (67%) prosthetic joints. Subsequent orally suppressive antibacterial therapy was administered to 17 of 31 survivors. Among the nine patients who failed therapy, seven required explantation of the device despite earlier attempted wash-out, one required repeated debridement, and four patients died. Furthermore, 14 of the 35 patients (40%) died within a median of 11 months of their joint infection. Four of the 50 patients (8%) without prosthetic joint infection subsequently developed joint infection over the next 3.4 years.

At least 1 million total hips and knees are replaced annually in the United States. An estimated 4.2% of Americans older than the age of 50 have at least one prosthetic hip or knee joint. While the risk of surgically related prosthetic joint infection is estimated to be < 1.2%, these joints remain at risk for hematogenous seeding throughout the life of the patient. ■

## CME INSTRUCTIONS

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## CME QUESTIONS

**1. Which of the following is known to be true about Zika virus infection?**

a. Pregnant women are at high risk of becoming symptomatic with infection.

b. Mortality is common in endemic areas.

c. No one of child-bearing age should travel to Brazil.

d. Microcephaly is possibly associated with infection in pregnant women.

**2. Which of the following is correct about the Danish nationwide study of fluconazole administration during pregnancy?**

a. No statistically significant adverse events on pregnancy were detected.

b. Fluconazole exposure was associated with a significant risk of spontaneous abortions.

c. There was an increased risk of stillbirths but this did not differ between higher and lower dose exposure.

d. There was no significant risk in stillbirths.

**3. Which of the following is correct?**

a. All reported cases of Hansen's disease in the United States are in individuals with prolonged prior residence in endemic countries.

b. In the United States, armadillos are restricted to zoos, although some individuals surreptitiously keep them as pets.

c. Circumstantial evidence indicates that armadillos may be a source of human infection with *Mycobacterium leprae*.

d. Despite the presence of armadillos, the incidence of Hansen's disease is decreasing in Florida.

## CME OBJECTIVES

**Upon completion of this educational activity, participants should be able to:**

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.