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Hot News

Evolving RNA Virus Pandemics: HIV, HCV, Ebola, Dengue, Chikunguya, and now Zika!

The Zika virus (ZIKV), a flavivirus related to yellow fever, dengue, and West Nile, originated in the Zika forest in Uganda and was discovered in a rhesus monkey in 1947. The disease now has "explosive" pandemic potential, with outbreaks in Africa, Southeast Asia, the Pacific Islands, and the Americas. To date, the CDC has issued travel alerts for at least 30 countries and territories in Latin America, the Caribbean, Polynesia, and Cape Verde in Africa.

Since Brazil reported the first ZIKV cases in May 2015, infections have occurred in at least 20 countries in the Americas. Puerto Rico reported the first locally transmitted infection in December 2015, but Zika is likely to spread to the USA[1].

Zika virus infection usually is asymptomatic or causes mild illness, such as fever, rash, muscle/joint pain, and conjunctivitis. Severe disease and fatalities are uncommon, but there are reports of neurological and autoimmune-like illness, particularly Guillain-Barré syndrome (GBS) and congenital neurological malformations. Most concerning is a possible association between ZIKV and microcephaly in babies born to infected mothers during pregnancy in Brazil and, retrospectively, in French Polynesia.

Brazil has reported more than 4,000 cases of suspected microcephaly in 2015, representing a 20-fold increase from 2010 through 2014 annual incidence. Evidence of the virus has been found in the placenta and amniotic fluid of mothers and in the brains of fetuses or newborns. Yet causation between ZIKV and microcephaly is not definitive.

Collecting neurological, autoimmune, and congenital malformation associated with ZIKV should allow proper surveillance of Zika spreading and clinical burden. To minimize harm to high-risk travelers, agencies should consider issuing travel advisories. The CDC launched a "level 2" Alert on January 15, alerting pregnant women to consider postponing travel to countries with ongoing ZIKV transmission; the agency's first-ever alert for pregnant women[2].

Targeting mosquitos

The *Aedes* mosquito is a daytime biter that transmits ZIKV as well as dengue, chikungunya, and yellow fever. It is present worldwide, posing a high risk for global transmission. While *Aedes aegypti* is the most common vector in tropical areas, *Aedes albopictus* may spread ZIKV in other latitudes where this mosquito is now well adapted, such as the coasts of the USA and the Western Mediterranean basin. What steps are required now to halt it?

Mosquito-borne diseases require reducing source populations, including physical (e.g., removing water-containing sources) and biological (e.g., fish that feed on larvae) controls. Insecticide spraying of mosquito habitats or adult populations can be effective. Although it remains controversial due to ecological concerns, releasing genetically modified sterile male mosquitoes could reduce disease-transmitting mosquito larvae.

Health information campaigns should advise the public to avoid mosquito exposure, such as by wearing appropriate clothing, using insect repellents, and spraying insecticide in indoor spaces. Staying inside protected dwellings during peak mosquito biting hours can also reduce risk. Using physical barriers such as screens, closed windows, and bed nets can reduce mosquito bites.

Zika transmission by transfusion and sex

Given its potential for transmission by transfusion, the U.S. Red Cross has requested blood donors to defer 28 days after visiting Zika areas.

On February 5, 2016, the CDC recommended that men with a pregnant partner should use a condom or abstain from sex for the duration of the pregnancy if they have visited, or live in, an area where mosquitos are spreading ZIKV, which is strongly suspected of causing microcephaly in newborns. Although ZIKV has recently been isolated from saliva, the CDC acknowledged that it lacked the data to make any pronouncement on the risk for transmission by saliva shared in a kiss. The CDC also said that pregnant women who have visited countries and territories plagued by the virus, mostly in Latin America, should be tested for it even if they do not exhibit symptoms of infection. Earlier guidelines had limited testing to symptomatic pregnant women.

The issue of sexual transmission loomed large earlier this week when the health department of Dallas County, Texas, announced that a person had acquired the virus after sexual contact with another person who had just returned from a Zika outbreak region[3]. Semen may have large quantities of viable virus, for at least a short period of time. The data on saliva and urine is less clear. The CDC is trying to determine the length of "virus persistence" in semen, but the research results are weeks or months away, they said.

An estimated 80% of Zika infections are asymptomatic, and most of the remainder are self-limited. No specific antiviral treatment is available and care is supportive, with symptoms usually resolving within seven days. Severe GBS cases can require intensive care, including mechanical ventilation. Diagnostic testing is not optimal because antibody tests could cross-react, giving false-positive results due to other flavivirus infections (e.g., dengue) or immunizations (e.g., yellow fever). Commercial tests are unavailable. Research on ZIKV vaccines has become a priority[4]. Similarly, understanding which individuals are at increased risk of GBS could allow specific antiviral treatment. The NIH launched a Zika vaccine initiative in late 2015, and Brazil has expedited vaccine development. Vaccines against yellow fever have been licensed for decades, and Brazil, Mexico, and the Philippines approved the first dengue vaccine in 2015.

Countries experiencing major ZIKV outbreaks, such as Brazil, with possible neurological, autoimmune, and congenital malformation associations should implement special measures. This is of particular concern as the 2016 Olympics in Rio de Janeiro loom.

References

1. Fauci AS, Morens DM. Zika Virus in the Americas--Yet Another Arbovirus Threat. N Engl J Med. 2016;374:601-4.
2. Centers for Disease Control and Prevention. Zika and pregnancy. 2016. Available at: www.cdc.gov/zika.
3. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015;21:359-61.
4. Lucey, DR, Gostin LO. The Emerging Zika Pandemic: Enhancing Preparedness. JAMA. 2016. (Epub ahead of print).

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New Insights into HIV-1 Persistence in Sanctuary Sites During Antiretroviral Therapy

Current combinations of antiretroviral drugs for the treatment of HIV infection can successfully achieve and maintain long-term suppression of HIV-1 replication in plasma. Still, none of these therapies is capable of eradicating the virus from the long-lived cellular reservoir that represents the major barrier to HIV cure.

Lymphoid tissue is a key reservoir established by HIV-1 particles during acute infection. It is largely responsible for virus production, even in a context of suppressed plasma viremia. Viral rebound detected in blood from HIV-treated patients with suppressed viremia is thought to occur by intermittent HIV production, due to the reactivation of a small number of latently infected cells, from the long-lived reservoir, instead of low-level ongoing HIV replication. This idea is supported because viral genetic evolution or selection of drug resistance occurs over time in the blood of HIV patients who have maintained suppressed viremia. On the other hand, several studies have suggested that antiretroviral drug concentrations in lymphoid tissue are lower than in blood. Thus, it remains unknown if viral replication still takes place in lymphoid tissue reservoirs.

New insights into the dynamics of HIV-1 infection within the host have been recently published[1], revealing that HIV-1 can continue to replicate and replenish the HIV reservoir despite potent antiretroviral therapy and undetectable plasma viremia. The authors deep sequenced HIV-1 DNA from blood and inguinal lymph nodes collected from three HIV patients at different time points during the first six months of antiretroviral therapy. They found how the virus evolved over time, reflecting ongoing HIV replication, but without selecting drug resistance mutations. To provide an explanation of these findings, they presented a spatial and dynamic model of HIV-1 persistence in the lymphoid tissue sanctuary sites where drug pressure was not enough to block virus replication.

Considering this model, in a context of low drug concentration, drug-sensitive HIV variants are more fit and replicate at higher levels than partially drug-resistant strains. The drug selective pressure on the replicating virus population is too low to confer a competitive advantage to drug resistance strains. Therefore, only in a context of intermediate drug concentrations, drug-resistant strains would start to emerge and finally dominate at high drug concentrations.

This study provides a new look at HIV persistence in patients with suppressed viremia, and highlights the relevance of adequate penetrance and spatial distribution of antiretroviral drugs in lymphoid tissue to fully suppress HIV replication. These findings must be considered for the design of new strategies to eliminate the HIV reservoir in the complex path to find a HIV cure. The availability of drugs against HIV infection with greater tissue penetration and greater ability to completely inhibit viral replication in reservoirs is still an unmeet need.

References

1. Lorenzo-Redondo R, Fryer HR, Bedford T et al. Persistent HIV-1 replication maintains the tissue reservoir during therapy. Nature. 2016;530:51-6.

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