

# UPDATES FROM US HEALTH AGENCIES

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Recent activity in government and non-government agencies may affect readers of *Ethnicity & Disease* and other healthcare professionals working with ethnic minority and under-served populations. Below are some current items of interest.

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## FROM THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

### Influenza Virus in 1918 and Today

The influenza virus that wreaked worldwide havoc in 1918 and 1919 founded a viral dynasty that persists to this day, according to scientists from NIAID. Authors Anthony S. Fauci, MD, Jeffery K. Taubenberger, MD, PhD, and David M. Morens, MD, argue that we have lived in an influenza pandemic era since 1918, and they describe how the novel 2009 H1N1 virus now circling the globe is yet another manifestation of this enduring viral family.

“The 1918–1919 influenza pandemic was a defining event in the history of public health,” says NIAID Director Fauci. “The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for nine decades.”

Influenza viruses have 8 genes, 2 of which code for virus surface proteins—hemagglutinin (H) and neuraminidase (N)—

that allow the virus to enter a host cell and spread from cell to cell. There are 16 H subtypes and 9 N subtypes, and therefore, 144 possible HN combinations. However, only 3 (H1N1, H2N2, and H3N2) have ever been found in influenza viruses that are fully adapted to infect humans. Other combinations, such as avian influenza H5N1, occasionally infect people, but they are bird viruses, not human viruses.

“The eight influenza genes can be thought of as players on a team: certain combinations of players may arise through chance and endow the virus with new abilities, such as the ability to infect a new type of host,” says Dr Morens. That is likely what happened to spark the 1918 pandemic. Scientists have shown that the founding virus was an avian-like virus. The virus had a novel set of 8 genes and—through still-unknown mechanisms—gained the ability to

infect people and spread readily from person to person.

Not only did the 1918 H1N1 virus set off an explosive pandemic in which tens of millions died, during the pandemic the virus was transmitted from humans to pigs, where—as it does in people—it continues to evolve to this day. “Ever since 1918, this tenacious virus has drawn on a bag of evolutionary tricks to survive in one form or another... and to spawn a host of novel progeny viruses with novel gene constellations, through the periodic importation or exportation of viral genes,” write the NIAID authors.

“All human-adapted influenza A viruses of today—both seasonal variations and those that caused more dramatic pandemics—are descendants, direct or indirect, of that founding virus,” notes Dr Taubenberger. “Thus we can be said to be living in a pandemic era that began in 1918.”

While the dynasty founded by the virus of 1918 shows little

evidence of being overthrown, the NIAID authors note that there may be some cause for optimism. When viewed through a long lens of many decades, it does appear that successive pandemics and outbreaks caused by later generations of the 1918 influenza dynasty are decreasing in severity, notes Dr Morens. This is due in part to advances in medicine and public health measures, he says, but this trend also may reflect viral evolutionary pathways that favor increases in the virus’s ability to spread from host to host, combined with decreases in its tendency to kill those hosts.

“Although we must be prepared to deal with the possibility of a new and clinically severe influenza pandemic caused by an entirely new virus, we must also understand in greater depth, and continue to explore, the determinants and dynamics of the pandemic era in which we live,” conclude the authors.

FROM THE NATIONAL INSTITUTE OF ALLERGY AND  
INFECTIOUS DISEASES (NIAID)

Scientists Learn Why Even Treated Genital Herpes  
Sores Boost the Risk of HIV Infection

New research helps explain why infection with herpes simplex virus-2 (HSV-2), which causes genital herpes, increases the risk for HIV infection even after successful treatment heals the genital skin sores and breaks that often result from HSV-2. Scientists have uncovered details of an immune-cell environment conducive to HIV infection that persists at the location of HSV-2 genital skin lesions long after they have been treated with oral doses of the drug acyclovir and have healed and the skin appears normal.

“The findings of this study mark an important step toward understanding why HSV-2 infection increases the risk of acquiring HIV and why acyclovir treatment does not reduce that risk,” says NIAID Director Anthony S. Fauci, MD. “Understanding that even treated HSV-2 infections provide a cellular environment conducive to HIV infection suggests new directions for HIV prevention research, including more powerful anti-HSV therapies and ideally an HSV-2 vaccine.”

One of the most common sexually transmitted infections worldwide, HSV-2 is associated with a 2- to 3-fold increased risk for HIV infection. Some HSV-2-infected people have recurring sores and breaks in genital skin,

and it has been hypothesized that these lesions account for the higher risk of HIV acquisition. However, recent clinical trials, including an NIAID-funded study completed last year, demonstrated that successful treatment of such genital herpes lesions with the drug acyclovir does not reduce the risk of HIV infection posed by HSV-2. The current study sought to understand why this is so and to test an alternative theory.

The research team took biopsies of genital skin tissue from 8 HIV-negative men and women who were infected with HSV-2. These biopsies were taken at multiple time points: when the patients had genital herpes sores and breaks in the skin, when these lesions had healed, and at 2, 4, and 8 weeks after healing. The researchers also took biopsies from 4 of the patients when herpes lesions reappeared and the patients underwent treatment with oral acyclovir. The scientists continued to take biopsies at regular intervals for 20 weeks after the lesions had healed. For comparison, the investigators also took biopsies from genital tissue that did not have herpes lesions from the same patients.

Previous research has demonstrated that immune cells involved in the body’s response to

infection remain at the site of genital herpes lesions even after they have healed. The scientists conducting the current study made several findings about the nature of these immune cells. First, they found that CD4+ T cells—the cells that HIV primarily infects—populate tissue at the sites of healed genital HSV-2 lesions at concentrations 2–37 times higher than in unaffected genital skin. Treatment with acyclovir did not reduce this long-lasting, high concentration of HSV-2-specific CD4+ T cells at the sites of healed herpes lesions.

Second, the scientists discovered that a significant proportion of these CD4+ T cells carried CCR5 or CXCR4, the cell-surface proteins that HIV uses (in addition to CD4+ T cells) to enter cells. The percentage of CD4+ T cells expressing CCR5 during acute HSV-2 infection and after healing of genital sores was twice as high in biopsies from the sites of these sores as from unaffected control skin. Moreover, the level of CCR5 expression in CD4+ T cells at the sites of healed genital herpes lesions was similar for patients who had been treated with acyclovir as for those who had not.

Third, the scientists found a significantly higher concentration of immune cells called dendritic cells with the surface protein called DC-SIGN at the

sites of healed genital herpes lesions than in control tissue, whether or not the patient was treated with acyclovir. Dendritic cells with DC-SIGN ferry HIV particles to CD4+ T cells, which the virus infects. The DC-SIGN cells often were near CD4+ T cells at the sites of healed lesions—an ideal scenario for the rapid spread of HIV infection.

Finally, using biopsies from 2 study participants, the scientists found laboratory evidence that HIV replicates 3–5 times as quickly in cultured tissue from the sites of healed HSV-2 lesions than in cultured tissue from control sites.

All 4 of these findings help explain why people infected with HSV-2 are at increased risk of acquiring HIV than people who are not infected with HSV-2, even after successful acyclovir treatment of genital lesions.

The investigators conclude that reducing the HSV-2-associated risk of HIV infection will require diminishing or eliminating the long-lived immune-cell environment created by HSV-2 infection in the genital tract, ideally through an HSV vaccine. Further, they hypothesize that other sexually transmitted infections may create similar cellular environments conducive to HIV infection, explaining why sexually transmitted infections in general are a risk factor for acquiring HIV.

FROM THE NATIONAL INSTITUTE OF ALLERGY AND  
INFECTIOUS DISEASES (NIAID)

**Genes Key to *Staphylococcus* Disease Severity, Drug Resistance Found Hitchhiking Together**

Scientists studying staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA), have discovered a potent toxin responsible for disease severity. They also found the gene for the toxin traveling with a genetic component of staphylococci that controls resistance to antibiotics. The study shows for the first time that genetic factors that affect staphylococcal virulence and drug resistance can be transferred between strains in 1 exchange event.

One of the ways staphylococci become drug resistant is through horizontal gene transfer, whereby resistance genes move from one bacterium to another. Staphylococci also can exchange virulence genes using the same

mechanism, but this was previously assumed to occur separately from the transfer of antibiotic resistance.

The research involved more than 100 strains of *S aureus* and *S epidermidis*, both bacteria found on the skin of most people. In recent decades, these bacteria have become increasingly virulent, often causing severe disease that can be resistant to traditional antibiotics such as methicillin.

The studies were directed by NIAID senior investigator Michael Otto, PhD. In 2007, he and his colleagues found that staphylococci secrete toxins of the phenol-soluble modulins (PSM) family that are primarily responsible for attracting and killing human neutrophils. This

process is critical for the ability of *S aureus*—including community-acquired MRSA—to cause disease.

While screening *S aureus* and *S epidermidis* strains, Dr Otto's group noticed that some strains produced 1 additional, previously unknown, PSM toxin. The researchers hypothesized that the toxin was somehow connected to drug resistance. This idea surfaced because the toxin appeared in 10% of all MRSA strains and 68% of all methicillin-resistant *S epidermidis* strains analyzed—whereas the researchers did not find it in strains of *S aureus* or *S epidermidis* that were sensitive to methicillin.

The research group confirmed its theory by identifying the specific location that encodes the toxin, which was in gene clusters that control drug resis-

tance, known as SCC*mec*. The group named the new toxin PSM-*mec*.

“This work represents a previously unknown example of a toxin hitchhiking on staphylococcal mobile genetic elements that are primarily in charge of transferring antibiotic resistance,” says Dr. Otto. He adds that the finding “should alert the research community that aggressive, drug-resistant staph can evolve more quickly than we assumed.”

The research group is continuing its study of PSM-*mec* in *S epidermidis*, where the toxin is more prevalent. Ultimately, being able to neutralize PSM-*mec* and other toxins that attack human defenses could lead to new treatments for *S aureus* and *S epidermidis* disease.