University of Southern California School of Dentistry

Center for Diagnostic Sciences BULLETIN

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This bulletin focuses on Influenza. We thank Dr. Matt Lee for his contribution to this issue. As always, we invite your comments, questions, and suggested topics for future bulletins. Please forward your comments to Ms. Latresa Lawson at llawson@usc.edu or (213) 821-2336.

Influenza, Avian Flu, and the Potential for a 2004 Pandemic

Why do we worry about influenza?

Influenza represents the most significant viral cause of morbidity, contributing to 20,000 U.S. deaths per year. Despite enormous economic burdens, the greater concern is the potential for devastating pandemics. The Spanish influenza pandemic of 1918 infected 25 to 30% of the world's population and resulted in 40 million deaths, including 600,000 Americans. It was the most catastrophic epidemic since the "Black Death" of the 14th century. At its peak, some U.S. cities were recording 10,000 deaths per week, mostly in the 18 to 30 age range. Subsequent pandemics in 1957 (the "Asian flu") and 1968 (the "Hong Kong flu"), while less devastating, also contributed to tens of thousands of American deaths.

How can I recognize influenza?

Influenza is a seasonal respiratory tract infection, usually with a sudden onset and including the following symptoms: fever, headache, fatigue (often severe), dry cough, sore throat, nasal congestion, and myalgia. Influenza viruses do **not** infect the gastrointestinal tract. The peak incidence is in the winter, usually February. Infection is usually spread through the deposition of respiratory droplets (e.g., coughing or sneezing) on oral or nasal mucosa. Infection can occur through hand-mouth or hand-nose transmission. The incubation period is 1 to 4 days, and usually 2 days. Adults are infectious 1 day before symptoms begin, and continue to shed virions for approximately 6 days. Young children may begin shedding virus up to 6 days prior to the beginning of symptoms, and immunocompromised hosts may shed virus for weeks or months.

Influenza infections may be difficult to distinguish from that of other viruses, and laboratory testing may be helpful. From a public health standpoint, the most important assay is viral culture, which allows viral subtyping. This may require 5 to 10 days. Rapid antibody-based diagnostic tests are available from a number of manufacturers and are more commonly used in outpatient settings. These are approximately >70% sensitive and >90% specific.

What causes influenza?

The causative organisms are influenza A and B, which are RNA viruses found in mammals and birds. In the 1990's, approximately 90% of U.S. influenza cases were due to influenza A, which is the type associated with pandemic influenza. Influenza A variants are antigenically classified on the basis of the two major surface glycoproteins: hemagglutinin protein (HA), which attaches the incoming virus to sialic-acid containing receptors on host-cell plasma membranes; and neuraminidase (NA), which mediates the release of progeny virus from host-cell membranes. The 1918 Spanish flu strain is designated H1N1, the 1957 Asian flu strain is H2N2, and the 1968 Hong Kong flu is H3N2. The antigenic drift of the virus has prevented the development of a vaccine that induces long-lasting protection, and public health agencies worldwide strive to identify incipient epidemic strains in order to have appropriate vaccines available prior to the start of the next influenza season.

Where do unusually pathogenic strains of influenza come from?
Unusually pathogenic influenza A strains arise when nonhuman influenza genes are incorporated into human viruses, creating novel subtypes to which humans have little if any natural immunity.

A large influenza reservoir is found in wild waterfowl, and genetic material from avian influenza is occasionally incorporated into human strains. However, avian influenza strains must acquire a number of specific adaptations before they can efficiently replicate in humans. Pigs may play an important intermediate role in this process. Swine are susceptible to both avian and mammalian influenza, and a number of viral recombinations have been isolated from pigs.

Why is there increased attention to influenza this year?
In 1997, an avian H5N1 strain spread directly from chickens into people, killing 6. Until then, direct infection of humans by avian influenza had not been reported. This significant development may accelerate adaptations necessary for avian strains to pass from human to human, thereby fulfilling the conditions necessary for a new pandemic. In early 2003, the H5N1 strain reappeared in Hong Kong, where two family members died and a third was hospitalized after a visit to Mainland China. Concomitant rumors of a rampant respiratory disease in China (subsequently identified as SARS, caused by a novel coronavirus) prompted the World Health Organization to issue a pandemic alert.

Fortunately, the 2003 outbreak did not represent the appearance of a human-competent influenza A strain, as initially feared. However, one year later H5N1 has reappeared in Southeast Asia, passing directly from chickens to humans in Thailand and Vietnam. At the date of this writing (9 February 2004), 23 laboratory-confirmed cases and 18 deaths have been reported, the most recent being 2 young women, aged 16 and 17, and a young man of 23.

This is in sharp contrast to the usual restriction of influenza mortality to the elderly, immunocompromised, or neonatal populations. Development of human competence in this strain could recapitulate the 1918 pandemic.

What can be done about avian influenza?
The primary control measure being implemented is destruction of infected poultry flocks. This may prove difficult among impoverished rural areas of Vietnam and Thailand, where most households maintain small poultry flocks.

In this context, the recombination of human and avian strains, while statistically improbable on an individual basis, may become very likely. If H5N1 avian influenza does acquire the ability to spread among humans, the primary response would be to develop a vaccine as rapidly as possible. Against human influenza A, vaccines are nearly 90% effective and should be considered for all individuals at high risk, including the elderly, immunocompromised individuals, and selected health professionals. Currently available vaccines will not be effective against avian influenza.

What can I do to protect my staff and my patients?
In the outpatient clinic setting, a number of infection control procedures are recommended for seasonal influenza, and may become mandatory in an epidemic situation. Signs in appropriate languages should be posted requesting patients and escorts to inform staff of a respiratory infection, and to practice appropriate respiratory etiquette.

Respiratory Hygiene/Cough Etiquette: Cover the mouth and nose when coughing or sneezing; contain secretions with tissues and deposit them immediately in a closed waste receptacle; wash hands after contact with secretions. Clinics should provide tissues, no-touch waste receptacles, and hand-washing facilities or alcohol-based hand rubs. Clinical staff should observe droplet precautions and use masks (N-95 respirators are not required). Health care workers should be immunized and, if ill, restricted from working. Patients who are ill should be encouraged to reschedule non-emergency appointments.

What medications can be used against influenza?

Two classes of drugs have been used against influenza. The neuraminidase inhibitors oseltamivir (Tamiflu, Roche) and zanamivir (Relenza, Glaxo Wellcome), which prevent detachment of the progeny virus from the cell wall, are most effective taken prophylactically. The M2 blockers amantadine (Symmetryl, DuPont) and rimantidine (Flumadine, Forest) interfere with the uncoating of the virus; they are inexpensive and well-tolerated.

For human influenza, antiviral medications are most useful for arresting the spread of institutional outbreaks. Chemoprophylaxis should be considered for unvaccinated health care workers who have close contact with influenza patients, and, ideally, should be continued for 2 weeks following vaccination. When used prophylactically, these agents are 70 to 90% effective for preventing illness among adults. When started within 48 hours of the onset of symptoms, the duration of illness and the shedding of viruses may both be reduced. However, in the event of a major outbreak, the use of antiviral agents must be balanced against available supplies. Initial reports from Vietnam suggest that the M2 blockers are uniformly ineffective against H5N1 influenza.

Do antibiotics have a role in influenza?

Antibiotic therapy is ineffective against viruses; however, the majority of the 1918 pandemic victims succumbed to bacterial pneumonia superinfections. The existence of viruses was controversial at the time, and the gram negative bacillus *Hemophilus influenzae* was proposed by eminent bacteriologist Richard Pfieffer as the pathogenic organism for the 1889 influenza epidemic. The most common bacteria associated with influenza are *Streptococcus pneumonia* and *Staphylococcus aureus*. While routine antibiotic coverage for influenza is not recommended, a high index of suspicion should be maintained, and presumptive antibiotic therapy should be directed against these organisms.

Did you know?

- 1557 screenings were done in CDS between 9/29/03 and 2/26/04.
- 1201 new patients were accepted for treatment in Group Practices during that period.
- 258 patients were referred to other programs at USCSD during that period.