



EDUCATIONAL OBJECTIVE: Readers will be aware of the latest recommendations for vaccination against 2009 pandemic influenza A (H1N1)

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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Update on 2009 pandemic influenza A (H1N1) virus

ABSTRACT

The pandemic of a novel strain of swine-origin influenza A (H1N1) is expected to make this a difficult flu season. Fortunately, this strain is relatively mild, and the principles of prevention, diagnosis, and treatment remain the same. Physicians will have a number of complex decisions to make about when to test, when to treat, and when to simply reassure.

KEY POINTS

Vaccination this season will require two vaccines: a trivalent vaccine for seasonal influenza and a monovalent vaccine for 2009 pandemic influenza A (H1N1).

Recent studies indicate that the monovalent vaccine for 2009 pandemic influenza A (H1N1) may require only one injection.

To date, 2009 pandemic influenza A (H1N1) virus has not been exceptionally virulent and differs from conventional influenza in that it seems to disproportionately affect children and young adults. Pregnant women are at a higher risk of complications.

Most people with 2009 pandemic influenza A (H1N1) do not need to be tested, treated, or seen by a clinician.

Antiviral drugs should be reserved only for those at high risk of influenza complications.

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A 69-YEAR-OLD OHIO MAN with leukemia was treated in another state in late June. During the car trip back to Ohio, he developed a sore throat, fever, cough, and nasal congestion. He was admitted to Cleveland Clinic with a presumed diagnosis of neutropenic fever; his absolute neutrophil count was $0.4 \times 10^9/L$ (reference range 1.8–7.7). His chest radiograph was normal. He was treated with empiric broad-spectrum antimicrobials. On his second day in the hospital, he was tested for influenza by a polymerase chain reaction (PCR) test, which was positive for influenza A. He was moved to a private room and started on oseltamivir (Tamiflu) and rimantadine (Flumadine). The patient's previous roommate subsequently tested positive for influenza A, as did two health care workers working on the ward. All patients on the floor received prophylactic oseltamivir.

The patient's condition worsened, and he subsequently went into respiratory distress with diffuse pulmonary infiltrates. He was transferred to the intensive care unit, where he was intubated. Influenza A was isolated from a bronchoscopic specimen. He subsequently recovered after a prolonged course and was discharged on hospital day 50. Testing by the Ohio Department of Health confirmed that this was the 2009 pandemic influenza A (H1N1) virus.

THE CHALLENGES WE FACE

We are now in the midst of an influenza pandemic of the 2009 influenza A (H1N1) virus, with *pandemic* defined as “worldwide sustained community transmission.” The circulation of seasonal and 2009 pandemic influenza A (H1N1) strains will make this flu season both

interesting and challenging.

The approaches to vaccination, prophylaxis, and treatment will be more complex. As of this writing (mid-September 2009), it is clear that we will be giving two influenza vaccines this season: a trivalent vaccine for seasonal influenza, and a monovalent vaccine for pandemic H1N1. It appears the monovalent vaccine may require only one dose to provide protective immunity.¹ Fortunately, the vast majority of cases of pandemic H1N1 are relatively mild and uncomplicated. Still, some people are at higher risk of complications, including young patients, pregnant women, and people with immune deficiency or concomitant health conditions that put them at higher risk of flu-associated complications. Thus, clinicians will need to be educated about whom to test, who needs prophylaxis, and who should not be treated.

As our case demonstrates, unsuspected cases of influenza in hospitalized patients or health care workers working with influenza pose the greatest threat for transmission of influenza within the hospital. Adults hospitalized with influenza tend to present late (more than 48 hours after the onset of symptoms) and tend to have prolonged illness.² Ambulatory adults shed virus for 3 to 6 days; virus shedding is more prolonged for hospitalized patients. Antiviral agents started within 4 days of illness enhance viral clearance and are associated with a shorter stay.³ Therefore, we should have a low threshold for testing for influenza and for isolating all suspected cases.

This is also creating a paradigm shift for health care workers, who are notorious for working through an illness. If you are sick, stay home! This applies whether you have pandemic H1N1 or something else.

■ EPIDEMIOLOGY OF PANDEMIC 2009 INFLUENZA A (H1N1) VIRUS

The location of cases can now be found on Google Maps; the US Centers for Disease Control and Prevention (CDC) provides weekly influenza reports at www.cdc.gov/flu/weekly/fluactivity.htm.

Pandemic H1N1 appeared in the spring of 2009, and cases continued to mount all summer in the United States (when influenza is

normally absent) and around the world. In Mexico in March and April 2009, 2,155 cases of pneumonia, 821 hospitalizations, and 100 deaths were reported.⁴

In contrast with seasonal influenza, children and younger adults were hit the hardest in Mexico. The age group 5 through 59 years accounted for 87% of the deaths (usually, they account for about 17%) and 71% of the cases of severe pneumonia (usually, they account for 32%). These observations may be explained in part by the possibility that people who were alive during the 1957 pandemic (which was an H1N1 strain) have some immunity to the new virus. However, the case-fatality rate was highest in people age 65 and older.⁴

As of July 2009, there were more than 43,000 confirmed cases of pandemic H1N1 in the United States, and actual cases probably exceed 1 million, with more than 400 deaths. An underlying risk factor was identified in more than half of the fatal cases.⁵ Ten percent of the women who died were pregnant.

Pandemic H1N1 has several distinctive epidemiologic features:

- The distribution of cases is similar across multiple geographic areas.
- The distribution of cases by age group is markedly different than that of seasonal influenza, with more cases in school children and fewer cases in older adults.
- Fewer cases have been reported in older adults, but this group has the highest case-fatality rate.

■ 2009 PANDEMIC H1N1 IS A MONGREL

There are three types of influenza viruses, designated A, B, and C. Type A undergoes antigenic shift (rapid changes) and antigenic drift (gradual changes) from year to year, and so it is the type associated with pandemics. In contrast, type B undergoes antigenic drift only, and type C is relatively stable.

Influenza virus is subtyped on the basis of surface glycoproteins: 16 hemagglutinins and nine neuraminidases. The circulating subtypes change every year; the current circulating human subtypes are a seasonal subtype of H1N1 that is different than the pandemic H1N1 subtype, and H3N2.

The 2009 pandemic H1N1 is a new virus

For updates,
see
[www.cdc.gov/
flu/weekly/
fluactivity.htm](http://www.cdc.gov/flu/weekly/fluactivity.htm)

never seen before in North America.⁶ Genetically, it is a mongrel, coming from three recognized sources (pigs, birds, and humans) which were combined in pigs.⁷ It is similar to subtypes that circulated in the 1920s through the 1940s.

Most influenza in the Western world comes from Asia every fall, and its arrival is probably facilitated by air travel. The spread is usually unidirectional and is unlikely to contribute to long-term viral evolution.⁸ It appears that 2009 H1N1 virus is the predominant strain circulating in the current influenza season in the Southern Hemisphere. Virologic studies indicate that the H1N1 virus strain has remained antigenically stable since it appeared in April 2009. Thus, it appears likely that the strain selected by the United States for vaccine manufacturing will match the currently circulating seasonal and pandemic H1N1 strains.

■ VACCINATION IS THE FIRST LINE OF DEFENSE

In addition to the trivalent vaccine against seasonal influenza, a monovalent vaccine for pandemic H1N1 virus is being produced. The CDC has indicated that 45 million doses of pandemic influenza vaccine are expected in October 2009, with an average of 20 million doses each week thereafter. It is anticipated that half of these will be in multidose vials, that 20% will be in prefilled syringes for children over 5 years old and for pregnant women, and that 20% will be in the form of live-attenuated influenza vaccine (nasal spray). The inhaled vaccine should not be given to children under 2 years old, to children under 5 years old who have recurrent wheezing, or to anyone with severe asthma. Neither vaccine should be given to people allergic to hen eggs, from which the vaccine is produced.

An ample supply of the seasonal trivalent vaccine should be available. Once the CDC has more information about specific product availability of the pandemic H1N1 vaccine, that vaccine will be distributed. It can be given concurrently with seasonal influenza vaccine.

Several definitions should be kept in mind when discussing vaccination strategies. *Supply*

is the number of vaccine doses available for distribution. *Availability* is the ability of a person recommended to be vaccinated to do so in a local venue. *Prioritization* is the recommendation to vaccination venues to selectively use vaccine for certain population groups first. *Targeting* is the recommendation that immunization programs encourage and promote vaccination for certain population groups.

The Advisory Committee on Immunization Practices and the CDC recommend both seasonal and H1N1 vaccinations for anyone 6 months of age or older who is at risk of becoming ill or of transmitting the viruses to others. Based on a review of epidemiologic data, the recommendation is for targeting the following five groups for H1N1 vaccination: children and young adults aged 6 months through 24 years; pregnant women; health care workers and emergency medical service workers; people ages 25 through 64 years who have certain health conditions (eg, diabetes, heart disease, lung disease); and people who live with or care for children younger than 6 months of age. This represents approximately 159 million people in the United States.

If the estimates for the vaccine supply are met, and if pandemic H1N1 vaccine requires only a single injection, there should be no need for prioritization of vaccine. If the supply of pandemic H1N1 vaccine is inadequate, then those groups who are targeted would also receive the first doses of the pandemic H1N1 vaccine. It should be used only with caution after consideration of potential benefits and risks in people who have had Guillain-Barré syndrome during the previous 6 weeks, in people with altered immunocompetence, or in people with medical conditions predisposing to influenza complications.

A mass vaccination campaign involving two separate flu vaccines can pose challenges in execution and messaging for public health officials and politicians. In 1976, an aggressive vaccination program turned into a disaster, as there was no pandemic and the vaccine was associated with adverse effects such as Guillain-Barré syndrome. The government and the medical profession need to prepare for a vaccine controversy and to communicate and continue to explain the plan to the public. As pointed out in a recent op-ed piece,⁹ we

The 2009 pandemic H1N1 is a new virus never seen before in North America

would hope that all expectant women in the fall flu season will get the flu vaccines. We also know that, normally, one in seven pregnancies would be expected to miscarry. The challenge for public health officials and physicians will be to explain to these patients that there may be an association rather than a causal relationship.

In health care workers, the average vaccination rate is only 37%. We should be doing much better. Cleveland Clinic previously increased the rate of vaccination among its employees via a program in which all workers must either be vaccinated or formally declare (on an internal Web site) that they decline to be vaccinated.¹⁰ This season, even more resources are being directed at decreasing the barriers to flu vaccinations for our health care workers with the support from hospital leadership.

■ INFECTION CONTROL IN THE HOSPITAL AND IN THE COMMUNITY

Influenza is very contagious and is spread in droplets via sneezing and coughing (within a 3-foot radius), or via unwashed hands—thus the infection-control campaigns urging you to cover your cough and wash your hands.

As noted, for patients being admitted or transferred to the hospital, we need to have a low threshold for testing for influenza and for isolating patients suspected of having influenza. For patients with suspected or proven seasonal influenza, transmission precautions are those recommended by the CDC for droplet precautions (www.cdc.gov/ncidod/dhqp/gl_isolation_droplet.html). A face mask is deemed adequate to protect transmission when coming within 3 feet of an infected person. CDC guidelines for pandemic H1N1 recommends airborne-transmission-based precautions for health care workers who are in close contact with patients with proven or possible H1N1 (www.cdc.gov/ncidod/dhqp/gl_isolation_airborne.html). This recommendation implies the use of fit-tested N95 respirators and negative air pressure rooms (if available).

The recent Institute of Medicine report, *Respiratory Protection for Health-care Workers in the Workplace Against Novel H1N1 Influenza A* (www.iom.edu/

[CMS/3740/71769/72967/72970.aspx](http://www.cdc.gov/ncidod/dhqp/gl_isolation_airborne.html)) endorses the current CDC guidelines and recommends following these guidelines until we have evidence that other forms of protection or guidelines are equally or more effective.

Personally, I am against this requirement because it creates a terrible administrative burden with no proven benefit. Requiring a respirator means requiring fit-testing, and this will negatively affect our ability to deliver patient care. Recent studies have shown that surgical masks may not be as effective¹¹ but are probably sufficient. Lim et al¹² reported that 79 (37%) of 212 workers who responded to a survey experienced headaches while wearing N95 masks. This remains a controversial issue.

Besides getting the flu shot, what can one do to avoid getting influenza or transmitting to others?

- Cover your cough (cough etiquette) and sneeze.
- Practice good hand hygiene.
- Avoid close contact with people who are sick.
- Do not go to school or work if sick.

A recent study of influenza in households suggested that having the person with flu and household contacts wear face masks and practice hand hygiene within the first 36 hours decreased transmission of flu within the household.¹³

The United States does have a national influenza pandemic plan that outlines specific roles in the event of a pandemic, and I urge you to peruse it at www.hhs.gov/pandemicflu/plan/.

■ RECOGNIZING AND DIAGNOSING INFLUENZA

The familiar signs and symptoms of influenza—fever, cough, muscle aches, and headache—are nonspecific. Call et al¹⁴ analyzed the diagnostic accuracy of symptoms and signs of influenza and found that fever and cough during an epidemic suggest but do not confirm influenza, and that sneezing in those over age 60 argues against influenza. They concluded that signs and symptoms can tell us whether a patient has an influenza-like illness, but do not confirm or exclude the diagnosis of influenza: “Clinicians need to consider whether influenza is circulat-

Health care workers who have the flu should stay home

ing in their communities, and then either treat patients with influenza-like illness empirically or obtain a rapid influenza test.”¹⁴

The signs and symptoms of pandemic 2009 H1N1 are the same as for seasonal flu, except that about 25% of patients with pandemic flu develop gastrointestinal symptoms. It has not been more virulent than seasonal influenza to date.

Should you order a test for influenza?

Most people with influenza are neither tested nor treated. Before ordering a test for influenza, ask, “Does this patient actually have influenza?” Patients diagnosed with “influenza” may have a range of infectious and noninfectious causes, such as vasculitis, endocarditis, or any other condition that can cause a fever and cough.

If I truly suspect influenza, I would still only order a test if the results would change how I manage the patient—for example, a patient being admitted to the hospital where isolation would be required.

Pandemic H1N1 will be detected only as influenza A in our current PCR screen for human influenza. The test does not differentiate between seasonal strains of influenza A (which is resistant to oseltamivir) and pandemic H1N1 (which is susceptible to oseltamivir). This means if you intend to treat, you will have to address further complexity.

Testing for influenza

The clinician should be familiar with the types of tests available. Each test has advantages and disadvantages¹⁵:

Rapid antigen assay is a point-of-care test that can give results in 15 minutes but unfortunately is only 20% to 30% sensitive, so a negative result does not exclude the diagnosis. The positive predictive value is high, meaning a positive test means the patient does have the flu.

Direct fluorescent antibody testing takes about 2.5 hours to complete and requires special training for technicians. It has a sensitivity of 47%, a positive predictive value of 95%, and a negative predictive value of 92%.

PCR testing takes about 6 hours and has a sensitivity of 98%, a positive predictive value of 100%, and a negative predictive value of

98%. This is probably the best test, in view of its all-around performance, but it is not a point-of-care test.

Culture takes 2 to 3 days, has a sensitivity of 89%, a positive predictive value of 100%, and a negative predictive value of 88%.

These tests can determine that the patient has influenza A, but a confirmatory test is always required to confirm pandemic H1N1. This confirmatory testing can be done by the CDC, by state public health laboratories, and by commercial reference laboratories.

■ ANTIVIRAL TREATMENT

Since influenza test results do not specify whether the patient has seasonal or pandemic influenza, treatment decisions are a sticky wicket. Most patients with pandemic H1N1 do not need to be tested or treated.

Several drugs are approved for treating influenza and shorten the duration of symptoms by about 1 day. The earlier the treatment is started, the better: the time of antiviral initiation affects influenza viral load and the duration of viral shedding.³

The neuraminidase inhibitors oseltamivir and zanamivir (Relenza) block release of virus from the cell. Resistance to oseltamivir is emerging in seasonal influenza A, while most pandemic H1N1 strains are susceptible.

Oseltamivir resistance in pandemic H1N1

A total of 11 cases of oseltamivir-resistant pandemic H1N1 have been confirmed worldwide, including 3 in the United States (2 in immunosuppressed patients in Seattle, WA). Ten of the 11 cases occurred with oseltamivir exposure. All involved a histidine-to-tyrosine substitution at position 275 (H275Y) of the neuraminidase gene. Most were susceptible to zanamivir.

Supplies of oseltamivir and zanamivir are limited, so they should be used only in those who will benefit the most, ie, those at higher risk of influenza complications. These include children under 5 years old, adults age 65 and older, children and adolescents on long-term aspirin therapy, pregnant women, patients who have chronic conditions or who are immunosuppressed, and residents of long-term care facilities. ■

I would test for influenza only if the results would change the way I manage the patient

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