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2009 H1N1 influenza: a pandemic

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The first cases of 2009 pandemic influenza A (H1N1) virus infection were documented in March 2009 and have subsequently caused a worldwide outbreak. The World Health Organization declared the first phase 6 global influenza pandemic of the century on June 11, 2009. As of November 2009, more than 47 million people in the United States have been infected and there have been more than 213,000 H1N1-related hospitalizations and approximately 10,000 H1N1-related deaths. The majority of illness is reported in the 18-64 years age group. The risk of illness, hospitalization, and death related to 2009 H1N1 is very age-specific and very different from seasonal influenza.

Seasonal outbreaks of influenza occur annually in the winter months of the Northern and Southern hemispheres. The factors that contribute to the course of the disease include virulence of the specific strain, the population infected, and underlying host medical conditions. The epidemiologic pattern reflects the changing nature of the antigenic properties of influenza viruses, and their subsequent spread depends on the susceptibility of the population.[1] Influenza A is an RNA virus that has a remarkable ability to undergo periodic changes in the antigenic characteristics of the envelope glycoproteins, the hemagglutinin, and the neuraminidase.

Influenza hemagglutinin (H) is a surface glycoprotein that binds to the respiratory epithelial cell surface glycoproteins. This process is necessary for the initiation of infection. After viral replication, progeny virions are also bound to the host cell. The protein neuraminidase (N) cleaves these links and liberates the new virions.[1,2] Major changes in these glycoproteins are referred to as *antigenic shifts* and minor changes are called *antigenic drifts*. Antigenic shifts are associated with epidemics and pandemics of influenza A, whereas antigenic drifts are associated with more localized outbreaks of varying extent and are more typical of what is seen between pandemics.[1]

Among influenza A viruses that infect humans, three major subtypes of hemagglutinins (H1, H2, and H3) and two subtypes of neuraminidases (N1 and N2) have been described. Influenza B viruses have a lesser propensity for antigenic changes, and only antigenic drifts in the hemagglutinin have been described. Influenza C causes mild disease that is not seasonal and only antigenic drifts have been reported.[1]

Pandemic influenza differs from epidemic influenza in that there are severe outbreaks that progress to involve all parts of the world, and it is associated with the emergence of a new virus to which the overall population has little or no immunity. Other characteristics include rapid transmission with concurrent outbreaks worldwide; the occurrence of diseases outside the usual seasonality, including the summer months; high attack rates in all age groups, with high levels of mortality, particularly in healthy young adults; and multiple waves of disease. The period between pandemics is variable (Table 1).[2]

The infamous pandemic Spanish influenza of 1918-1919 has remained a well-cited testament to the morbidity and mortality of influenza. This virus was associated with the

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Table 1 Major pandemics of the last century

Year	Designation	Name	Severity
1918	H1N1	Spanish (Swine) Flu	Severe
1957	H2N2	Asian Flu	Severe
1968	H3N2	Hong Kong Flu	Moderate
1977	H1N1	Russian Flu	Mild
2009	H1N1	Swine Flu	Severe

emergence of antigenic shifts in both hemagglutinin (H1) and neuraminidase (N1). It is estimated that approximately 50 million people worldwide (500,000 in the United States) died during this pandemic, with one-third of the world's population being infected. Fortunately, since that time there has been no influenza strain that has carried the same morbidity or mortality. The case mortality rate was >2.5% for the Spanish flu, whereas other pandemics have been <0.1%.[3]

The 1918-1919 Spanish influenza virus spread in three distinct waves—in Europe, Asia, and North America—with the first beginning in the spring of 1918 followed by more fatal second and third waves in the fall and winter months.[3] The pathogenicity has been investigated in a mouse model using a recombinant virus containing the same proteins as the original virus. Studies suggest hemagglutinin conferred enhanced pathogenicity in mice.[4] In addition, these recombinant viruses could induce high levels of chemokines and cytokines, resulting in inflammatory cell infiltration and severe hemorrhage, which were hallmarks of the illness seen during the pandemic.[2]

In March 2009, a respiratory illness outbreak occurred in Mexico, which was later identified as the 2009 H1N1 influenza A virus. As a result of airline travel, this illness spread to the United States and Canada, and subsequently around the world. The virus is a reassortment of two swine strains, one human strain, and one avian strain of influenza; the largest proportion of genes comes from the swine influenza viruses. This represented a major shift from the strains of virus responsible for seasonal influenza in the previous years. To date >99% of circulating influenza A has been identified as 2009 H1N1. At the time of this writing, 2009 H1N1 influenza A activity has peaked and is declining in North America and Canada. However, there is concern for a third wave of illness, especially for those who have not been immunized.[3]

The transmission of 2009 H1N1 is through respiratory secretions via large-particle droplets, just as it occurs for seasonal influenza. Sneezing, coughing, or contact with contaminated surfaces can lead to spread of the disease. Respiratory secretions and other body fluids should be considered infectious and avoided (i.e., diarrhea) (Table 2). According to the Centers for Disease Control and Prevention (CDC), the transmission rates are similar to seasonal influenza. The incubation period typically ranges from one to seven days, with the highest level of shedding occurring on days one to three and lasting for five to seven days. Viral shedding may last longer in immunocompromised patients, young children, and those with chronic illness.[3]

The signs and symptoms of influenza are: fever or feeling feverish, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, and fatigue. The H1N1 virus has been noticed to cause more gastrointestinal symptoms than previously recognized in seasonal influenza.[3] In one review, diarrhea or vomiting was reported in 39% of patients, including 42% of children (<18 years) and 37% of adults.[5] As with other illnesses, children are less likely to present with common signs and symptoms, often showing no respiratory symptoms and instead presenting with fever and fatigue. Severe disease may present with apnea, tachypnea, cyanosis, dehydration, extreme irritability, and changes in mental status. Although the majority of individuals infected will have a mild illness and will not require medical care or antiviral treatment, certain groups are at increased risk for severe infection and complications (Table 3).[3]

The more severe complications to be reported have been rapidly progressive pneumonia, respiratory failure, acute respiratory distress syndrome, and multisystem organ failure,[3,5] the most common being bacterial co-infection, which was seen in 29% of fatal H1N1 cases.[3] Among these fatalities, *Streptococcus pneumoniae* was the most common pathogen, followed by *Staphylococcus aureus* and *Streptococcus pyogenes* (group A strep).[3] Diffuse alveolar damage has been frequently noted in patients who died from pandemic 2009 H1N1 Influenza A.[6]

The epidemiologic characteristics of 2009 H1N1 are different than seasonal influenza, which often targets the

Table 2 Caring for people who have the flu

When caring for people who have the flu:

- Try to give the sick person their own room. If there is more than one sick person, they can share the sick room if needed.
- If you have more than one bathroom, have sick people use one bathroom and well people use the other one
- Give each sick person their own drinking glass, washcloth, and towel.
- Avoid being face to face with the sick person. If possible, it is best to spend the least amount of time in close contact with a sick person.
- When holding sick children, place their chin on your shoulder so they will not cough in your face.
- Wash your hands often and the right way: sing the "Happy Birthday" song two times or count slowly to 20 as you wash.
- If soap and water are not available, use an alcohol-based hand rub.
- Make sure to wash your hands after touching the sick person. Wash after handling their tissues or laundry.
- Give plenty of liquids at the first sign of flu. Sick people with the flu need to drink extra fluids to keep them from getting dehydrated. Mild fluid loss can most often be treated at home. Yet, severe dehydration is VERY serious and must be treated in the hospital.

Table 3 Patients at increased rate for complications

Patients at increased risk for complications
• Children younger than 2 years old
• Adults 65 years of age or older
• Pregnant women and women up to 2 weeks postpartum
• Persons with certain medical conditions
○ Asthma
○ Neurological and neurodevelopmental conditions
○ Chronic lung disease
○ Heart disease
○ Blood disorders
○ Endocrine disorders
○ Kidney disorders
○ Liver disorders
○ Metabolic disorders (inherited and mitochondrial disorders)
○ Weakened immune system (e.g., HIV/AIDS, cancer, chronic steroids)
○ People younger than 19 years of age who are receiving long-term aspirin

extremes of age. The median age of infected persons with pandemic flu has been in the low to mid 20s, similar to the Spanish Influenza. More than 7% of these individuals had an underlying medical condition, including 60% of children and 83% of adults. Among individuals older than age 65, 100% had an underlying medical condition.[5] In both groups, asthma was the most common comorbid condition.[7] Pregnant and postpartum women appear to have an increased risk of severe disease. The CDC estimates that between April and November 2009, approximately 47 million people in the US had contracted the 2009 H1N1 infection; there were approximately 213,000 hospitalizations and approximately 10,000 deaths. The majority of illness has been reported in the 18-64 years age group. The data continues to confirm previous findings that this disease primarily affects people younger than 65 year old, with the number of cases, hospitalizations, and deaths overwhelmingly occurring in people 64 years and younger.[5] The risk of illness, hospitalization, and death related to 2009 H1N1 is very age-specific and very different from seasonal influenza.[3]

Diagnostic testing

Most individuals with a clinical illness consistent with uncomplicated influenza who reside in an area where influenza is known to be present do not require further diagnostic testing for clinical management. Clinical judgment is an important factor in making decisions regarding testing. The CDC recommends testing (1) patients who are hospitalized with suspected influenza; (2) patients for whom a diagnosis of influenza will inform decisions regarding clinical care, infection control, or management of close contacts; and (3) patients (perimortem) who died of an acute illness in which influenza was suspected.[8]

There are a number of tests available to identify the presence of influenza viruses in respiratory specimens. Rapid influenza diagnostic tests (RIDTs) are commercial diagnostic tests that can provide a result in 30 minutes or less. Some of these tests can distinguish between influenza A and B but do not specifically identify 2009 H1N1 or other subtypes. These tests vary in their ability to miss an influenza infection. For example, the sensitivity of these tests for detecting 2009 H1N1 varies from 10% to 70%. Therefore, a negative test does not exclude the possibility of an influenza infection.[8]

Viral culture is another test that is available. However, it is only performed by certain laboratories and does not provide results in a timely fashion for clinical decision-making. It is a highly sensitive and specific test.[8]

Direct immunofluorescence assays (DFAs) and indirect immunofluorescence assays (IFAs) may be available at some hospital or commercial laboratories. The assays typically take two to four hours to run and sensitivities are higher than RIDTs but less than viral culture or real-time reverse transcriptase polymerase chain reaction (rRT-PCR). Sensitivity varies for detecting 2009 H1N1 (range, 47-93%). These tests are also capable of differentiating influenza A and B viruses but do not distinguish among different influenza A subtypes.[8]

The most sensitive and specific influenza diagnostic test is the rRT-PCR nucleic acid amplification. These tests are usually available only through larger laboratories and results may take from one to several days before they are available. Performance depends on the individual rRT-PCR assay. If specific testing for the 2009 H1N1 influenza virus is required, testing with a rRT-PCR assay specific for 2009 H1N1 influenza or viral culture should be requested.[8]

A positive or negative test must be interpreted considering the diagnostic test used, stage of the patient's illness (tests are more likely to be positive when performed in the first three days of illness when viral shedding is high), and local surveillance information on circulating influenza viruses and other respiratory viruses.

Treatment and prevention

Through December of 2009, influenza A (H1N1) virus (2009 H1N1) has been the strain responsible for >99% of all influenzal illness for the 2009/2010 season. A majority of 2009 H1N1 viruses tested are susceptible to oseltamivir and zanamivir but resistant to amantadine and rimantadine.

In general, it is best to start antiviral therapy as soon as possible after the onset of typical influenza-like symptoms.[5] Initiation of treatment is recommended for persons with suspected or confirmed influenza and (1) illnesses requiring hospitalization; (2) progressive, severe, or complicated illnesses, regardless of previous health status; and/or (3) patients at risk for severe diseases (Table 3). The drugs of choice for treatment of 2009 H1N1 are a class of drugs

called neuraminidase inhibitors and include oseltamivir, zanamivir, and peramivir.[9,10]

Oseltamivir (trade name Tamiflu, Roche Laboratories, Burlington, NC) is a neuraminidase inhibitor that is formulated as a capsule or an oral suspension. It has been approved by the Food and Drug Administration (FDA) for the treatment of uncomplicated influenza in patients older than 1 year of age who have been symptomatic for no longer than 48 hours. The standard adult dose for treatment is 75 mg every 12 hours. However, the FDA has issued an Emergency Use Authorization (EUA) with recommendations for the treatment of 2009 H1N1 influenza in patients less than 1 year old, and for the treatment of any patient who has been symptomatic for more than 2 days and sick enough to require hospitalization. The commercially manufactured oseltamivir oral suspension concentration is 12 mg/mL; the compounded suspension concentration is 15 mg/mL. When prescribing oseltamivir for children, make sure to specificy the concentration if prescribing in milliliters or teaspoons, or prescribe in milligrams. Oseltamivir resistance has been reported in severely immunocompromised patients, those who received prophylaxis with the drug, and those receiving subtherapeutic doses.[9,10]

Zanamivir (trade name Relenza) is another neuraminidase inhibitor that is formulated for oral inhalation and is FDA-approved for the treatment of influenza in patients 7 years of age or older with symptoms for no more than 48 hours. The standard adult dose is 2 inhalations every 12 hours. An EUA was also issued for zanamivir authorizing treatment for patients with 2009 H1N1 with symptoms longer than 2 days and sick enough to require hospitalization. There has been no reported resistance to zanamivir, and some experimental work done with an intravenous formulation of zanamivir shows promise.[9,10]

Peramivir is a third neuraminidase inhibitor that is formulated for intravenous use and is currently an investigational drug. On October 23, 2009, the FDA issued an EUA for treating certain adult and pediatric patients with suspected or confirmed cases of 2009 H1N1 influenza. The drug is available through the CDC upon request by a licensed physician when (1) the patient has not responded to either oral or inhaled antiviral therapy, (2) drug delivery by a route other than intravenously is not expected to be dependable or is not feasible, or (3) the clinician judges intravenous therapy is appropriate because of other circumstances. The treatment of pediatrics with peramivir is approved if either of the first two criteria applies.[11]

Initiation of treatment should be based on clinical judgment and not be delayed while waiting for the definitive laboratory test to confirm the diagnosis.[8] As noted before, the sensitivity of the rapid test is less than stellar, and clinical judgment outweighs the lab test. Treatment is most effective when started within the first 48 hours of illness.[5] Treatment recommendations for vaccinated individuals should parallel those for unvaccinated persons. Individuals who receive the live attenuated influenza vaccine and who are given antiviral drugs within 48 hours before or up to two weeks after vaccination may not develop an adequate antibody response and should be revaccinated.[10]

Aspirin or aspirin-containing products should not be given to any child or adolescent less than 19 years of age with confirmed or suspected influenza because of the risk of Reye's syndrome. Other over-the-counter relief and antipyretics such as acetaminophen or nonsteroidal antiinflammatory drugs should be used in this population.

Chemoprophylaxis should be considered for close contacts of a person with suspected or confirmed 2009 H1N1 influenza during the infectious period; those at high risk for complications of influenza are health care workers or emergency medical personnel and women who are pregnant. Prophylaxis is not necessary in groups of healthy children or adults based on potential exposure in the community if >48 hours has elapsed since last contact or close contact did not occur during the infectious period (Table 4).[10]

Table 4 Antiviral treatment and prophylaxis

Medication	Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir		
Adults	75 mg twice daily	75 mg once daily
Children ≥12 months		
Body weight kg		
<15 kg	30 mg twice daily	30 mg once daily
15-23 kg	45 mg twice daily	45 mg once daily
23-40 kg	60 mg twice daily	60 mg once dialy
>40 kg	75 mg twice daily	75 mg once daily
Children 3 mos to <12 mos	3 mg/kg/ twice daily	3 mg/kg/day
Children 0 to <3 mos	3 mg/kg/twice daily	Not recommended unless situation judged critical (limited data)
Zanamivir		
Adults	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
Children (≥7 years or older, ≥5 years for chemoprophylaxis	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

One of the most cited uses for the efficacy of osteopathic manipulative medicine in the treatment of infection occurred during the 1918 Spanish Influenza. R. Kendrick Smith MD, DO, wrote an article in a 1920 issue of *The Journal of American Osteopathic Medicine* in which he noted a decrease in death rates, from 5% to 0.25%, in patients who received osteopathic treatment. During this pandemic, treatment was limited to cough syrup and aspirin for fever control. Osteopathic physicians, recognizing fever as the body's natural response to infection, instead used manipulation and antitussives. Although Dr. Smith's paper remains a significant comment to the role of Osteopathic Manipulative Therapy in disease treatment, it is important to note that his paper was based on a noncontrolled, observational study, which would not meet the rigorous scientific standards to which we are held today.[12] Also of note, the American Osteopathic Association does not have Dr. Smith's original data, nor do they know of its location (personal communication).

Despite this, the use of OMT in treating upper respiratory infections should not be discounted. The use of many techniques, including lymphatic pump, muscle energy, counterstrain, and sinus drainage can aid in symptom relief and may shorten illness duration.

Vaccination

There are 5 key groups that have been targeted for 2009 H1N1 vaccination: (1) Pregnant women, (2) people who live with or care for children younger than 6 months of age, (3) health care and emergency medical services personnel, (4) people age 6 months to 24 years, and (5) people age 25 to 65 who are at increased risk of infection secondary to comorbid conditions. Supplies of the vaccines to protect against the 2009 H1N1 virus are increasing. Providers are encouraged to open up vaccination to anyone who wants it as soon as the needs of the initial prioritized populations have been met.[13]

There are 2 forms of the H1N1 vaccine: standard injectable (inactivated vaccine) and a live attenuated intranasal vaccine (LAIV). A preservative-free formulation of the injectable vaccine is available. The inactivated vaccine is recommended for anyone ages 6 months and older. Individuals with severe (life-threatening) allergy to eggs or other components of the vaccine should not receive the inactivated 2009 H1N1 vaccine. The vaccine may be given at the same time as other vaccines including seasonal influenza vaccine.[13] Please see product insert for specific recommendations from the manufacturer.

The LAIV intranasal vaccine is recommended for those between the ages of 2 and 49. This vaccine is not indicated for people with long-term health problems (e.g., asthma, heart disease, etc.), anyone in contact with a person with a severely weakened immune system, pregnant women, children younger than 2, or adults older than 50. The 2009 H1N1 LAIV may be given at the same time as most other vaccines. However, the H1N1 LAIV and seasonal LAIV should not be given together or within 4 weeks of each other. Any combination of a LAIV and inactivated vaccine may be given at the same time.[13]

Both the inactivated vaccine and LAIV vaccines underwent the same quality control measures and premarket testing as the seasonal flu vaccine. They are expected to be as effective and safe as seasonal flu vaccines.

Frequently asked questions

Q: Can I get H1N1 more than once?

A: Infection with any influenza virus should produce immunity to that particular strain of virus, making it unlikely to be re-infected by the same virus. However, people with weakened immune systems may not develop complete immunity, increasing the possibility of re-infection.[14]

Q: How long are infected people contagious?

A: People with seasonal and H1N1 can spread the disease from one day before symptoms appear to five to seven days after. This can be longer in children and those with weakened immune systems.[14]

Q: How can I protect myself from getting sick?

A: Cover your nose and mouth with a tissue when you cough or sneeze, then throw the tissue away; wash your hands frequently with soap and water or use alcohol-based sanitizer when these are not available; avoid touching your eyes, nose and mouth; avoid close contact with sick individuals; if you are sick with an influenza-like illness, stay home until you are fever-free for 24 hours.[14]

Q: How long can the flu virus remain viable on inanimate objects?

A: The influenza virus can remain on surfaces and infect people for 2-8 hours after being deposited on the objects.[14]

Q: What are the risks associated with the H1N1 vaccination?

A: The risks are similar to any immunization and include; soreness, redness, tenderness or swelling at the injection site; headache, muscles aches; fainting (mostly adolescents); fever; nausea. More serious reactions include the possibility of life-threatening allergic reactions, which is very rare and usually occur within minutes to an hour after the vaccine is given. Unique to the H1N1 immunization is the concern of Guillain-Barré syndrome. In 1976, a different swine flu vaccination was associated with cases of this syndrome; however, since then, no flu vaccines have shown this link, and no cases have been reported with the current vaccination. It is important to note that the manufacturers of the seasonal flu vaccine, which is produced every year, also manufacture the H1N1 immunization. As such, this injection is subject to the same regulations and quality control measures as the seasonal influenza injection.[14]

Q: Should I get the H1N1 vaccination if I have already had swine flu?

A: Because influenza symptoms can be seen in many other illnesses, anyone with flu symptoms who was NOT diagnosed with H1N1 by rRT-PCR should still be vaccinated. If someone was diagnosed with H1N1 by positive rRT-PCR, they do not need to receive the immunization.[13]

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Useful websites

Centers for Disease Control and Prevention: Season Influenza (Flu). Available at: http://www.cdc.gov/flu/weekly/Flu.gov: Home Page. Available at: http://flu.gov

Centers for Disease Control and Prevention: H1N1 Flu; Emergency Use Authorization of Peramivir IV. Availabe at: http://www.cdc.gov/h1n1flu/eua/peramivir.htm

Berks County Pandemic Advisory Council Official Website: Home Page. Available at: http://www.flutoolbox.com