

2009 H1N1 Influenza

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Within 2 months of its discovery last spring, a novel influenza A (H1N1) virus, currently referred to as 2009 H1N1, caused the first influenza pandemic in decades. The virus has caused disproportionate disease among young people with early reports of virulence similar to that of seasonal influenza. This clinical review provides an update encompassing the virology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of the 2009 H1N1 virus. Because information about this virus, its prevention, and treatment are rapidly evolving, readers are advised to seek additional information. We performed a literature search of PubMed using the following keywords: H1N1, influenza, vaccine, pregnancy, children, treatment, epidemiology, and review. Studies were selected for inclusion in this review on the basis of their relevance. Recent studies and articles were preferred.

Mayo Clin Proc. 2010;85(1):64-76

CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; GBS = Guillain-Barré Syndrome; HA = hemagglutinin; ILI = influenza-like illness; NA = neuraminidase; PB = basic polymerase; RIDT = rapid influenza diagnostic test; RT-PCR = real-time reverse transcriptase polymerase chain reaction; WHO = World Health Organization

On April 21, 2009, the Centers for Disease Control and Prevention (CDC) confirmed 2 cases (originally identified by the Department of Defense) of a febrile respiratory illness in children from southern California caused by infection with a novel influenza A (H1N1) virus.¹ The 2 viral isolates were found to be genetically similar, to be resistant to amantadine and rimantadine, and to contain a novel genetic combination of segments from previous swine influenza viruses that have circulated in the United States since 1999, genes from swine viruses of the Eurasian lineage, and genes from avian influenza viruses. Neither of these

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The views in this article are the personal views of the authors and do not necessarily represent the views of the professional organizations or institutions within which we are members.

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children had exposure to swine or to each other, indicating that this virus was capable of human-to-human transmission. Several days later, the CDC reported that H1N1 viruses of the same strain had been confirmed among samples from patients in Mexico, where there was a cluster of 47 cases of rapidly progressive severe pneumonia that resulted in 12 known deaths.^{2,3}

In response to these cases, investigations and enhanced surveillance were implemented by the Mexican Ministry of Health with the assistance of the World Health Organization (WHO). By June 11, 2009, nearly 30,000 cases of 2009 H1N1 virus had been confirmed across 74 countries, compelling the WHO to signal the phase 6 alert level, officially declaring the start of the 2009 influenza pandemic (Table 1).⁴

This clinical review provides an update encompassing the virology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of the 2009 H1N1 virus. To identify relevant literature, we searched PubMed using the following keywords: *H1N1, influenza, vaccine, pregnancy, children, treatment, epidemiology, and review*. Studies were selected for inclusion in this review on the basis of their relevance and currency.

BACKGROUND

The known historical roots of the influenza A H1N1 virus can be traced to 1918, when a virus currently thought to be of avian origin overcame the complex species barriers required to infect humans.⁵ Thus began an influenza pandemic that would result in an estimated 50 to 100 million deaths, more than any other influenza pandemic in history. During the second and more severe wave of human disease in 1918, herds of swine were reported to be infected with a respiratory illness of similar scope and severity. Shope,⁶ a veterinarian, determined that a virus was the causative agent of this swine illness and hypothesized that the human pandemic influenza strain of 1918 must be closely related. His work with mice and other subsequent studies have supported his hypothesis.^{7,8} Thereafter, the swine and human influenza viruses rapidly diverged antigenically, and H1N1 continued to infect humans in seasonal epidemics.⁹ In 1957, the H1N1 virus was replaced by a new strain, designated *H2N2*, that combined genetic material from its H1N1 predecessor and an avian influenza virus.¹⁰ However, influenza A/H1N1 reemerged in a

TABLE 1. World Health Organization (WHO) Pandemic Phases

Phase 1	No viruses circulating among animals have been reported to cause infections in humans
Phase 2	An animal influenza virus has been confirmed to have caused infection in humans and is therefore considered a potential pandemic threat
Phase 3	Small clusters of disease in people have not resulted in human-to-human transmission sufficient to sustain community-level outbreaks
Phase 4	Human-to-human transmission able to cause community-level outbreaks has been verified
Phase 5	Human-to-human spread of the virus into at least 2 countries in 1 WHO region
Phase 6	Human-to-human spread of the virus into at least 1 other country in a different WHO region in addition to phase 5 criteria

Data from reference 4.

1976 outbreak among 230 Army soldiers at Fort Dix, NJ, resulting in 1 death.^{11,12} The virus did not extend to the civilian population. One year later, another A/H1N1 strain emerged in China, Hong Kong, and the former Soviet Union.¹¹ This reemergence was thought to result from an unintended laboratory release and caused mild symptoms in predominantly young people.^{11,13,14} Since 1977, the H1N1 influenza virus has persistently contributed to seasonal epidemics alongside the often more dominant H3N2 subtype.¹⁴

In 1998, a novel triple reassortant virus was identified in the North American swine population; it contained 5 gene segments from the classical North American A/H1N1 swine virus that Shope had described with polymerase gene segments from birds and humans.^{15,16} The first reported human infection with this triple reassortant virus was reported in late 2005 in a 17-year-old male adolescent from Wisconsin who had butchered a pig.¹⁶ The patient recovered, as did the 10 subsequent but unrelated cases reported to the CDC before February 2009. Nearly all the patients had exposure to pigs. Although no fatalities occurred, some of the patients had unusually severe lower respiratory tract infection and diarrhea.¹⁶

The 2009 H1N1 virus is derived from a reassortment of 6 gene segments from the triple reassortant swine-origin virus and 2 gene segments from the Eurasian influenza A (H1N1) swine virus lineage^{5,17,18} (Figure 1).

VIROLOGY

Like influenza B and C, influenza A belongs to the *Orthomyxoviridae* family. It contains a genome made up of 8 segments of negative-sense RNA that encodes 11 proteins (Figure 2).²⁰ Standard influenza nomenclature includes the

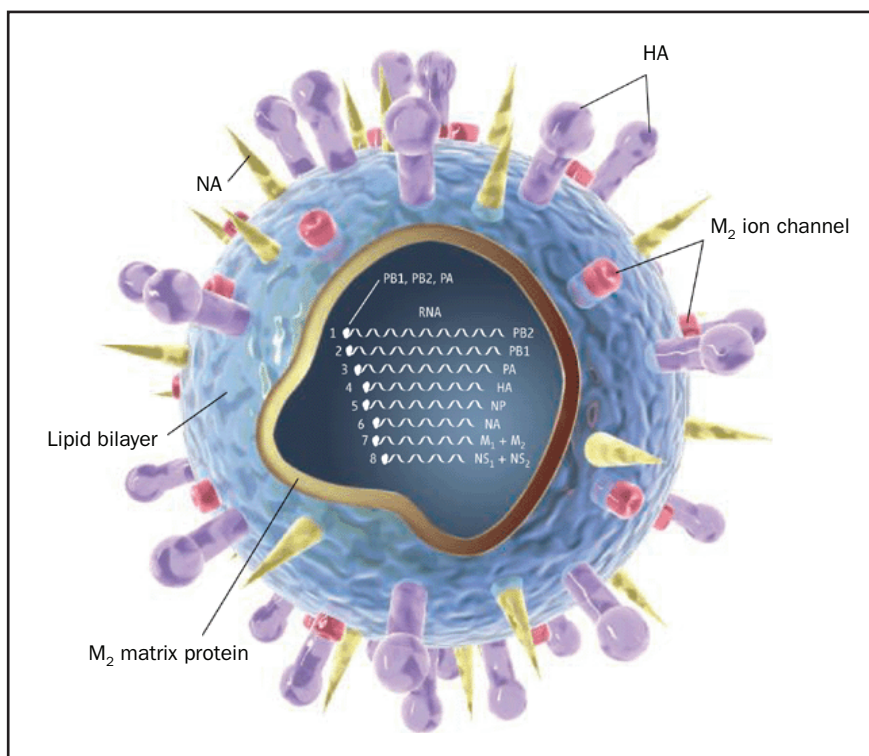


FIGURE 1. Structural diagram of the H1N1 virus. H = hemagglutinin; M = matrix; N = neuraminidase; NP = nucleoprotein; NS = nonstructural; PA = acidic polymerase; PB = basic polymerase. From Science,¹⁹ with permission.

of animals.²¹ Antigenic shifts in HA subtypes are associated with pandemics, 3 of which occurred in the past century.¹¹ The most infamous was the “Spanish flu” pandemic of 1918 that resulted in between 50 and 100 million deaths worldwide. In 1957, the introduction of H2N2 resulted in the “Asian flu” pandemic and claimed about 70,000 lives in the United States and about 2 million worldwide. Eleven years later, a novel H3N2 virus caused the “Hong Kong flu” of 1968 and resulted in about 70,000 deaths in the United States and about 1 million worldwide.

The emergence of the 2009 H1N1 virus is an unprecedented event in modern virology. The 2009 H1N1 virus does not fit the classic definition of a new subtype for which most of the population has no previous infection experience. Since 1977, H1N1 viruses have been in continuous circulation, and most persons born before 1956 have previous infection experience with H1N1 strains in the pre-H2N2 era. The 2009 H1N1 virus also does not fit the classic definition of drift because it has no direct evolutionary relationship with recently circulating H1N1 viruses of human origin.²³ However, all H1N1 strains share subtype antigens identified by immunodiffusion tests, which is the basis for influenza virus subtype classification. Immune recall exists within each subtype (all H1N1 strains).²⁴ For example, populations born before 1957 (during the period of H1N1 circulation) responded well to 1 dose of swine influenza virus vaccine in 1976, despite low or no preexisting antibodies to the HA, just as persons currently 10 years or older have responded well to a single dose of the 2009 H1N1 vaccine.²³

The natural reservoir for all influenza A subtypes is waterfowl, with certain subtypes transmissible among humans, pigs, and 16 other mammals.^{23,25} Human influenza viruses bind to receptors composed of a sialic acid and galactose linked by an α 2,6 bond (SA α 2,6Gal) on epithelial cells within the respiratory tract.²⁶ Avian influenza viruses, however, preferentially bind to receptors composed of sialic acid and galactose linked by an α 2,3 bond (SA α 2,3Gal) on epithelial cells within the intestinal tract of waterfowl. The epithelial cells lining the trachea of swine express both receptors, making swine a “mixing vessel” for coinfection with influenza A subtypes and reassortment.²⁷

Once the virus binds to columnar epithelial cells of the respiratory tract, it interferes with host cell protein synthesis and, through unclear mechanisms, induces apoptosis of the host cell.^{21,28,29} Before cell death, new virions are produced and released to infect adjacent cells.²¹ Necrotizing bronchitis and intra-alveolar hemorrhage and edema result.³⁰

EPIDEMIOLOGY

Influenza-like illness (ILI) is defined by the CDC as fever (temperature $\geq 100^{\circ}\text{F}$ or 37.8°C) and either cough or

sore throat in the absence of another known cause.³¹ A confirmed case of 2009 H1N1 infection is defined by ILI with positive test results for the 2009 H1N1 virus by either real-time reverse transcriptase polymerase chain reaction (RT-PCR) or viral culture. A probable case is ILI with positive influenza A test results but negative results for seasonal H1 and H3 by RT-PCR. A suspected case does not meet either definition but is either a person younger than 65 years hospitalized for ILI or a person of any age with ILI and an epidemiological link to a confirmed or probable case within 7 days of illness onset.

Because of resource limitations, both the CDC and WHO stopped reporting confirmed and probable cases of 2009 H1N1 on July 24, 2009. However, through traditional systems, including surveillance for new viral subtypes, new resistance patterns, geographic spread of the virus, visits to the physician for influenza-related symptoms, hospitalizations for confirmed cases of influenza, and deaths attributable to influenza or pneumonia, the CDC will continue to report weekly statistics on the number of hospitalizations and deaths that can be attributed to the virus. Between August 30, 2009, and November 28, 2009, 31,320 laboratory-confirmed influenza-associated hospitalizations and 1336 laboratory-confirmed influenza-related deaths were reported to the CDC, and more than 99% of the most recently subtyped influenza viruses were 2009 H1N1 influenza. These data are published weekly in *FluView* and can be accessed at <http://cdc.gov/h1n1flu/reportingqa.htm>.

Like seasonal influenza, 2009 H1N1 is thought to be transmissible by 3 routes: contact exposure (when a contaminated hand is exposed to facial membranes), droplet spray exposure (when infectious droplets are projected onto mucous membranes), and airborne exposure (via inhalation of infectious airborne particles). The relative contribution of each of these modes is unknown and likely dependent on such factors as temperature and humidity. The complexities involved with human research to understand influenza transmissibility leave animal studies and mathematical models to inform us. One such model illustrated that the relative importance of each route of transmission differs with the concentration of the virus in saliva.³² Evidence exists for seasonal influenza transmission via fine particles generated during tidal breathing.³³ Recent evidence suggests that the 2009 H1N1 virus is transmitted via large particle droplets.³⁴ Because large droplets remain suspended in the air for a short time, transmission via this route requires close contact (<1.83 m [<6 ft]) between the source and the recipient. The possibility of indirect transmission from fomites and contaminated surfaces has prompted the CDC to recommend that all body fluids (eg, stool, respiratory secretions) be treated as potentially infectious. Given the uncertainties surrounding the relative

importance of each of these routes of transmission, the Institute of Medicine convened, at the request of the CDC and of the Occupational Safety and Health Administration, to provide recommendations to protect health care workers against 2009 H1N1. These recommendations are discussed in the sections that follow.

The incubation period for the 2009 H1N1 virus has been estimated to be between 1 and 7 days, similar to that of seasonal influenza.^{35,36} Clinicians should assume that infected persons start shedding virus 1 day before the onset of symptoms and shed at least until symptoms resolve. Recent data have suggested that up to 80% of patients are still shedding virus at 5 days, 40% at 7 days, and 10% at 10 days.³⁷ Children and younger adults may shed for as long as 10 or more days, and immunosuppressed persons may shed virus for weeks.³⁸⁻⁴⁰

Most cases have occurred in patients with a median age of 12 to 17 years. However, severe cases also occur in slightly older populations. More recent reports indicate that the median age of cases may increase as infection becomes more widespread in the population.⁴¹

To determine whether previous seasonal vaccinations provide cross-protection against the 2009 H1N1 (A/California/04/2009) virus, the CDC performed microneutralization assays on preseasonal and postseasonal stored sera in 100 recipients of the 2005-2006 through 2008-2009 seasonal influenza vaccines.⁴² Among children, investigators found no prevaccination or postvaccination cross-reactivity; among those aged 18 to 40 years, 6% prevaccination and 7% postvaccination cross-reactivity; among those aged 18 to 64 years, 9% prevaccination and 25% postvaccination cross-reactivity; and among those older than 60 years, 33% prevaccination and 43% postvaccination cross-reactivity. These results suggest that recent seasonal influenza vaccines would not provide adequate protection against the 2009 H1N1 virus, particularly among younger people.

However, virus neutralization test results alone do not fully represent the complex immune-mediated functions involved in protection from or amelioration of influenza disease. Current disease patterns suggest that, despite low levels of cross-reacting neutralizing antibodies, adults and older children who have experienced repeated natural exposure to seasonal H1N1 viruses have an immunologic advantage in protection against disease or in moderation of clinical response to a new H1N1 infection.

CLINICAL MANIFESTATIONS

Analyses have suggested that clinical manifestations of 2009 H1N1 influenza and seasonal influenza are similar.^{43,44} One review of 44 confirmed 2009 H1N1 cases in a New York City high school revealed that cough (98%),

fever (96%), headache (82%), sore throat (82%), rhinorrhea (82%), chills (80%), and muscle aches (80%) were commonly reported.⁴⁵ Fewer patients had nausea (55%), diarrhea (48%), dyspnea (48%), joint pain (46%), or stomach ache (36%).

Patients requiring hospitalization for 2009 H1N1 infection are much more likely to have underlying medical conditions, especially asthma, chronic obstructive pulmonary disease, immunosuppression, diabetes, obesity, or chronic heart conditions.⁴⁶ Such patients present with fever, cough, dyspnea, vomiting, and/or abnormal chest radiographs and are typically released after short hospital stays.

Hypoxia and chest radiographs consistent with acute respiratory distress syndrome have been characteristic of patients requiring intensive care.⁴⁷ A prospective observational study of 168 critically ill patients with 2009 H1N1 in Canada found a mean age of 32.3 years and a median time of 4 days between symptom onset and hospitalization.⁴⁸ Overall mortality among this group was 17.3% at 90 days and correlated with a higher severity of illness and greater organ dysfunction at presentation. All these patients were severely hypoxic at presentation, with a mean PaO₂ to fraction of inspired oxygen ratio of 147. Similarly, an observational study of 58 critically ill patients with 2009 H1N1 in Mexico revealed that nonsurvivors were more likely to present with severe organ dysfunction and hypoxia than survivors.⁴⁹ Both studies validated the use of either SOFA (Sequential Organ Failure Assessment) or APACHE (Acute Physiology and Chronic Health Evaluation) II scores to identify patients at risk of death. A review of medical records of patients with confirmed 2009 H1N1 infection requiring intensive care in Spain showed that chest radiographic findings were abnormal in all patients, with most (72%) demonstrating patchy alveolar opacities affecting 3 of 4 quadrants.⁵⁰ In all 3 analyses, obese patients (body mass index [calculated as the weight in kilograms divided by height in meters squared] >30 kg/m²) accounted for approximately one-third of the cases requiring intensive care.

Clinicians have been advised to expect that complications from the 2009 H1N1 virus will be similar to those of the seasonal influenza virus.⁵¹ These include exacerbations of underlying chronic illness; complications in both the upper (sinusitis, otitis media, croup) and lower (pneumonia, asthma exacerbation, and bronchiolitis) respiratory tracts; neurologic (encephalopathy, encephalitis, febrile seizures, status epilepticus), cardiac (pericarditis and myocarditis), and musculoskeletal (rhabdomyositis) complications; toxic shock syndrome; and secondary bacterial infections with sepsis.

Postmortem lung specimens of 77 fatal H1N1 cases were evaluated by the CDC to determine the role of bacterial coinfection in fatal outcomes.⁵² Evidence of bacterial

TABLE 2. Groups at High Risk of Influenza-Related Complications

Children <5 y ^a
Adults ≥65 y ^b
Pregnant women
Persons with certain chronic medical conditions ^c
Immunosuppressed patients
Adolescents <19 y receiving long-term aspirin therapy

^a Especially children <2 y.

^b This age group is at decreased risk of acquiring 2009 H1N1; however, if they become infected, they are considered at high risk of complications.

^c Chronic medical conditions include those of cardiac (not hypertension), pulmonary (especially asthma), renal, hepatic, hematologic (including sickle cell disease), neurologic, neuromuscular, and metabolic (including diabetes) origin.

coinfection was discovered in 22 cases (29%) by means of histopathologic, molecular, and immunohistochemical analyses. In these 22 cases, *Streptococcus pneumoniae* predominated (10 cases); however, both methicillin-resistant and -susceptible *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus mitis*, and *Haemophilus influenzae* were also discovered, in decreasing order of frequency. These findings highlight the importance of early detection and treatment of bacterial pneumonia in patients with 2009 H1N1 influenza and underscore the importance of the pneumococcal vaccine for those in whom it is indicated. Classically, bacterial pneumonia complicates influenza infection 4 to 14 days after near resolution of influenza symptoms and presents with fever, dyspnea, productive cough, and abnormal chest radiographic findings.^{53,54} This complication should be treated in accordance with current treatment guidelines.⁵⁵

Those at highest risk of developing complications include children younger than 5 years, patients 65 years or older, pregnant women, and patients with chronic underlying medical conditions (particularly asthma, but including other pulmonary, cardiac, hematologic, hepatic, neurologic, and metabolic diseases)^{56,57} (Table 2). Also at increased risk are immunocompromised patients and residents of long-term care facilities. Clinicians should recall the risk of Reye syndrome, an acute, noninflammatory encephalopathy, in children or adolescents younger than 19 years with influenza who receive aspirin or aspirin-containing products. Obese patients may be at higher risk as well, although the nature of this risk is not yet completely understood.⁴⁷

DIAGNOSIS

Persons with suspected or confirmed 2009 H1N1 influenza who require hospitalization should be given priority for 2009 H1N1 testing.⁵⁸ Others may be eligible for priority testing as determined by state and local health departments. When considering the diagnosis, physicians should

keep in mind that atypical presentations occur in infants and in elderly and immunocompromised persons. In addition to the CDC's published guidance on specimen collection, processing, and testing, state and local health department recommendations should be followed.⁵⁹

A nasopharyngeal or oropharyngeal swab, nasal aspirate, or combined nasopharyngeal and oropharyngeal swab should be used for sampling. Swabs should be made of inert materials, such as synthetic tips and aluminum or plastic shafts. Endotracheal aspirates or bronchoalveolar lavage should be obtained from intubated patients. Samples should be transported in 1 to 3 mL of viral transport media, cooled with ice or refrigerated, and stored at 4°C for no longer than 4 days. Shipped specimens should be transported on wet ice or cold packs and clearly labeled with the information requested by the appropriate state public health laboratory.

Real-time reverse transcriptase polymerase chain reaction is recommended for confirmation of cases of 2009 H1N1 infection. With RT-PCR, 2009 H1N1 will test positive for influenza A and negative for seasonal H1 or H3. Strong reactivity for influenza A (cycle threshold value <30) is indicative of 2009 H1N1. Although not approved by the Food and Drug Administration (FDA) for this indication, RT-PCR assays can be performed by public health laboratories in the United States. However, clinicians should bear in mind the limitations of this testing. In the review of medical records of 32 Spanish patients requiring intensive care described previously, 4 (13%) tested negative for 2009 H1N1 at admission to the intensive care unit.⁵⁰

Commercially available rapid influenza diagnostic tests (RIDTs) detect influenza viral nucleoprotein antigen and can provide results within 30 minutes. Although some RIDTs can distinguish between influenza A and B viruses, no FDA-approved RIDT can discriminate among viral subtypes (H1 from H3). The sensitivity of RIDTs for detecting 2009 H1N1 has varied from 10% to 70% and is directly related to the amount of virus in the specimen and inversely related to the threshold cycle value of the test.⁶⁰⁻⁶³ Thus, negative findings on a test do not "rule out" infection with the 2009 H1N1 virus; when clinical suspicion remains high despite negative test findings, the clinician should empirically treat high-risk patients and institute appropriate infection control measures. Positive results on an RIDT test for influenza type A likely mean that influenza A is present but do not distinguish among 2009 H1N1, seasonal influenza A, and influenza A of animal origin. Thus, for definitive diagnosis of 2009 H1N1 infection, only viral culture or RT-PCR can be used.

TREATMENT

To date, with few exceptions, the 2009 H1N1 virus remains susceptible to NA inhibitors (oseltamivir and zanamivir)

TABLE 3. Influenza Antiviral Medication Dosing Recommendations

Agent	Treatment	Chemoprophylaxis
Neuraminidase inhibitors		
Oseltamivir		
Adults	75-mg capsule twice daily for 5 d	75-mg capsule once daily
Children >12 mo, weight (kg)		
<15	60 mg/d, divided into 2 doses	30 mg once daily
15-23	90 mg/d, divided into 2 doses	45 mg once daily
24-40	120 mg/d, divided into 2 doses	60 mg once daily
>40	150 mg/d, divided into 2 doses	75 mg once daily
Zanamivir		
Adults	Two 5-mg inhalations (10 mg total) twice daily	Two 5-mg inhalations (10 mg total) once daily
Children	Two 5-mg inhalations (10 mg total) twice daily (age >7 y)	Two 5-mg inhalations (10 mg total) once daily (age >5 y)
Adamantanes		
Rimantadine		
Adults	200 mg/d, either as a single daily dose or divided into 2 doses	200 mg/d, either as a single daily dose or divided into 2 doses
Children		
1-9 y	6.6 mg/kg/d (maximum, 150 mg/d), divided into 2 doses	5 mg/kg once daily, not to exceed 150 mg
10 y	200 mg/d, either as a single daily dose or divided into 2 doses	200 mg/d, either as a single daily dose or divided into 2 doses
Amantadine		
Adults	200 mg/d, either as a single daily dose or divided into 2 doses	200 mg/d, either as a single daily dose or divided into 2 doses
Children		
1-9 y	5-8 mg/kg/d, divided into 2 doses or as a single daily dose (maximum, 150 mg/d)	5-8 mg/kg/d divided into 2 doses or as a single daily dose (maximum, 150 mg/d)
9-12 y	200 mg/d divided into 2 doses	200 mg/d divided into 2 doses

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and resistant to the adamantanes (amantadine and rimantadine).⁶⁴⁻⁶⁶ Antiviral treatment is recommended for all hospitalized patients with confirmed, probable, or suspected 2009 H1N1 infection and patients at high risk of complications (Table 2). Because low-risk persons with uncomplicated febrile illness are unlikely to derive substantial benefit from antiviral therapy, treatment is not recommended for these patients. Treatment benefit is greatest if antiviral medications are started within 48 hours of illness onset; however, studies have suggested that hospitalized patients benefit from treatment initiation even later.^{57,67} Treatment dosages and duration are the same as for seasonal influenza (Table 3).⁶⁸

Because infants are at high risk of influenza-related complications and limited safety data are favorable, the FDA issued an Emergency Use Authorization approving the use of oseltamivir for treatment and prophylaxis in pediatric patients younger than 1 year (Table 4).⁶⁹

Postexposure chemoprophylaxis with oral oseltamivir or inhaled zanamivir can be considered for high-risk persons, health care workers, public health workers, or first responders who have, within the past 48 hours, been in close contact with a case of confirmed, probable, or suspected 2009 H1N1 during the infectious period.⁵⁸ Although the infectious period starts 1 day before and can extend at least 7 to 10 days after illness onset, for purposes of postexposure prophylaxis

the infectious period is considered to begin 1 day before symptoms and to end 24 hours after resolution of fever. The prophylactic course should extend for 10 days from the most recent contact with the infectious person. The patient should be informed that influenza can be acquired despite prophylaxis and to seek medical attention if influenza-like symptoms develop. Alternatively, clinicians can consider forgoing postexposure prophylaxis in appropriate patients reliable enough to seek immediate care if symptoms develop.

Preexposure prophylaxis with oseltamivir or zanamivir should generally be considered for high-risk persons

TABLE 4. Emergency Use Authorization by the Food and Drug Administration for Oseltamivir in Infants <12 Mo

Treatment ^a	
6-11 mo	25 mg twice daily
3-5 mo	20 mg twice daily
<3 mo	12 mg twice daily
Prophylaxis ^b	
6-11 mo	25 mg once daily
3-5 mo	20 mg once daily
<3 mo	Not recommended ^c

^a Recommended for 5 d, to be started within 48 h of symptom onset.

^b Recommended for 10 d, to be started within 48 h of exposure.

^c Consider only if infant had considerable exposure and is at high risk of severe illness.

From the Food and Drug Administration.⁶⁹

with frequent exposures (health care workers, public health workers, or first responders) to 2009 H1N1 after consultation with local public health authorities. For this indication, the antiviral agent should be given during the potential exposure and continued for 10 days after the last known exposure.

If an outbreak in a nursing home or long-term care facility were to occur, chemoprophylaxis with oseltamivir or zanamivir should be administered to all healthy residents and continued for a minimum of 7 days after illness onset in the last patient or 2 weeks, whichever comes later. This strategy also applies for use in other closed settings, such as correctional facilities; however, it does not apply to settings where lower-risk populations congregate, such as schools and workplaces.

Special treatment considerations exist for pregnant women because of their high risk of complications from both seasonal and 2009 H1N1 influenza.⁷⁰⁻⁷³ They should receive oseltamivir or zanamivir for 5 days, and the drug should ideally be initiated within 48 hours of illness onset. Although both of these agents are pregnancy category C (controlled human studies are unavailable), pregnancy should not be considered a contraindication to their use.⁷⁴ Pregnant women in contact with a confirmed, probable, or suspected case of infection with the 2009 H1N1 virus should receive 10 days of prophylactic therapy with zanamivir or oseltamivir. Because of its limited systemic absorption, inhaled zanamivir may be the preferred prophylactic agent in these women who do not otherwise have contraindications for its use.

All patients should be counseled regarding potential adverse effects and reactions from these antiviral agents. Oseltamivir can cause nausea and vomiting that can be alleviated if taken with food. Transient neuropsychiatric events, such as self-injury and delirium, have been reported from postmarketing surveillance studies of oseltamivir.^{75,76} Zanamivir is licensed only for persons without underlying respiratory (especially asthma) or cardiac disease. Cases of respiratory deterioration and allergic reactions (including angioedema) have been reported from postmarketing surveillance of zanamivir.⁷⁷

Clinicians should be aware that use of peramivir, an intravenous NA inhibitor, has been authorized by the FDA under an Emergency Use Authorization.⁶⁹ Although still being evaluated in phase 3 trials, limited data regarding its safety and efficacy are available (Fact Sheet for Health Care Providers, available at http://www.cdc.gov/h1n1flu/eua/Final%20HCP%20Fact%20sheet%20Peramivir%20IV_CDC.pdf). Its use is restricted to hospitalized patients who are not responding to either oral or inhaled antiviral therapy or to those for whom oral or inhaled therapy is not expected to be effective. The standard dose is 600 mg intra-

venously once daily for 5 to 10 days. Although no children have received the drug in clinical trials, its use in children has been permitted under emergency investigational new drug procedures. Peramivir has not been administered to pregnant women or nursing mothers in clinical trials. Adverse effects have included nausea, vomiting, diarrhea, and neutropenia.

VACCINATION/PREVENTION

Vaccination is the most effective means of preventing influenza-associated morbidity and mortality. Because previous seasonal vaccinations do not appear to confer protection against 2009 H1N1, new vaccines have been licensed and are available.⁷⁸ The manufacturing and licensure process for this vaccine was based on the same standards as the seasonal influenza vaccines. The vaccine is based on the A/California/07/2009 (H1N1) strain and is available in both live-attenuated and inactivated formulations. Given the prior broad H1N1 infection experience in the population, a single dose is adequate for those older than 9 years.⁷⁹ With a single administration of the 2009 H1N1 vaccine, a robust immune response was seen in 80% to 96% of adults aged 18 to 64 years and in 56% to 80% of adults aged 65 years or older.⁸⁰ Children younger than 10 years will require 2 administrations of the vaccine separated by at least 21 days. Although clinicians are advised to start providing the 2009-2010 seasonal vaccine as soon as it becomes available, some patients will likely present for vaccination for both seasonal and 2009 H1N1 influenza. Although the 2009 H1N1 vaccine in either form can be given simultaneously with the inactivated 2009-2010 seasonal vaccine, live-attenuated versions of both vaccines should not be used simultaneously. The live-attenuated vaccine is only licensed for persons aged 2 through 49 years who are not pregnant, are not immunocompromised, and have no chronic medical conditions. Children younger than 5 years who have asthma, those in close contact with immunosuppressed persons, and children receiving long-term aspirin therapy should not receive the live vaccine. The inactivated vaccine should not be given to patients with severe allergic reaction to eggs or any component of the vaccine.

In early studies, the immunogenicity and safety of the 2009 H1N1 vaccine have been similar to the seasonal influenza vaccine.⁷⁸ Concerns regarding the risk of Guillain-Barré syndrome (GBS) after influenza vaccination have been raised.⁸¹ These concerns stem from the suspension of the 1976 H1N1 National Influenza Immunization Program because of reports of vaccine-related GBS. Subsequent analysis estimated an attributable risk of developing vaccine-related GBS from the 1976 H1N1 vaccine at just less

TABLE 5. Initial Target Groups for 2009 H1N1 Vaccine

Children and young adults aged 6 mo through 24 y
Adults aged 25 through 64 y at risk of influenza-related complications because of underlying chronic medical conditions
Pregnant women
Persons who live with or provide care for infants <6 mo
Health care and emergency medical services personnel ^a

^a Includes all persons working in health care facilities with potential exposure to influenza-infected patients or infectious material.

than 1 per 100,000 persons in the adult population.⁸² Studies have been unable to show a consistent association between GBS and influenza vaccination, and studies suggest a higher risk of GBS from influenza itself rather than from the vaccine.^{83,84} Patients should be advised that adverse effects from the 2009 H1N1 vaccine are expected to be similar to those of the seasonal vaccine and notably involve the possibility of self-limited tenderness at the injection site of the inactivated vaccine and nasal congestion, rhinorrhea, or cough with the live-attenuated vaccine.

On July 29, 2009, the CDC's Advisory Committee on Immunization Practices convened to review current epidemiological and clinical data to establish priority groups to receive 2009 H1N1 vaccine.⁸⁵ Five such groups were established: pregnant women, caregivers for and cohabitants of infants younger than 6 months, health care and emergency services personnel, persons aged 6 months through 24 years, and persons aged 25 through 64 years with medical conditions that increase risk of influenza-related complications (Table 5). Members of these 5 groups constitute approximately half of the US population and are at higher risk of influenza-related complications, have an occupational risk of acquiring and subsequently transmitting influenza, or are contacts of infants younger than 6 months who are too young to be vaccinated.

If vaccine production does not meet the demand for these 5 priority groups, the Advisory Committee on Immunization Practices has designated 5 population subsets for highest priority in receiving vaccine: pregnant women, caregivers for and cohabitants of infants younger than 6 months, health care and emergency services personnel in direct contact with patients or infectious material, children aged 6 months to 4 years, and children or adolescents aged 5 to 18 years at higher risk of influenza-related complications. In the event of any local vaccine shortages, members of these highest priority subsets, numbering approximately 42 million in the United States, should be vaccinated first. Once demand among all high-priority groups has been met, vaccination should be extended to other persons aged 25 through 64 years, followed by those older than 65 years.

Unfortunately, supplies of the 2009 H1N1 vaccine have been limited. Several reasons for the shortage can be identified (http://cdc.gov/h1n1flu/vaccination/qa_vac_supply.htm).

Not only has the virus necessary for vaccine production grown more slowly than expected, larger than anticipated quantities of the virus were necessary to produce an acceptably potent vaccine. These issues have been addressed and, as of December 1, 2009, nearly 60 million doses of vaccine had been shipped from the manufacturers for distribution (<http://cdc.gov/h1n1flu/vaccination/vaccinesupply.htm>).

According to an Internet-based survey of 2067 US adults conducted by the RAND corporation between May 26, 2009, and June 8, 2009, approximately half (49.6%) of the respondents indicated that they intended to receive the 2009 H1N1 vaccine when it became available.⁸⁶ Intention to receive the vaccine was strongly correlated with receipt of the seasonal influenza vaccine. Similarly, anonymous questionnaires completed by 2255 health care professionals in Hong Kong indicated that only 47.9% were willing to accept 2009 H1N1 influenza vaccine.⁸⁷ In this study, willingness to receive pandemic influenza vaccination was not affected by changes in the WHO pandemic alert level.

Patients should be educated regarding other preventive measures, including using tissues to cover their mouth and nose when coughing and sneezing, developing good hand-washing technique, using alcohol-based hand cleaners, avoiding contact with ill persons if possible, and staying home when ill unless medical attention must be sought.

The CDC has provided recommendations for infection control of 2009 H1N1 in health care settings.⁸⁸ In order of importance, they are as follows: elimination of potential exposures, use of engineering controls (ie, partitions in triage areas), administrative controls (ie, promoting and providing vaccinations and enforcing policies for ill staff members), and use of personal protective equipment. Standard isolation precautions, including the use of nonsterile gloves for any patient contact and the use of gown and eye protection for activities involving respiratory secretions or other infectious material, should also be observed. Aerosol-generating procedures (Table 6)⁸⁸ should ideally be performed in an airborne infection isolation room with as few people present as necessary. Isolation precautions should be continued for 7 days after illness onset in confirmed or suspected cases in whom 2009 H1N1 infection has not been excluded. If the patient is transported from the room, he or she should wear a mask if tolerable and should be encouraged to perform hand and cough hygiene practices

TABLE 6. Aerosol-Generating Procedures

Bronchoscopy
Sputum induction
Endotracheal intubation and extubation
Open suctioning of airways
Cardiopulmonary resuscitation
Autopsies

From the Centers for Disease Control and Prevention.⁸⁸

frequently. Health care personnel should observe standard precautions and wear respiratory protection equivalent to a fitted N95 respirator plus eye protection during aerosol-generating procedures.

After review of the evidence regarding the efficacy of various types of available respiratory protective equipment, the Institute of Medicine has recommended that health care workers use fit-tested N95 respirators or the equivalent when in close contact with persons who have ILIs or are infected with the 2009 H1N1 virus. Supporting this recommendation are data that fit-tested N95 respirators filter 95% to 99% of infectious particles, whereas variable filtration results have been reported for surgical masks. Despite this, perhaps for economic considerations, some institutions have implemented policies that call for the use of masks for routine patient care activities and reserve N95 masks for aerosol-generating activities only.

At the end of the patient encounter, immediately after removing gloves, health care workers should wash their hands with soap and water or alcohol-based sanitizer. Health care personnel with febrile respiratory illness should notify their supervisor or infection control officer and be instructed not to work or to avoid patient care duties for 7 days from illness onset and until they have been asymptomatic for 24 hours, whichever is longer. Finally, all health care personnel should receive both seasonal and pandemic influenza vaccines.^{89,90}

Readers should be advised that these infection control recommendations are subject to rapid change and should consult their local health departments and infection control officers for further guidance.

FUTURE CONSIDERATIONS

Influenza activity in the southern hemisphere can be informative regarding the impact of 2009 H1N1 in the months ahead. Reports from Peru indicate that 8381 cases were confirmed between May 9, 2009, and September 27, 2009, with 137 confirmed influenza-related deaths.⁹¹ This translated to an estimated case fatality rate of 1.71% based on confirmed cases. Because the number of confirmed cases is undoubtedly lower than actual, this estimated case fatality rate is likely higher than actual. By comparison, the crude case fatality rate of the 1918 influenza pandemic is estimated to have been greater than 2.5%.⁹² The basic reproduction number (R_0), used to define the average number of secondary cases generated in a susceptible population from 1 primary case, was estimated to be between 1.2 and 1.7, consistent with other reports.⁹³⁻⁹⁵ If the R_0 is greater than 1, a pandemic can occur; however, when R_0 is less than 1, a pandemic will not occur.^{96,97} By comparison, the R_0 of the 1918 virus was estimated to have exceeded 1.3 and may have approached 3.1.⁹⁸

On the basis of historical interpretations of the waves of impact during the 1918 pandemic, some have speculated that this current 2009 H1N1 virus has potential to become more virulent.⁹⁹ The first wave in 1918 was mild. The second was more virulent and within weeks had spread to most of the world's cities. The first wave seemed to provide seroprotection for the second; however, neither the first nor the second wave provided seroprotection for the third.¹⁰⁰ Current data do not show increasing influenza virulence over time with this virus; however, different countries, regions, and populations have experienced differing degrees of epidemic severity depending on multiple host and environmental factors. No evidence of the evolution of the 2009 H1N1 virus toward a more transmissible or pathogenic phenotype has been reported. Experience in the southern hemisphere has been similar to observations in the northern hemisphere between April and June 2009.

Despite efficient human transmission, the 2009 H1N1 virus lacks the molecular determinants usually associated with transmission.¹⁸ For example, 2009 H1N1 contains a glutamate at position 627 in the PB2 protein, characteristic of avian influenza viruses; human influenza viruses traditionally have a lysine at that position.¹⁰¹⁻¹⁰³ Such findings suggest that this virus could enhance our knowledge of molecular determinants for transmissibility.

Although it has maintained susceptibility to NA inhibitors, multiple cases of oseltamivir-resistant 2009 H1N1 have been reported.¹⁰⁴ Two immunocompromised patients infected with 2009 H1N1 in the state of Washington with no epidemiological link developed oseltamivir resistance during treatment. Isolates from both patients were initially susceptible to oseltamivir; however, during treatment with the drug, a mutation involving the substitution of a histidine for tyrosine at position 275 (H275Y) of the NA gene occurred, rendering the virus resistant. Zanamivir remains active against isolates with the H275Y mutation. Subsequently, the first epidemiologically linked cases of oseltamivir-resistant 2009 H1N1 infection were reported in 2 adolescent girls in North Carolina who had stayed in the same cabin during a summer camp.⁶⁵ These isolated viruses contained the H275Y mutation in addition to a second previously unreported 2009 H1N1 mutation (I223V). If oseltamivir resistance is suspected, physicians may choose to treat with zanamivir or a combination of oseltamivir and amantadine or rimantadine.

CONCLUSION

The 2009 H1N1 virus has created the first influenza pandemic in more than 4 decades. Unlike previous pandemics, some of the population has had prior infection experience with this subtype. Thus far, in contrast to seasonal influenza

viruses, the 2009 H1N1 virus has disproportionately affected younger populations. Its virulence is similar to that of seasonal influenza viruses. The 2009 H1N1 virus is resistant to adamantanes but has remained susceptible to the NA inhibitors with few exceptions. Vaccine trials confirm that only 1 dose is required for persons older than 9 years and 2 doses for children aged 6 months to 9 years. Larger vaccine trials are in progress. Whether this virus will displace or cocirculate with the current seasonal strains is unknown. Clinicians are advised to stay up to date regarding H1N1 by frequently checking Web sites authored by the CDC and state health departments. An effective response to this pandemic and the amelioration of the associated morbidity and mortality must be predicated on a vaccinated, working, and informed health care population.

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