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Novel H1N1 Pandemic

When Pigs Fly

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On April 21, 2009, the "Morbidity and Mortality Weekly Report" Dispatch was entitled "Swine Influenza A (H1N1) Infection in 2 Children—Southern California, March to April 2009."[1,2] This marked the beginning of a long awaited influenza pandemic. Within days, there were reports of widespread influenza with high mortality in young adults in Mexico. These cases were subsequently confirmed to be due to a novel strain. The viral genome is part swine, part avian, and part human influenza; thus, it is truly novel.[3] Following the initial 2 cases in California, there were dozens and then hundreds of cases throughout the United States and across the Northern hemisphere.

In April and May, there were daily updates provided by the Centers for Disease Control and Prevention (CDC).[2] A health advisory was released on April 25 and CDC activated its Emergency Operations Center. On April 26, the Secretary of the Department of Homeland Security, Janet Napolitano, announced a public health emergency in the United States. This released funds, medicines, and supplies to support the public health response. On April 27, a travel warning recommended that nonessential travel to Mexico be cancelled. An Emergency Use Authorization for use of antivirals and diagnostic influenza tests was released on April 27. The next day, the World Health Organization (WHO) raised the worldwide pandemic alert to Phase 4. See Table 1 for the definitions of pandemic phases or levels.[4,5] On April 29, the pandemic alert level was raised to Phase 5. The first death in the United States was recorded on April 29. By May 5, cases were reported in 38 states with the majority from New York, Texas, and California. By June, over 13,000 cases with 27 deaths had been reported and cases had occurred in every state. On June 11, WHO raised the worldwide pandemic alert level to the highest, Phase 6. By the end of July there were over 40,000 cases, 5000 hospitalizations, and 302 deaths; the CDC decided to stop reporting case counts. Although case counts were widely reported by the media and by spokespersons, the counts were dramatically biased because of variations in the criteria used to select which patients would be tested. Each state determined which specimens to collect and when to test; as soon as infection became epidemic in a community, testing was generally halted. Furthermore, most outpatients were not tested. Finally, the rapid screening tests were found to have limited sensitivity. In August, the sensitivity of 3 commercially available rapid influenza diagnostic tests were reported to range from 40% to 69% for novel influenza A H1N1 as compared with 80% to 83% for seasonal influenza A H3N2 strains. Furthermore, the rapid tests were unable to detect low levels of virus. The CDC confirmatory test was a real-time reverse transcription polymerase chain reaction (rRT-PCR) assay which has a sensitivity of 99% and specificity of 92% for seasonal influenza A virus.[1]

Influenza cases continued throughout August and the incidence of healthcare visits for influenza-like illness remained higher than expected. Clearly this was a novel strain which caused a significant number of infections off season. The northern hemisphere waited while the virus spread through the southern hemisphere where it was in season. By late summer, there was no evidence of increasing virulence.

It was interesting to watch the terminology evolve. The term swine influenza A (H1N1) evolved to human swine influenza, new influenza virus of swine origin, then novel H1N1, and as of August, just 2009 H1N1 (Swine flu). For this concise review, I will use the term novel H1N1. The genetics of the virus revealed a quadruple reassortant with genes from the influenza of pigs in Europe, Asia, and North America plus genes

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This article was written in late August 2009; the situation is evolving daily so some of the guidance will be out of date by the publication time. Readers are advised to use the web sites referenced in the report.

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TABLE 1. World Health Organization Pandemic Levels[5]

Phase 1—no viruses circulating among animals have been reported to cause infections in humans.
Phase 2—an animal influenza virus circulating among domesticated or wild animals is known to have caused infection in humans, and is therefore considered a potential pandemic threat.
Phase 3—an animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks. Limited human-to-human transmission may occur when there is close contact between an infected person and an unprotected caregiver, but the virus is not widely transmitted among humans.
Phase 4—verified human-to-human transmission of an animal or human-animal influenza reassortant virus able to cause "community-level outbreaks." The risk for a pandemic is significantly raised.
Phase 5—human-to-human spread of the virus into at least 2 countries in one WHO region. The declaration of Phase 5 is a strong signal that a pandemic is imminent.
Phase 6—the pandemic phase is characterized by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. A global pandemic is under way.

TABLE 2. Doses of Antivirals for Use Against the Novel H1N1 Influenza[2]

Antiviral Agent	Treatment	Chemoprophylaxis
Oseltamivir		
Adults	75 mg bid for 5 d	75 mg once daily
Children over 1 yr of age		
Over 40 kg	75 mg bid for 5 d	75 mg once daily
24–40 kg	60 mg bid for 5 d	60 mg once daily
16–23 kg	45 mg bid for 5 d	45 mg once daily
Less than 16 kg	30 mg bid for 5 d	30 mg once daily
Children less than 1-yr-old		
Age 6–11 mo	25 mg bid for 5 d	25 mg once daily
Age 3–5 mo	20 mg bid for 5 d	20 mg once daily
Under 3 mo	12 mg bid for 5 d	Not recommended
Zanamivir		
Adults	Two 5 mg inhalations bid for 5 d	Two 5 mg inhalations once daily
Children 7 yr and older	Two 5 mg inhalations bid for 5 d	Two 5 mg inhalations once daily
Children under 7 yr	Not recommended	Not recommended

from avian strains and from human strains.[3] The viral evolution of this novel strain dates back to 1918. The final step in the process was likely a reassortment between 2 swine viruses which themselves contained both avian and human influenza genes.[6]

Guidance for the public and for physicians was issued almost daily throughout the spring.[2,7] Revisions were frequent. Initial guidance was aimed at limiting spread of the virus. Cough hygiene and hand washing were stressed and ill people were urged to stay home. Facts regarding transmission of the virus were stressed. The public was assured that the virus was not acquired by eating pork and that there was no reason to slaughter pigs. Guidance for use of antiviral medication was released as soon as susceptibility of the virus was determined; both oseltamivir and zanamivir were active against the novel strain while amantadine and rimantadine were not. The Emergency Use Authorization of Tamiflu (oseltamivir) allowed for use of oseltamivir in children under a year of age; see Table 2 for recommended doses.[2] Initial recommendations for treatment included affected people and their household contacts. These recommendations were revised as the disease became widespread. By May, the recommendation was changed to treatment for hospitalized patients and for patients at higher risk for complications. The first cases of oseltamivir resistant novel H1N1 were reported in patients receiving oseltamivir treatment or prophylaxis. As of August there was no transmission of resistant novel H1N1 strains.[1] However, during 2007 to 2008, seasonal influenza A of the H1N1 type with oseltamivir resistance emerged unrelated to oseltamivir use. These strains caused illness similar to sensitive strains.[8] During 2008 to 2009, over 99% of seasonal influenza A H1N1 isolates were resistant to oseltamivir, whereas 100% of seasonal influenza A H3N2 and influenza B isolates were sensitive to oseltamivir.[2] There is clinical evidence that when used appropriately in children infected with susceptible influenza strains, oseltamivir therapy reduces the risks of influenza-related complications and hospitalizations for children with chronic medical conditions.[9]

Information for specific groups was released as the epidemic progressed: parents and caregivers, pregnant women, day and residential camps, child care programs, schools, colleges and universities, travelers and travel industry, clinicians, laboratorians, adults with HIV infection, people with diabetes, people with cardiovascular disease, tribal nations, businesses and employers, deaf and hard of hearing, people in contact with pigs, and people with certain medical conditions.[2] Guidance was provided and updated: epidemiology and surveillance; clinical guidance regarding detection, care, data collection, and use of 23-valent pneumococcal vaccine during the H1N1 outbreak; infection control in obstetric settings, for homeless and emergency shelters, for postmortem care and safe autopsy, for correctional and detention facilities, for healthcare settings, for laboratories, and for outpatient hemodialysis centers; laboratory testing using rapid diagnostic tests, specimen collection, processing and testing, submission of tissue specimens, antiviral susceptibility testing, sequencing, real-time RT-PCR; patient guidance regarding caring for sick people in the home, physician directions; guidance for pregnant and breast-feeding women; guidance for emergency personnel, for community settings; guidance for travel, cruise ships, and flight crews. All this information was available on the CDC website and was updated regularly.[2]

In Mexico, schools, museums, libraries, and social events were cancelled. Travel advisories went into effect. When the disease began to cause outbreaks in New York City, schools were closed. In many areas, hospitals and physicians offices were overrun with both sick individuals and with the worried well. School closures sent children into the community; the timing was like a second spring break. Social distancing was discussed in the pandemic plans but when schools were closed, there were few efforts made to keep children at home. The initial recommendation for how long ill children should stay at home was 7 days.[2] School closure and isolation of ill and exposed children led to loss of educational time. Over the summer, camps experienced outbreaks and the need for a 7-day isolation period was questioned. As school opening approached, the time a sick person was to stay at home was revised to 24 hours after resolution of fever, in the absence of antipyretic use. However, the 7-day furlough for healthcare workers continued to be recommended as of late August. The guidance issued for state and local public health officials and school ad-

ministrators for school responses to influenza during the 2009–2010 school year is designed to decrease exposure while limiting disruption of learning.[2] School closure and dismissals may be required but should be avoided wherever possible; it will be a difficult balancing act to protect the health of students as well as providing optimal education. Strategies to handle schools if the severity of the novel H1N1 strain remains the same as well as if severity increases are outlined in a Technical report for state and local public health officials and school administration (Available at: www.cdc.gov/h1n1flu/schools/technicalreport.htm). Strategies if conditions are similar to spring 2009 include the following: (1) Stay home when sick—students and staff with flu-like illness should stay home for at least 24 hours after they no longer have fever, without use of fever-reducing medicines; (2) Separate ill students and staff—persons with flu-like illness should be sent to a separate room until they can be sent home. If possible the ill person should wear a mask as should those who care for them; (3) Hand hygiene and respiratory etiquette as outlined elsewhere; (4) Routine cleaning—there is no need for special cleaning with bleach or other agents; (5) Early treatment of high risk students and staff—high risk includes those who are pregnant, have asthma or diabetes, have compromised immune systems or neuromuscular diseases; early treatment may prevent hospitalizations and deaths; (6) Consideration of selective school dismissal—this might be appropriate for medically fragile children and those at high risk. Additional measures should be considered under conditions of increased severity compared with spring 2009: (1) Active screening of students and staff for fever and flu-like illness upon arrival to school—separate ill persons and send them home as soon as possible; (2) High risk students and staff stay home; (3) Students with ill household members stay home—they should stay home for 5 days as this is the time when they are most likely to become ill; (4) Increase distance between people at schools—consider separating desks and avoiding classes that bring together multiple groups of children; (5) Extend the period for ill persons to stay home to at least 7 days; (6) School dismissals—if done, the decision should be reassessed weekly and every effort should be made to find ways to continue to provide education through other means. All decisions regarding school dismissal or closure should be made at the local level with consultation with local and state health departments.

Recommendations regarding infection control within healthcare settings were released in April and updated in May.[2] Respiratory hygiene and cough etiquette in healthcare settings are recommended to prevent transmission of all respiratory infections (available at: www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm). Components include the following: visual alerts, respiratory hygiene/cough etiquette, masking, and separation of persons with respiratory symptoms and droplet precautions. Visual alerts should be placed at entrances and should be in languages appropriate for the population. Alerts should be posted regarding reporting of flu symptoms, covering a cough, and proper use of personal protective equipment. Respiratory hygiene and cough etiquette recommends covering the nose and mouth when coughing or sneezing, using tissues to contain secretions and disposing of them, and performing hand hygiene after contact with respiratory secretions and contaminated objects. Masks should be offered to persons who are coughing; coughing individuals should sit at least 3 feet away from others. Droplet precautions should be used by healthcare personnel when examining a patient with respiratory symptoms; this includes the use of surgical or procedure masks. For care of patients with suspected, probable or confirmed H1N1, fit-tested disposable N95 respirator should be worn rather than surgical or procedure masks. Patients with novel H1N1 should be considered contagious from 1 day before symptoms to 7 days after symptoms begin. Young children often shed virus for longer intervals of time. Routine cleaning and disinfection are sufficient for environmental areas.

In a recently published study, soap and water hand hygiene was statistically superior to hand hygiene with alcohol rubs; all methods of hand hygiene were highly effective in reducing the titer of a seasonal influenza A strain applied to the hands.[10] Interestingly, hand drying without any hygiene resulted in an immediate drop in titer of virus as determined by either culture or real time reverse transcription polymerase chain reaction.

In July, a summary of characteristics of patients hospitalized in April and May was published.[1] The most common reasons for admission were pneumonia and dehydration. Almost two-thirds of patients had an underlying condition; the most common were chronic lung disease, immunosuppression, chronic cardiac disease, diabetes, and obesity. The association of obesity with severe illness and respiratory failure was remarkable. Severe illness was reported in pregnant women as well. In June, the initial report of infection among healthcare personnel provided details of 13 cases of illness acquired in healthcare settings. In the majority of cases, the healthcare provider had not worn a mask during patient contact. As of August 2009, the majority of hospitalized patients and deaths have been in children and young adults; only 5% of hospitalizations and 8% of deaths were in patients 65 years of age and older.

As soon as the extent of spread became clear, efforts to develop a vaccine were begun. Five manufacturers are developing vaccines for the novel H1N1; testing for safety and efficacy began in the summer of 2009.[2] It is anticipated that vaccine will be available by mid October. The strain chosen for the monovalent vaccine is A/California/07/2009; the same manufacturing methods are being used for the vaccine. Both inactivated and live attenuated formulations are being manufactured. No adjuvants will be used initially although vaccines with adjuvants are being developed and may be available later. It is anticipated that 2 doses of the vaccine will be necessary for protection of individuals without prior cross reacting antibody. In May 2009, serologic studies of stored serum collected during vaccine studies showed that children under 18 years of age had no cross reacting antibody to the novel H1N1 strain.[1] Antibody was detected in 6% to 8% of adults aged 18 to 64 and in 33% of those over age 60; furthermore, these levels of antibody were boosted following seasonal influenza immunization. No boosting was found among children. Analysis of hospitalization data (as of July 2009) showed the median age was 20 years and the highest incidence of hospitalization was among children under 4 years. Medical risk factors for severe illness were similar to those for severe seasonal influenza: chronic heart, lung, renal, liver disease, cancer, or immunosuppression and pregnancy.

The Advisory Committee on Immunization Practices (ACIP) recommends that when vaccine for the novel H1N1 strain becomes available, it should be used for the following target groups: pregnant women; household contacts and those caring for infants under 6 months of age; health care and emergency medical service personnel; people age 6 months to 24 years; people aged 24 to 64 years of age with medical conditions that put them at higher risk for complications of influenza.[1] The estimated number of people in these target groups is 159 million. If the supply of vaccine is not adequate initially or later, the following priorities are recommended: pregnant women; persons who live with or provide care for infants aged less than 6 months; health care and emergency medical services personnel who have direct contact with patients or infectious material; children aged 6 months through 4 years; children and adolescents aged 5 through 18 years who have medical conditions that put them at higher risk for influenza-related

complications. The estimated number of people in this subset is 42 million. It is not yet established how many doses of vaccine are required for protection. As vaccine production will be ongoing, it is recommended that vaccine be used as soon as available and not held in reserve for subsequent doses. Simultaneous administration of seasonal vaccine with the monovalent H1N1 vaccine is permissible provided different anatomic sites are used. However, simultaneous administration of live, attenuated vaccines against seasonal and novel H1N1 is not recommended. Seasonal influenza vaccination should begin as soon as possible for all persons for whom it is recommended.

Several methods for surveillance for adverse events following immunization are planned.[11] The Vaccine Adverse Events Reporting System should be used by all providers and can be used by patients and families. The Vaccine Safety Database will be used to test hypotheses. The American Academy of Neurologists is collaborating with the CDC to monitor for neurologic events following immunization. The Vaccine Analytic Unit and the Emerging Infections Program will be involved in surveillance for adverse events. The Clinical Immunization Safety Assessment Network will be involved in evaluating patients with adverse events.

The Advisory Commission on Childhood Vaccines has developed the following paragraph to remind care givers of the Vaccine Injury Compensation Program[12]; seasonal influenza vaccine is a covered vaccine: Vaccine administrators and other care providers should be mindful of the National Vaccine Injury Compensation Program, a "no fault" Federal program that can provide significant funding to children and adults seriously injured by covered vaccines. A "table" of the specific vaccines and the injuries presumed to be compensable can be found at http://www.hrsa.gov/Vaccinecompensation/table.htm. Other vaccine-related injuries may be proved legally under certain circumstances. Although you do not need an attorney to file a petition for compensation, the program provides for payment of legal expenses at no cost to the injured party. Basic information on the program can be found at http://www.hrsa.gov/Vaccinecompensation/. The Clerk of the US Court of Federal Claims (202 357–6400) will provide a list of experienced attorneys upon request. A 3-year statute of limitations on filing a claim for injury and a more complex statute of limitations on vaccine-related death make it imperative that patients or their parents or representatives be informed promptly of the program by medical care providers whenever the provider believes that the possibility of a vaccine-related injury exists. Any suspected adverse vaccine event should be reported to the Vaccine Adverse Events Reporting System (available at: http://vaers.hhs.gov/).

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