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SYMPOSIUM ON INFECTIONS OLD AND NEW

Novel Swine—Origin Influenza A: The 2009 H1N1 Influenza Virus

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Abstract During April-May 2009, a novel H1N1 influenza virus was determined to be the cause of influenza outbreaks in North America. By June 2009, widespread infections were recorded all over the world and an ongoing pandemic was declared. The clinical manifestations ranged from a self limited illness to fatal disease. Current clinical data suggest that the highest infection rates and complications occur in children and young adults. In contrast to seasonal influenza, the rates of hospitalization and death in adults 65 years or older were low. Risk factors for severe disease are similar to those of seasonal influenza and include diverse medical conditions. However, pregnant women and children with neurodevelopmental disorders or chronic pulmonary conditions are at highest risk of developing severe disease. Rapid antigen detection tests have variable and suboptimal sensitivity for diagnosis of novel H1N1 influenza. Diagnosis is confirmed by real-time reverse transcriptase polymerase chain reaction or by virus isolation in cell culture. Treatment is recommended with oral oseltamivir or inhaled zanamavir for patients who are at risk of complications as well as those who are worsening clinically or have evidence of lower respiratory tract infection. Treatment with intravenous peramivir can be used in special situations when oral or inhaled antiviral therapy is not tolerated or considered inadequate. Inactivated and live attenuated vaccines are available. Current vaccination recommendations and infection control measures are discussed.

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In April 2009, the US Centers for Disease Control and Prevention (CDC) identified the first two cases of a novel swine origin (H1N1) virus. These were two children, a 10 year old boy and a 9 year old girl, residing in Southern California and who had no exposure to pigs [1]. Concerns emerged when it was revealed that the virus had a unique gene segment combination not previously reported in human or swine [2]. At the same time the H1N1 virus was also determined to be the cause of outbreaks of respiratory illness in Mexico [3]. The virus was unique and substantially different from the seasonal influenza vaccine H1N1 strain. No prior swine exposure was needed and the virus was transmitted person-to-person. By May 2009, the novel H1N1 virus had infected over 10,000 people in North America as well as other countries. The lack of immunity to this virus and the ease of its human-human transmission have resulted in widespread outbreaks in different countries prompting the World Health Organization to declare an ongoing world pandemic of the novel influenza H1N1 virus on June 11, 2009 [4]. Based on global experience, the 2009 H1N1 influenza virus is expected to be the predominant circulating virus in the next influenza season.

Clinical Manifestations

Most cases of H1N1 influenza are self limited particularly among healthy persons. Laboratory confirmation underestimates the true incidence of H1N1 influenza because it is mainly done for those hospitalized with severe symptoms. The clinical manifestations of 2009 H1N1 influenza are

similar to seasonal influenza [5]. The risk factors for severe infection due to H1N1 influenza are also similar to seasonal influenza and include different chronic underlying medical conditions such as heart, lung, renal and liver disease, cancer, immunosuppression, as well as pregnancy [6, 7]. The incidence of hospitalization among pregnant women is five times higher than the general population [8]. However, there appears to be a shift of hospitalization and death cases to the younger age groups among those infected with H1N1 compared to seasonal influenza [5]. The age distribution and severity of disease are similar in different countries.

CDC data as of July 31, 2009 showed the highest infection rate occurring in persons 5–24 years; the median age of confirmed influenza cases is 12 years [9]. The incidence is lowest in people ≥65 years. The median age of hospitalized patients with H1N1 influenza is 20 years, while the median age of deaths was 37 years and the highest rate of hospitalization was among children younger than 4 years. In contrast to seasonal influenza, the rates of hospitalization and death from H1N1 influenza were unexpectedly low in adults ≥65 years; 5% and 8% respectively [9].

In a CDC surveillance study of 36 deaths among children due to 2009 H1N1 influenza, 7 (19%) were younger than 5 years and 24 (76%) had underlying medical conditions [10]. Of those 24 children, 22 (92%) had neurodevelopmental disorders including cerebral palsy and developmental delay; 9 of whom had concomitant chronic pulmonary disorders [10]. Neurological and neuromuscular disorders are known risk factors of severe and complicated influenza in children [11].

In a clinical study of 642 cases of novel H1N1 influenza virus in 41 states, the age range was 3 months to 81 years [5]. However, most patients (60%) were 18 years of age or younger; 40% were 10–18 years of age. Only 5% of patients were 51 years or older. This suggests that young people are most susceptible to H1N1 influenza than older persons; the teenage children were most commonly affected in the 2009 H1N1 pandemic. The clinical manifestations were similar to seasonal influenza. The clinical spectrum of H1N1 illness is wide and varies from a self-limited illness to fatal disease. Patients most frequently presented with fever (94%), cough (92%) and sore throat (92%), vomiting (25%) and diarrhea (25%). Hospitalization rate was 9%; 36 of 399 patients for whom hospitalization status was known [5]. The age range of hospitalized patients was 19 months to 51 years. Of the 22 patients who had data available, chronic medical conditions were present in 41%. Eleven (50%) had radiologically confirmed pneumonia. Eight (36%) were admitted to intensive care units and 4 (18%) required mechanical ventilation. Fourteen (74%) patients were treated with oseltamivir [5].

In a study of 272 hospitalized patients with 2009 H1N1 influenza, the median age was 21 years and 45% of patients were children under the age of 18 years [12]. Only 5% were 65 years of age or older. Underlying medical conditions were present in 73% of patients including asthma (25%), diabetes mellitus (15%) and immunosuppressive conditions (15%). Pregnant women accounted for 7% of admissions. Antiviral therapy was initiated at a median of 3 days after onset of illness [12]. Data suggest that antiviral therapy was beneficial when given early; of the 19 (7%) patients who died, none received antiviral therapy within 48 h of onset of illness [12].

Clinicians should be aware of the potential of severe bacterial infections during the course of influenza in children including those who had no underlying medical conditions. Similar to seasonal influenza, the severe illness and mortality associated with H1N1 influenza may be related to secondary bacterial infections and exacerbation of underlying conditions. In the CDC surveillance study of pediatric deaths, 10 (43%) of 23 children with available microbiological data had invasive bacterial infections including 6 of 8 children who are 5 years of age or older [10]. The most common bacterial pathogens identified in influenza patients including H1N1 are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and group A streptococcus [10, 13, 14].

Outbreaks of H1N1 influenza virus occur most frequently among young people gatherings such as schools, camps and colleges and can serve as a point of community spread. These H1N1 outbreaks have also resulted in the closure of different schools and camps during the 2009 spring and summer in the USA and other countries [15, 16].

As with other seasonal influenza viruses, 2009 H1N1 influenza virus has been associated with neurological complications [17]. Severe encephalopathy and death from neurological complications were previously reported in children who had seasonal influenza [18, 19]. Such severe complications have not yet been reported in the 2009 H1N1 influenza virus infected patients. The frequency of neurological complications is such patients is unknown. Seizures and altered mental status were reported in 4 children aged 7 to 17 years in the Dallas area [17]. They presented with influenza-like illness and seizures or altered mental status. Three of these children had abnormal electroencephalograms. All had H1N1 RNA detected by rRT-PCR detected in nasopharyngeal secretions but not in the cerebrospinal fluid. All received oseltamivir and 3 of 4 received rimantadine. All recovered without neurological sequelae [17].

Diagnosis

Testing for novel influenza A (2009 H1N1) virus should be considered in patients with severe respiratory illness and as

early as possible after onset of symptoms [20, 21]. Confirmation of suspected infection should also be considered in immunocompromized patients as well as in pregnant and breast feeding women. Testing has been done in different communities and countries for surveillance purposes. A nasal wash, a nasopharyngeal swab, or a combined nasopharyngeal and oropharyngeal swabs can be used for testing [20]. Endotracheal aspirate or bronchoalveolar lavage should be collected in intubated patients. The swabs recommended for use are those with synthetic tips and with a plastic or aluminum shaft such as polyster or Dacron swabs [20]. Cotton swabs, those with wooden shafts as well as calcium alginate swabs are not recommended. Specimens should be placed in viral transport medium and held at 4°C by either refrigeration or placement in ice for laboratory transport [20].

Commercially available rapid influenza diagnostic tests including the direct and indirect immunofluorescence assays (DFA, IFA) are used to diagnose seasonal influenza and can differentiate between influenza A and B infections [22]. The sensitivity of the rapid tests is higher in specimens collected from children than adults. A patient with novel influenza A 2009 H1N1 may test positive for influenza A by the rapid tests [23]. A positive test for influenza A cannot differentiate seasonal and novel influenza A 2009 H1N1 viruses [23]. The rapid tests have suboptimal sensitivity for diagnosis of seasonal influenza and their sensitivity and specificity for diagnosis of novel influenza A 2009 H1N1 is unknown [24]. Preliminary studies suggest that these tests are significantly less sensitive than the polymerase chain reaction assays especially if the novel influenza A 2009 H1N1 virus is present in low concentrations in respiratory specimens [24]. The sensitivity ranged from 10% to 70% [24–26]. Moreover, the sensitivity for detection of novel influenza A (H1N1) virus is less than seasonal influenza viruses. Thus the use of these tests in cases of suspected of suspected novel influenza A (H1N1) infection may not be reliable. A negative rapid diagnostic test neither excludes novel influenza A (H1N1) infection nor should it be used to rule out an outbreak or dictate infection control measures [25].

The diagnosis of novel influenza H1N1 virus infection in a patient with influenza-like illness is confirmed by detection of influenza specific RNA with real-time reverse trascriptase polymerase chain reaction (rRT-PCR) or by virus isolation in culture [5, 24, 25]. The rRT-PCR is available at the CDC and state public health laboratories. However, testing for the 2009 H1N1 virus by rRT-PCR should be prioritized for persons with suspected or confirmed influenza requiring hospitalization and according to guidelines from local health authorities [20, 25].

Isolation of novel influenza A (H1N1) virus by culture is diagnostic of infection. However, the viral culture is time consuming and a negative culture cannot exclude infection [20].

Serological testing by detecting antibodies in acute and convalescent sera (2–3 weeks apart) can be used to establish a retrospective diagnosis of infection for epidemiological purposes. However, these tests are not routinely available and their clinical utility is limited [24].

Treatment

Most patients with 2009 H1N1 influenza infection have self limited disease similar to seasonal influenza and do not require antiviral therapy. As of September 2009, The CDC recommended giving a priority of antiviral therapy to patients who are hospitalized and those who are at risk of complications including immunocompromized patients [21, 27]. Persons with suspected or confirmed influenza and who are at highest risk of complications include children younger than 2 years, adults older than 65 years, pregnant women, patients with underlying medical conditions, immunocompromized patients and those younger than 19 years of age who are receiving chronic aspirin therapy [8, 21, 27, 28]. About 70% of patients hospitalized with H1N1 influenza had a recognized risk factor [27]. Children 2 to 4 years of age with mild illness and no underlying conditions do not require antiviral therapy. Most patients who have self limited disease and appear to be recovering from influenza do not need any antiviral therapy. However, persons with suspected influenza who are clinically worsening or have evidence of lower respiratory tract infection should receive antiviral therapy, regardless of age or underlying medical conditions [27].

Obesity may be associated with increased risk of complications from H1N1 influenza. However, obese persons frequently have underlying medical conditions that are associated with increased complications such as diabetes mellitus and respiratory diseases [27].

The two classes of anti-influenza medications are the adamantanes and the neuraminidase enzyme inhibitors. During 2008–2009 influenza season, oseltamivir-resistant H1N1 strains were present in the USA. However, current novel 2009 H1N1 influenza virus strain, which is antigenically distinct from the 2008–2009 strain, is susceptible to neuraminidase inhibitors but resistant to the adamantane antiviral agents, amantadine and rimantadine [2, 5, 27]. Sporadic cases of oseltamivir resistant isolates have been reported in the US and other countries. However, there is no evidence of ongoing community-wide spread.

Based on susceptibility data as of September 2009, antiviral therapy is recommended with one of the neuraminidase inhibitors: oseltamivir or zanamavir [21]. The recommended doses are similar to those used to treat

seasonal influenza (Table 1). Some experts recommended use of double the regular dose of oseltamivir for severely ill patients, but there is no clear data to support such practice [21]. The duration of treatment is 5 days. However, longer courses may be given to patients who remain hospitalized with severe symptoms. Therapy should be started as early as possible, preferably within the first 48 h of onset of symptoms [29]. Treatment should still be considered for ill patients presenting after 48 h of onset of symptoms. Treating physicians should neither await nor depend on the results of the rapid influenza tests because of the low and variable sensitivity of these tests for H1N1 influenza virus diagnosis (40–70%) [24, 26]. Oseltamivir is not routinely approved for children younger than 1 year. Infants experience high rates of mortality and morbidity from influenza. Although safety and efficacy of use of anti-influenza medications in infants is unclear, the CDC had issued an authorization for emergency use of oseltamivir in children younger than 1 year of age [21]. Infants receiving oseltamivir for prophylaxis or treatment should be carefully monitored for adverse events.

Prophylactic therapy is reserved for those at risk of complications who have been in contact with a person who is diagnosed or highly suspected of having H1N1 infection during the infectious period [21, 27]. Prophylaxis is also indicated for health care workers with unprotected close contact to a confirmed case of H1N1 or seasonal influenza. Prophylaxis should be given within 48h of exposure. Such individuals should also be counseled about reporting early signs and symptoms of influenza. Prophylaxis is not indicated for healthy adults or children in the setting of potential exposure at school, camp or in the community [21]. For post-exposure prophylaxis, either oseltamivir or zanamavir is given at half the daily treatment dose for a total of 10 days (Table 1) [21].

The US Department of Health and Human Services declared the incidence and spread of 2009 H1N1 influenza a public health emergency. In response, on October 23, 2009, the FDA authorized the use of the unapproved drug, Peramivir intravenous (IV), for treatment of certain adults and children with suspected or confirmed 2009 H1N1 infection [30]. Peramivir should not be used to treat seasonal influenza A or B infections or outpatients with acute uncomplicated 2009 H1N1 infection. Peramivir should not also be used for chemoprophylaxis [30]. Clinicians requesting peramivir IV under the Emergency Use Authorization are advised to go to www.cdc.gov/h1n1flu/eua.

Peramivir is a neuraminidase inhibitor, is still being evaluated in phase 3 clinical trials. Commonly reported adverse events in these trials are nausea, vomiting and neutropenia. No trials have been conducted in children or pregnant women [30]. The standard adult dose is 600 mg once daily for 5 to 10 days. Suggested pediatric doses vary with age (Table 1) [30]. Peramivir dosage should be adjusted in patients with impaired renal function. No adjustment is needed in patients with hepatic dysfunction. Indications for use include patients in whom IV therapy is considered appropriate such as those not responding to oral oseltamivir or inhaled zanamavir therapy, or if delivery of these medications is considered or expected to be not feasible or dependable [30]. Treating clinicians should report any adverse events.

Because of the risk of developing Reye syndrome, aspirin should not be administered to children 18 years of age and younger who have documented or suspected influenza including H1N1 virus [27]. Other antipyretics such as acetaminophen or non-steroidal anti-inflammatory medications can be used.

Vaccine

The most effective way to prevent influenza and its complications is vaccination. Current seasonal influenza vaccines are unlikely to protect against 2009 H1N1 influenza [2, 31]. This is particularly true for children who received seasonal influenza vaccine and in whom no cross reactive antibodies to 2009 H1N1 influenza virus were detected after vaccination [31]. Specific monovalent H1N1 influenza vaccines have recently been developed, and on September 15, 2009 four vaccines received approval from the USA Food and Drug Administration [32]. Both inactivated and live attenuated formulations are available (Table 2). All are produced by using embryonated hen eggs and no adjuvants are added in the vaccines. Two vaccine doses given 4 weeks apart are needed for children 6 months to 9 years of age [32, 33]. The vaccines contain the strain A/California/7/2009(H1N1)pdm [9]. Initial data suggest that 2009 H1N1 monovalent vaccines are safe and immunogenic. The most common reported adverse events in adult recipients are local discomfort and generalized symptoms such as malaise, headache and arthralgia. Among children who received the monovalent vaccine manufactured by Sanofi Pasteur Inc (Swiftwater, PA), adequate immunologic response was reported in 25%, 36% and 76% of children of children aged 6–35 months, 3–9 years and 10–17 years respectively [32]. Because initial supplies may not be enough for widespread immunization, the CDC' Advisory Committee on Immunization Practices (ACIP) recommended giving priority of vaccination to five groups considered at the highest risk of influenza complications. These include pregnant women, close contacts of children less than 6 months of age, health care personnel, children and young adults 6 to 24 years of age and persons 25–64 years of age with underlying medical conditions that are associated with increased

Table 1 Dosing recommendations for influenza treatment or chemoprophylaxis

Medication	Route	Age	Treatment dose (5 days[b])	Prophylaxis dose for 10 days	Body weight (kg)
Oseltamivir	Oral	Younger than 3 months	3 mg/kg/dose 2×/day	Not recommended unless critical situation due to limited data on use in this age group	N/A
		3–11 months	3 mg/kg/dose 2×/day	3 mg/kg/dose 1×/day	N/A
		≥ 12 months	30 mg 2×/day	30 mg 1×/day	≤15 kg
			45 mg 2×/day	45 mg 1×/day	>15 kg–23 kg
			60 mg 2×/day	60 mg 1×/day	>23 kg–40 kg
			75 mg 2×/day	75 mg 1×/day	> 40 kg
		Adults	75 mg capsule 2×/day	75 mg capsule 1×/day	N/A
Zanamivir	Inhalation	≥7 years	10 mg (two 5 mg inhalations) twice	10 mg (two 5 mg inhalations) once	N/A
		≥ 5 years	N/A	10 mg (two 5 mg inhalations) once	N/A
		Adults	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily	N/A
Peramivir[a]	Intravenous	0–30 days	6 mg/kg		N/A
		31–90 days	8 mg/kg		N/A
		91–180 days	10 mg/kg		N/A
		181 days–5 years	12 mg/kg		N/A
		6 years–17 years	10 mg/kg		N/A
		Adult (Maximum)	600 mg		N/A

[a] Not recommended for prophylaxis

[b] Peramivir may be given 5–10 days

Modified from CDC: Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 Season

influenza mortality and morbidity [9]. Vaccination is recommended to be given as early as possible and to as many as possible persons in the target groups. Recommendations to vaccinate additional groups are likely to occur as vaccine availability increases. If the supply of the vaccine does not meet the demand of the above targeted groups, the ACIP recommends giving the vaccine to the first three priority groups including pregnant women, close contacts of infants less than 6 months of age and health care workers [9]. Additionally children aged 6 months to 4 years and persons 5–18 years of age with underlying medical conditions that are associated with increased mortality and morbidity should be given vaccination priority [9].

Table 2 Influenza A (H1N1) 2009 monovalent vaccines approved for use in the United States, October 6, 2009

Vaccine type	Manufacturer	Presentation	Age group	No. of Doses	Route
Inactivated	Sanofi Pasteur	0.25 mL prefilled syringe	6–35 month	2	Intramuscular
		0.5 mL prefilled syringe	≥36 month	1 or 2	Intramuscular
		5.0 mL multidose vial	≥6 month	1 or 2	Intramuscular
Inactivated	Novartis Vaccines and Diagnostics Limited	5.0 mL multidose vial	≥4 year	1 or 2	Intramuscular
		0.5 mL prefilled syringe	≥4 year	1 or 2	Intramuscular
Inactivated	CSL Limited	0.5 mL prefilled syringe	≥18 year	1	Intramuscular
		5.0 mL multidose vial	≥18 year	1	Intramuscular
LAIV[a]	MedImmune LLC	0.2 mL sprayer	2–49 year	1 or 2	Intranasal

Modified from CDC: Update on influenza A (H1N1) monovalent vaccines. MMWR October 9, 2009

[a] Live Attenuated Influenza Vaccine

Infection Control/Isolation

Transmission of the 2009 H1N1 influenza virus appears to be similar to the seasonal influenza viruses. Continued identification of cases suggests sustained human-to-human transmission. The mode of transmission is believed to be via large droplets and possibly via smaller droplets generated during coughing [34]. There is a concern about transmission of the virus via contacts with contaminated fomites [35, 36]. Because of the increased frequency of gastrointestinal symptoms in novel H1N1 influenza virus infected patients, fecal-oral transmission remains a concern. All respiratory secretions and body fluids including diarrheal stools are considered potentially infectious [37].

The incubation period of 2009 H1N1 influenza appears to be 2 to 7 days. The duration of viral shedding is not known. However, guidelines for isolating patients with seasonal influenza can be followed. Influenza patients are potentially contagious starting 1 day before they are symptomatic. Such infected patients are assumed to be shedding the virus for the duration of their illness and until resolution of the fever or until 7 days from onset of illness [37]. However, young children and immunocompromized patients may continue shedding the virus for longer durations [38].

Standard Precautions include implementing hand hygiene appropriately as well as the use of nonsterile gloves for any contact with potentially infectious material. The use of gowns along with eye protection may be needed for situations in which splashes of secretions are generated. As of October 2009, CDC recommends the use of a fit-tested disposable N95 respirator or equally protective respirators for respiratory protection of healthcare personnel who are in close contact with suspected or confirmed 2009 H1N1 influenza patients [37]. This includes being within 6 ft of the patient or in a enclosed airspace such as an average patient room. Facemasks that are tested to be effective physical barriers to droplets are considered to be alternatives to respirators in situations of respirator shortage or unavailability [37].

Special precautions should be undertaken during procedures that generate aerosols such as bronchoscopy, endotracheal intubation and extubation, sputum induction, open suctioning of airways, resuscitation and performing autopsies. Such procedures should be conducted in an airborne infection isolation room when feasible to decrease the concentration of aerosols and prevent their spread [37]. Other procedures may also be associated with aerosol generation such as administration of nebulized medications, obtaining nasopharyngeal swabs or aspirates, and use of high-flow oxygen; however, the magnitude of aerosol generation and risk of exposure in these situations is not well known [37].

Advice to Clinicians

The clinical findings and infection control issues related to the novel 2009 H1N1 influenza virus are rapidly evolving and the recommendations of testing, treatment and prevention may change as more information becomes available. Clinicians are advised to monitor updates on CDC guidelines and recommendations at www.cdc.gov/h1n1flu.

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