REVIEW ARTICLE

MEDICAL PROGRESS

Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection

Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza*

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During the spring of 2009, a novel influenza A (H1N1) virus of swine origin caused human infection and acute respiratory illness in Mexico.[1,2] After initially spreading among persons in the United States and Canada,[3,4] the virus spread globally, resulting in the first influenza pandemic since 1968 with circulation outside the usual influenza season in the Northern Hemisphere (see the Supplementary Appendix, available with the full text of this article at NEJM.org). As of March 2010, almost all countries had reported cases, and more than 17,700 deaths among laboratory-confirmed cases had been reported to the World Health Organization (WHO).[5] The number of laboratory-confirmed cases significantly underestimates the pandemic's impact. In the United States, an estimated 59 million illnesses, 265,000 hospitalizations, and 12,000 deaths had been caused by the 2009 H1N1 virus as of mid-February 2010.[6] This article reviews virologic, epidemiologic, and clinical data on 2009 H1N1 virus infections and summarizes key issues for clinicians worldwide.

VIRAL CHARACTERISTICS

Pandemic 2009 H1N1 virus derives six genes from triple-reassortant North American swine virus lineages and two genes (encoding neuraminidase and matrix proteins) from Eurasian swine virus lineages.[4] Although the 2009 H1N1 virus is antigenically distinct from other human and swine influenza A (H1N1) viruses,[4] strains of this virus have been antigenically homogeneous, and the A/California/7/2009 strain that was selected for pandemic influenza vaccines worldwide is antigenically similar to nearly all isolates that have been examined to date.[7] Multiple genetic groups have been recognized, including one recently predominant lineage,[8] but any possible clinical importance of different lineages remains uncertain. Reassortment has not occurred with human influenza viruses to date. The level of pulmonary replication of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses in experimentally infected animals,[9-11] but the 2009 pandemic strain generally lacks mutations that are associated with increased pathogenicity in other influenza viruses (Table 1 in the Supplementary Appendix).

EPIDEMIOLOGY

INFECTION, ILLNESS, AND DISEASE BURDEN

Most illnesses caused by the 2009 H1N1 virus have been acute and self-limited, with the highest attack rates reported among children and young adults. The relative sparing of adults older than 60 years of age[3,12,13] is presumably due to the exposure

of persons in this age group to antigenically related influenza viruses earlier in life, resulting in the development of cross-protective antibodies (Table 2 in the Supplementary Appendix).[10,14]

Rates of illness from 2009 H1N1 virus infection have varied, but during one outbreak in New Zealand, the attack rate of illness was estimated at 7.5%, and the attack rate of overall infection was estimated at 11%.[15] An estimated one third of infections in one boarding school were subclinical.[16] After the peak of a second wave of infection in Pittsburgh, the seroprevalence of hemagglutination-inhibition antibody suggested that about 21% of all persons and 45% of those between the ages of 10 and 19 years had become infected.[17]

The overall case fatality rate has been less than 0.5%, and the wide range of estimates (0.0004 to 1.47%) reflects uncertainty regarding case ascertainment and the number of infections.[18-20] The case fatality rate for symptomatic illness was estimated to be 0.048% in the United States[21] and 0.026% in the United Kingdom.[13] In contrast to seasonal influenza, most of the serious illnesses caused by the pandemic virus have occurred among children and nonelderly adults, and approximately 90% of deaths have occurred in those under 65 years of age.

Rates of hospitalization and death have varied widely according to country.[22] Hospitalization rates have been highest for children under the age of 5 years,[22] especially those under the age of 1 year, and lowest for persons 65 years of age or older.[23] In the United States, among patients who were hospitalized with pandemic influenza, 32 to 45% were under the age of 18 years.[23,24] Approximately 9 to 31% of hospitalized patients have been admitted to an intensive care unit (ICU), where 14 to 46% of patients have died.[23-27] The overall case fatality rate among hospitalized patients appears to have been highest among those 50 years of age or older and lowest among children.[1,13,23,27]

TRANSMISSION AND OUTBREAKS

The mechanisms of person-to-person transmission of the 2009 H1N1 virus appear to be similar to those of seasonal influenza, but the relative contributions of small-particle aerosols, large droplets, and fomites are uncertain. Rates of secondary outbreaks of illness vary according to the setting and the exposed population, but estimates range from 4 to 28%. Household transmission is highest among children and lowest among adults over 50 years of age.[28,29] In the United Kingdom and the United States, the rates of secondary outbreaks in households were 7% and 13%, respectively, with children at increased risk for infection by a factor of two to four.[16,28] Many outbreaks have occurred in schools, day-care facilities, camps, and hospitals.[16,30,31] Estimates of the basic reproduction number (the mean number of secondary cases of infection transmitted by a single primary case in a susceptible population) generally range from 1.3 to 1.7 according to the setting, which are similar to or slightly higher than the estimates for seasonal influenza,[20,32,33] but may be as high as 3.0 to 3.6 in outbreaks in crowded schools.[31]

RISK GROUPS AND RISK FACTORS FOR SEVERE DISEASE

Approximately one quarter to one half of patients with 2009 H1N1 virus infection who were hospitalized or died had no reported coexisting medical conditions.[13,23,26,27,34] Underlying conditions that are associated with complications from seasonal influenza also are risk factors for complications from 2009 H1N1 virus infection (Table 1). Pregnant women (especially those in the second or third trimester), women who are less than 2 weeks post partum, and patients with immunosuppression or neurologic disorders have also been overrepresented among those with severe 2009 H1N1 virus infection.[23,24,26,35] Although pregnant women represent only 1 to 2% of the population, among patients with 2009 H1N1 virus infection, they have accounted for up to 7 to 10% of hospitalized patients,[22-24] 6 to 9% of ICU patients,[26,27] and 6 to 10% of patients who died.[23,35] There appears to be a particularly increased risk of death among infected women during the third trimester,[36] especially among those who have coinfection with the human immunodeficiency virus (HIV).[37]

Among patients with severe or fatal cases of 2009 H1N1 virus infection, severe obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥35) or morbid obesity (body-mass index, ≥40) has been reported at rates that are higher by a factor of 5 to 15 than the rate in the general population.[23,26,27,38] In addition to obesity-associated risks, such as cardiovascular disease and diabetes, possible adverse immunologic effects and management problems related to obesity may be contributory.

In certain disadvantaged groups, including indigenous populations of North America and the

Table 1. Risk Factors for Complications of or Severe Illness with 2009 H1N1 Virus Infection.*

Risk Factor	Examples and Comments
Age <5 yr	Increased risk especially for children <2 yr of age; highest hospitalization rates among children <1 yr
Pregnancy	Risk of hospitalization increased by a factor of 4 to 7, as compared with age-matched nonpregnant women, with highest risk in third trimester
Chronic cardiovascular condition	Congestive heart failure or atherosclerotic disease; hypertension not shown to be an independent risk factor
Chronic lung disorder	Asthma or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Neurologic condition	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Associated with HIV infection, organ transplantation, receipt of chemotherapy or corticosteroids, or malnutrition
Morbid obesity†	Suggested but not yet proved to be an independent risk factor for complications requiring hospitalization or ICU admission and possibly for death
Hemoglobinopathy	Sickle cell anemia
Chronic renal disease	Renal dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Long history of smoking	Suggested but not yet proved to be an independent risk factor
Long-term aspirin therapy in children	Risk of Reye's syndrome; drugs containing salicylates should be avoided in children with influenza
Age ≥65 yr	Highest case fatality rate but lowest rate of infection

* COPD denotes chronic obstructive pulmonary disease, HIV human immunodeficiency virus, and ICU intensive care unit.
† Morbid obesity is defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40 or more.

Australasia–Pacific region, rates of severe 2009 H1N1 virus infection have been increased by a factor of five to seven.[23,26,27] Factors that may contribute to this trend include crowding; an increased prevalence of underlying medical disorders, alcoholism, and smoking[27]; delayed seeking of or access to care; and possibly unidentified genetic factors. Aboriginal status, the presence of coexisting conditions, and delayed receipt of antiviral therapy were independently associated with severe disease in one Canadian study.[39]

PATHOGENESIS

VIRAL REPLICATION

Studies of hemagglutinin-receptor binding indicate that the 2009 H1N1 virus is well adapted to mammalian hosts and binds to both α2,6-linked cellular receptors (as do seasonal influenza viruses) and α2,3-linked receptors,[40] which are present in the conjunctivae, distal airways, and alveolar pneumocytes. The 2009 H1N1 virus shows increased ex vivo replication in human bronchial epithelium at 33°C, as compared with a seasonal influenza virus,[41] and is also characterized by increased replication and pathological changes in the lungs of nonhuman primates and increased replication in ex vivo human lung tissues.[10] Such observations may help explain the ability of the virus to cause severe viral pneumonitis in humans.

In uncomplicated illness, nasopharyngeal viral RNA loads peak on the day of onset of symptoms and decline gradually afterward.[42] However, viral replication may be more prolonged than in seasonal influenza, and on day 8 of uncomplicated illness in adults and teenagers, nasopharyngeal swabs have yielded viral RNA in 74% of patients and infectious virus in 13% of patients.[30,43] Infectious virus has been recovered from children up to 6 days after the resolution of fever.

Nasopharyngeal viral loads are increased in patients with severe pneumonia and decline slowly in critically ill patients.[44] Among intubated patients, viral RNA has been detected at higher levels and for longer periods in the lower respiratory tract than in the upper respiratory tract.[45] Viral RNA may be detected in secretions from the lower respiratory tract up to 28 days after the onset of

severe pneumonia[46] and longer in patients with immunosuppression. Viral RNA and (infrequently) infectious virus have been detected in the stool of patients, and viral RNA has been detected infrequently in blood or urine of patients,[44,45] although one small study reported the frequent detection of viral RNA in blood, regardless of the severity of the illness.[47]

IMMUNE RESPONSES

The patterns of innate and adaptive immune responses in patients with 2009 H1N1 virus infection are incompletely characterized. Seasonal and pandemic 2009 H1N1 viruses induce similar proinflammatory mediator responses in human cells in vitro[41] but do not activate effective innate antiviral responses in human dendritic cells and macrophages.[48] Increased plasma levels of interleukin-15, interleukin-12p70, interleukin-8, and especially interleukin-6 may be markers of critical illness.[45,47] High systemic levels of interferon-γ and mediators involved in the development of type 1 and type 17 helper T-cell responses have been reported in hospitalized patients.[47] As compared with patients with less severe illness, patients who died or who had the acute respiratory distress syndrome (ARDS) had increased plasma levels of interleukin-6, interleukin-10, and interleukin-15 throughout the illness and of granulocyte colony-stimulating factor, interleukin-1α, interleukin-8, interferon-inducible protein 10, and tumor necrosis factor α during the late phase of illness.[44] Levels of serum hemagglutination-inhibition and neutralizing antibodies rise promptly after infection in immunocompetent persons,[14] but symptomatic reinfections have been reported.[49]

PATHOLOGICAL FEATURES

In fatal cases of H1N1 virus infection, the most consistent histopathological findings are varying degrees of diffuse alveolar damage with hyaline membranes and septal edema, tracheitis, and necrotizing bronchiolitis[50-52] (Fig. 1). Other early changes include pulmonary vascular congestion and, in some cases, alveolar hemorrhage. In addition to infecting cells in upper respiratory and tracheobronchial epithelium and mucosal glands, the 2009 H1N1 virus targets alveolar lining cells (type I and II pneumocytes)[50] (Fig. 2). Viral antigens have been readily detectable in about two thirds of patients who died within 10 days after the onset of illness and may be detectable for more than 10 days.[50] Other autopsy findings include hemophagocytosis, pulmonary thromboemboli and hemorrhage, and myocarditis.[44] Bronchopneumonia with evidence of bacterial coinfection has been found in 26 to 38% of fatal cases.[50-52]

CLINICAL FEATURES

INCUBATION PERIOD

The incubation period appears to be approximately 1.5 to 3 days, which is similar to that of seasonal influenza.[18,28,31,32,53] In a minority of patients, the period may extend to 7 days.

CLINICAL PRESENTATION

Infection with the 2009 H1N1 virus causes a broad spectrum of clinical syndromes, ranging from afebrile upper respiratory illness to fulminant viral pneumonia. Mild illness without fever has been reported in 8 to 32% of infected persons.[53] Most patients presenting for care have typical influenza-like illness with fever and cough, symptoms that are sometimes accompanied by sore throat and rhinorrhea (Table 2).[2,24,34,53-56] Systemic symptoms are frequent. Gastrointestinal symptoms (including nausea, vomiting, and diarrhea) occur more commonly than in seasonal influenza, especially in adults.[3,57] Dyspnea, tachypnea in children, chest pain, hemoptysis or purulent sputum, prolonged or recurrent fever, altered mental status, manifestations of dehydration, and reappearance of lower respiratory tract symptoms after improvement are signs of progression to more severe disease or complications.[2,25-27,58]

The principal clinical syndrome leading to hospitalization and intensive care is diffuse viral pneumonitis associated with severe hypoxemia, ARDS, and sometimes shock and renal failure.[26,27] This syndrome has accounted for approximately 49 to 72% of ICU admissions for 2009 H1N1 virus infection.[26,27] Rapid progression is common, typically starting on day 4 to 5 after the onset of illness, and intubation is often necessary within 24 hours after admission. Currently available prognostic algorithms for community-acquired pneumonia, such as CURB-65 (a measure of confusion, urea nitrogen, respiratory rate, and blood pressure and an age of 65 years or older), may not apply.[58] Radiographic findings commonly include diffuse mixed interstitial and alveolar infiltrates, although lobar and multilobar distributions occur, particularly in patients with bacterial

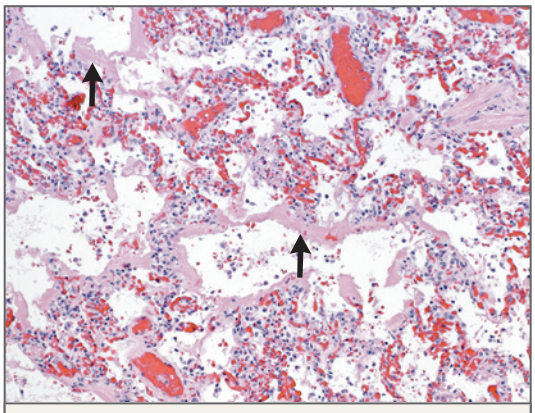

Figure 1. Lung-Tissue Specimen Obtained at Autopsy from a 13-Year-Old Boy after a 7-Day Clinical Course of 2009 H1N1 Virus Infection.

The specimen shows diffuse alveolar damage with hyaline membrane formation (arrows) and hemorrhage (hematoxylin and eosin). The patient, who had cerebral palsy, received oseltamivir for 2 days before he died. No evidence of bacterial coinfection was present. (Courtesy of Dr. Sherif R. Zaki, CDC.)

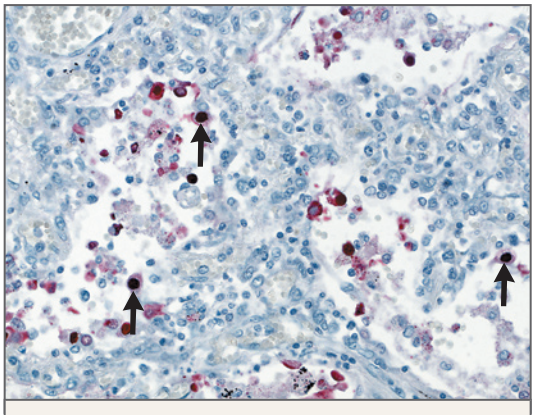

Figure 2. Immunostaining of Influenza Viral Antigens in Lung-Tissue Specimen Obtained at Autopsy from a 55-Year-Old Woman after a 7-Day Clinical Course of 2009 H1N1 Virus Infection.

The specimen shows viral antigens (red color) in the nuclei of alveolar-lining cells (arrows), including type I and type II pneumocytes. Many infected cells have detached and are seen in alveolar spaces. Evidence of *Streptococcus pneumoniae* coinfection was also present in the patient, who had Down's syndrome and hepatitis B infection (mouse anti-influenza nucleoprotein monoclonal antibody with naphthol fast-red substrate and hematoxylin counterstain). (Courtesy of Dr. Sherif R. Zaki, CDC.)

coinfection. Chest computed tomography has shown multiple areas of ground-glass opacities, air bronchograms, and alveolar consolidation, particularly in the lower lobes.[24] Small pleural effusions occur, but an increased volume suggests volume overload or possibly empyema. Pulmonary thromboemboli have occurred in some critically ill patients with ARDS.

Other important syndromes include severe, prolonged exacerbation of chronic obstructive pulmonary disease (COPD) or asthma (in about 14 to 15% of patients), bacterial coinfections, and decompensation of serious coexisting conditions (Table 1).[23,26,27] Among hospitalized patients with 2009 H1N1 infection, a history of asthma has been reported in 24 to 50% of children and adults, and COPD in 36% of adults.[23,24] Bacterial pneumonia, usually caused by *Staphylococcus aureus* (often methicillin-resistant), *Streptococcus pneumoniae*, *S. pyogenes*, and sometimes other bacteria, has been suspected or diagnosed in 20 to 24% of ICU patients and has been found in 26 to 38% of patients who died, often in association with a short clinical course.[26,27,50,52] Death from 2009 H1N1 virus and bacterial coinfection has occurred within 2 to 3 days in some cases. Sporadic cases of neurologic manifestations (confusion, seizures, unconsciousness, acute or postinfectious encephalopathy, quadriparesis, and encephalitis)[59] and myocarditis have been reported, including some fulminant cases.

Laboratory findings at presentation in patients with severe disease typically include normal or low-normal leukocyte counts with lymphocytopenia and elevations in levels of serum aminotransferases, lactate dehydrogenase, creatine kinase, and creatinine.[2,25,27] Myositis and rhabdomyolysis have occurred in severe cases. A poor prognosis is associated with increased levels of creatine kinase, creatinine, and perhaps lactate dehydrogenase, as well as with the presence of thrombocytopenia and metabolic acidosis (Table 3 in the Supplementary Appendix).[2]

SPECIAL POPULATIONS

Young children with 2009 H1N1 virus infection may have marked irritability, severe lethargy, poor oral intake, dehydration resulting in shock, and seizures.[56,60] Other complications include invasive bacterial coinfections, encephalopathy or encephalitis (sometimes necrotizing), and diabetic ketoacidosis.[59,61] Bronchiolitis in infants and croup in young children may require hospitalization but do not usually necessitate ICU care. Suspected transplacental transmission of the 2009 H1N1

Table 2. Symptom Profiles in Groups of Patients with Suspected or Confirmed Pandemic 2009 H1N1 Virus Infection Worldwide.*

Symptom	Mexico[54]		Japan[55]	United States[24]		Mexico[2]	China[53]	Argentina[34]	United Kingdom[56]
	All Inpatients and Outpatients (N=6376)†	Critically Ill Patients (N=255)	Laboratory-Confirmed Cases (N=217)	Hospitalized Patients <18 Yr Old (N=122)	Hospitalized Patients ≥18 Yr Old (N=150)	Critically Ill Patients (N=18)	Mildly Ill and Isolated Patients (N=426)	Hospitalized Patients <18 Yr Old (N=204)	Hospitalized Patients <17 Yr Old (N=78)
					number (percent)				
Temperature >38°C	2716 (43)	218 (85)	206 (95)	115 (94)	143 (95)	18 (100)	153 (36)	181 (89)	52 (81)
Myalgias	1900 (30)	80 (31)	41 (19)	22 (18)	76 (51)	8 (44)	43 (10)	6 (3)	20‡
Cough	2550 (40)	220 (86)	128 (59)	100 (82)	139 (93)	18 (100)	296 (70)	141 (69)	49 (73)
Headache	2480 (39)	75 (29)	28 (13)	24 (20)	68 (45)	4 (22)	83 (20)	6 (3)	19‡
Nasal congestion	1390 (22)	21 (8)	72 (33)	NA	NA	NA	68 (16)	NA	NA
Rhinorrhea	2104 (33)	63 (25)	72 (33)	55 (45)	48 (32)	5 (28)	101 (24)	63 (31)	45 (62)
Sore throat	1384 (22)	40 (16)	85 (39)	38 (31)	46 (31)	NA	156 (37)	8 (4)	26‡
Dyspnea	472 (7)	176 (69)	NA	52 (43)	110 (73)	18 (100)	NA	163 (80)§	30‡¶
Wheezing	NA	NA	NA	31 (25)	41 (27)	2 (11)	NA	24 (12)	20‡
Diarrhea	261 (4)	22 (9)	13 (6)	28 (23)	38 (25)	4 (22)	12 (3)	17 (8)	20‡
Abdominal pain or vomiting	625 (10)	26 (10)	5 (2)	39 (32)	39 (26)	NA	8 (2)	20 (10)	NA‖

* At the top of each column, the total number of study patients is indicated. However, many of the percentages were calculated with smaller denominators. NA denotes not available.
† Patients had either suspected or laboratory-confirmed cases of 2009 H1N1 virus infection.
‡ These numbers are percentages that were estimated from values in a figure in the published study.
§ These patients had hypoxemia.
¶ These patients had tachypnea.
‖ Of these patients, approximately 10% had abdominal pain, and 40% had vomiting.

virus has been reported,[62] and respiratory transmission from a symptomatic mother to a newborn can occur during the postpartum period. Newborn infants may also have apnea, tachypnea, cyanosis, and lethargy. Pregnant women are at increased risk for severe illness, spontaneous abortion, preterm labor and birth, and fetal distress.[35,36,57]

Afebrile or atypical presentations have occurred in pregnant women, patients with immunosuppression, those undergoing hemodialysis, and other risk groups (Table 1). Patients with severe immunosuppression are at increased risk for protracted viral replication and pneumonia.[63,64]

DIAGNOSIS

CLINICAL FACTORS

Clinical suspicion and the accuracy of diagnosis vary substantially, depending on whether the case occurs sporadically or during a recognized outbreak, when a typical presentation of influenza-like illness is likely to represent 2009 H1N1 virus infection. However, the wide clinical spectrum of 2009 H1N1 virus infection and its features that overlap with those of other common infections have sometimes led to the misdiagnosis of other potentially treatable infections (e.g., legionellosis, meningococcemia, leptospirosis, dengue, and malaria).[58] Coinfection with dengue or certain respiratory viruses (parainfluenza virus and respiratory syncytial virus) and detection of *S. pneumoniae* have been reported in some patients with severe 2009 H1N1 virus infection.[65] Coinfection with other respiratory viruses, including seasonal influenza virus, has also been reported.[34,65]

VIROLOGIC FACTORS

Viral RNA detection by conventional or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay remains the best method for the initial diagnosis of 2009 H1N1 virus infection.[58] Nasopharyngeal aspirates or swabs taken early after the onset of symptoms are suitable samples, but endotracheal or bronchoscopic aspirates have higher yields in patients with lower respiratory tract illness.[46,58,66] One study showed that among patients with detectable H1N1 viral RNA in bronchoscopic samples, 19% had negative upper respiratory tract samples.[66] Negative lower respiratory tract samples have been noted in 10% or more of patients with severe 2009 H1N1 virus infection. Consequently, negative results in single respiratory specimens do not rule out 2009 H1N1 virus infection, and repeated collection of multiple respiratory specimen types is recommended when clinical suspicion is high.

Commercially available rapid influenza antigen assays have poor clinical sensitivity (11 to 70%) for the detection of 2009 H1N1 virus in respiratory specimens and cannot differentiate among influenza A subtypes (Table 4 in the Supplementary Appendix). Consequently, negative test results should not be used to make decisions with respect to treatment or infection control. Direct or indirect immunofluorescence tests are less sensitive than RT-PCR.[66]

The 2009 H1N1 virus replicates in various cell types,[67] but isolation usually takes several days. Serologic assays (microneutralization and hemagglutination inhibition) that detect increases in antibody levels in paired serum samples provide a retrospective diagnosis; single high titers in serum samples from convalescent patients may be indicative of recent infection,[14] but routine testing of a single specimen to detect recent infection is not recommended.

CLINICAL MANAGEMENT

ANTIVIRAL THERAPY

The currently circulating 2009 H1N1 virus is susceptible to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) but is almost always resistant to amantadine and rimantadine.[3,10] Therapy with a neuraminidase inhibitor is especially important for patients with underlying risk factors, including pregnancy,[68] and those with severe or progressive clinical illness (Table 3).[69] Standard doses of oseltamivir or inhaled zanamivir can be used for the treatment of mild illness, unless viral resistance to oseltamivir has been documented or is suspected (e.g., because of chemoprophylaxis failure), in which case zanamivir is preferred.

Early therapy with oseltamivir in patients with 2009 H1N1 virus infection may reduce the duration of hospitalization[70] and the risk of progression to severe disease requiring ICU admission or resulting in death.[24,35,36] In one study involving 45 patients with 2009 H1N1 virus who had cancer or had undergone hematopoietic stem-cell transplantation, 18% had pneumonia and 37% were hospitalized; all patients received oseltamivir, and no deaths were reported.[71] Oseltamivir-

Table 3. Antiviral Therapy in Specific Subgroups of Patients.*

Subgroup of Patients	Antiviral Therapy	Comments
Patients at increased risk for severe or complicated illness	Start treatment with oseltamivir or inhaled zanamivir as soon as possible after the onset of illness if patient presents with uncomplicated illness.	Do not delay treatment pending laboratory diagnosis.
Patients with severe or progressive disease and hospitalized patients	Consider the use of an increased dose of oseltamivir (e.g., 150 mg twice daily) and an increased duration of treatment (e.g., 10 days). The use of intravenous peramivir or zanamivir (if available) provides reliable drug delivery, especially in critically ill patients.	Do not delay treatment pending laboratory diagnosis or stop treatment if initial test results are negative in suspected cases; treatment is warranted, even when delayed, whenever active viral replication is likely. Systemic corticosteroids are not recommended for routine treatment of lung injury.
Otherwise healthy patients with uncomplicated illness	Consider the use of oseltamivir or zanamivir, depending on clinical judgment and antiviral supply. Treatment is reasonable in patients presenting early (<48 hr) after the onset of febrile respiratory illness.	Instruct all patients to return for follow-up if signs or symptoms of progressive disease develop or if there is no improvement within 72 hours after symptom onset.
Neonates and young infants	Start weight-based oseltamivir (3.0 mg/kg/dose) once daily from birth to 13 days of age and twice daily from 14 days to 12 mo of age.	If an oral pediatric formulation of oseltamivir is not available, prepare a modified dose from hard capsules (www.tamiflu.com/hcp/dosing/extprep.aspx).
Pregnant women	Start oseltamivir or zanamivir as soon as possible after illness onset.	If antipyretic drugs are considered necessary, use acetaminophen (paracetamol); avoid the use of nonsteroidal antiinflammatory drugs, including aspirin, which have been associated with fetal risks and maternal bleeding.
Breast-feeding women	Start oseltamivir or zanamivir; breast-feeding can be continued.	Take appropriate infection-control precautions. Oseltamivir has been found in breast milk in laboratory animals.
Patients with immunosuppression	If oseltamivir is administered, consider an uninterrupted regimen of 10 days; inhaled zanamivir is an option for uncomplicated disease.	Monitor patients for the clearance of virus. If there is evidence of protracted replication, consider possible emergence of oseltamivir resistance.
Patients with suspected or proven oseltamivir-resistant virus	Start inhaled zanamivir in patients with uncomplicated illness; intravenous zanamivir (if available) should be used in patients with severe or progressive clinical illness.	The risk of oseltamivir resistance is increased among patients with prolonged illness, particularly those with severe immunosuppression receiving oseltamivir for an extended duration, and those in whom chemoprophylaxis has failed.

* Recommendations are based on the World Health Organization Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and Other Influenza Viruses.[69]

treated patients with HIV infection who were receiving highly active antiretroviral therapy had a clinical course similar to that in immunocompetent persons.[72] Deaths have occurred despite early therapy,[73] but the administration of oseltamivir even after an interval of more than 48 hours since the onset of illness has been associated with reduced rates of death among hospitalized patients infected with the 2009 H1N1 virus,[25] seasonal influenza virus, or H5N1 virus. Decisions regarding antiviral treatment should not await laboratory confirmation, and patients presenting with progressive illness more than 48 hours after the onset of illness should be treated empirically with oseltamivir as soon as possible. Patients with progressive or severe illness who have a negative initial test result for 2009 H1N1 virus should continue to receive therapy unless an alternative diagnosis is established.

In uncomplicated illness, the early use of oseltamivir is usually associated with prompt clearance of infectious 2009 H1N1 virus from the upper respiratory tract.[53] However, infectious virus has commonly been detected after the resolution of fever and has sometimes been detected after the completion of therapy,[30] and viral RNA of uncertain clinical significance may be detectable for up to 12 days after the onset of illness.[74] In one study, the independent risk factors for prolonged viral RNA detection were an age of less than 14 years, male sex, and an interval of more than 48 hours between the onset of illness and the start of oseltamivir treatment.[53]

In severely ill patients, viral RNA may be detectable in endotracheal aspirates for several weeks after the initiation of oseltamivir therapy.[45,46] An increased dose of the drug (e.g., 150 mg twice daily in adults) and particularly an increased duration of therapy (e.g., a total of 10 days) with avoidance of treatment interruptions are reasonable in patients with pneumonia or evidence of clinical progression.[69] Doses of up to 450 mg twice daily have been administered successfully in healthy adults, and controlled studies of higher-dose regimens are in progress. Higher weight-adjusted doses are also required in infants and young children to provide drug exposure similar to that in adults.[69,75] Bioavailability in critically ill patients receiving oseltamivir by nasogastric tube appears to be similar to that in patients with uncomplicated illness.[76] The tolerability and efficacy of inhaled zanamivir have not been adequately studied in patients with severe influenza. However, the failure of inhaled zanamivir therapy to clear virus in patients with pneumonia has been reported.[63] Some seriously ill patients treated with inhaled zanamivir have had respiratory distress, and nebulized delivery of extemporaneously prepared solutions of zanamivir powder with its lactose carrier has been associated with lethal ventilator dysfunction.[77]

OSELTAMIVIR RESISTANCE

A His275Tyr mutation in viral neuraminidase confers high-level resistance to oseltamivir but not to zanamivir.[3,78] Most oseltamivir-resistant 2009 H1N1 viruses have been sporadic isolates from treated patients, particularly those with immunosuppression who received prolonged oseltamivir therapy[63,64] or those in whom postexposure oseltamivir chemoprophylaxis failed.[78] However, oseltamivir-resistant isolates have been found in patients without known exposure to oseltamivir and in limited clusters of cases associated with person-to-person transmission in otherwise healthy patients and those with immunosuppression.[78,79] Although in most cases oseltamivir-resistant variants have caused mild, self-limited illness, they have been associated with pneumonia in children and with severe, sometimes fatal illness in patients with immunosuppression.[64,78,80]

INTRAVENOUS NEURAMINIDASE INHIBITORS

Intravenous administration of zanamivir or peramivir provides rapid drug delivery at high levels (Table 5 in the Supplementary Appendix). The efficacy of intravenous peramivir appeared to be similar to that of oseltamivir in one study of adults hospitalized with seasonal influenza,[81] but peramivir is less active by a factor of at least 80 for oseltamivir-resistant viruses carrying the His275Tyr mutation than for oseltamivir-susceptible viruses. Intravenous zanamivir (if available) is the preferred option for hospitalized patients with suspected or documented oseltamivir-resistant 2009 H1N1 virus infection.[63,64,80] Both drugs are available on a compassionate-use basis for treating seriously ill patients, and peramivir was recently authorized for emergency use in hospitalized patients in the United States[81] and licensed for use in Japan.

General principles of clinical management and prevention are summarized in WHO[58] and country-specific guidelines and are reviewed in the Supplementary Appendix.

FUTURE DIRECTIONS

A large amount of information about the natural history and clinical management of 2009 H1N1 virus infection has been obtained in a remarkably short period of time, but considerable gaps remain. The uncertain evolution of this virus among humans and potentially other species highlights the need for continued virologic surveillance for antigenic changes, viral reassortment, antiviral resistance, and altered virulence. Improvements in the global capacity for detection of influenza viruses by molecular analysis, such as RT-PCR assay, and by viral isolation are needed. A simple, inexpensive, highly accurate rapid influenza diagnostic test that is easily deployable worldwide has yet to be developed. The burden and character of disease in low-resource settings are still incompletely understood,[82] especially with respect to disadvantaged populations, including marginalized, refugee, and aboriginal populations. Poverty, homelessness, illiteracy, recent immigration, language barriers, and cultural factors may impede access to care, with the potential for more serious outcomes of influenza. Thus, public health efforts reduce risk factors and to identify at-risk populations for the purpose of providing immunization and early care, including the use of antiviral drugs, should focus on social as well as clinical factors. Both experience with previous pandemics and recent modeling efforts indicate that the age bias observed for outbreaks of 2009 H1N1 virus infection may shift in coming months toward older persons, with implications for the allocation of public health resources.[83]

Major gaps exist in our understanding of viral transmission, pathogenesis of disease, genetic and other host factors related to susceptibility[84,85] or disease severity, and optimal management of severe illness. The development of new antiviral regimens with improved effectiveness, combinations with targeted adjunctive therapies (i.e., immunodulators and neutralizing antibodies or immunotherapy), and improved management of influenza-associated ARDS are priorities, along with better prevention, recognition, and treatment of invasive bacterial coinfections. Available findings highlight the importance of early use of antiviral drugs and antibiotics in the treatment of serious cases and of the potential value of influenza-specific and pneumococcal vaccines for prevention. Both the gaps in knowledge and the experience to date underline the urgent need for better international collaboration in clinical research, particularly in the case of diseases with pandemic potential, for which rapid detection, investigation, and characterization of clinical syndromes are prerequisites for improved mitigation of their public health consequences.

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The opinions expressed in this article are those of the members of the Writing Committee and do not necessarily reflect those of the institutions or organizations with which they are affiliated.

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362:1708-19.

SUPPLEMENTARY MATERIALS (12 April 2010)

CLINICAL MANAGEMENT

Investigational Antivirals

Other investigational agents in clinical development including the polymerase inhibitor favipiravir (T-705), the topical neuraminidase inhibitor laninamivir (CS-8958), and the influenza virus receptor-destroying sialidase DAS181 are active in murine models of pH1N1 virus infection.[1,2] Intranasal interferon is effective for reducing transmission when used for treating experimentally infected guinea pigs and for prevention in guinea pigs exposed to pH1N1 virus-infected animals,[3] but was ineffective for prophylaxis of seasonal influenza in humans.[4,5,6] Combinations of oseltamivir with ribavirin and amantadine are reported to show greater *in vitro* inhibition of pH1N1 viruses than single agents or oseltamivir and ribavirin together, despite pH1N1 virus resistance to adamantanes, and combinations of oseltamivir and other NAIs (peramivir, zanamivir) show additive to antagonistic interactions depending on the concentrations tested.[7] The possible clinical relevance of such in vitro observations remains to be determined.

Supportive Care

Close monitoring of oxygen saturation with pulse oximetry for any patient in respiratory distress combined with early administration of supplemental oxygen is critical to correct hypoxemia.[8] Most elements of intensive care for patients with severe complications of pH1N1 virus infection are similar to those for any critically ill patient,

although many pH1N1 patients manifest persistent hypoxemia and require prolonged (medians, 1-3 weeks) ventilatory support.[9,10,11,12,13,14] While severe pH1N1 cases have isolated single organ failure in most cases, shock, renal failure, and other organ dysfunction occur. Renal replacement therapy has been required in 10% or more of ICU patients.[14a]

Many patients with progressive pneumonitis require intubation within 24 hours of hospitalization, and non-invasive ventilatory support is usually ineffective.[12,13] Standard initial pressure and volume limited lung protective ventilatory strategies are appropriate,[15] with high frequency oscillation (HFO) for children.[16,17] Controlled mandatory ventilation is least useful in severe cases, whereas pressure-cycled modes including pressure support at very high levels (25-35 cm), pressure control with inverse ratio, airway pressure release ventilation and HFO has been used with apparent benefit in some patients.[17a]

For patients with refractory hypoxemia, some centres have reported benefit from controlled diuresis early in the course of disease.[17b] Prone positioning may be helpful but extremely difficult to perform due to illness severity and obesity in many patients. In highly resourced settings, severe hypoxemia may be reduced by advanced respiratory support including nitric oxide at 5-40 ppm, HFO, and/or extracorporeal membrane oxygenation (ECMO).[13] ECMO was associated with 21% mortality in one pH1N1 case series,[18] and one controlled trial in non-pH1N1 ARDS reported improved survival with ECMO.[19] Independent predictors of mortality among ventilated adult ICU patients with pH1N1 virus infection in Argentina included APACHE II score, lowest PaO_2/FIO_2,

inotropic use, hemodialysis, prone positioning, and pneumonic co-infection with *S. pneumoniae.*[20]

Antibiotic Therapy

Initial antibiotic therapy based on national guidelines and local antimicrobial susceptibility patterns should cover pathogens associated with community-acquired pneumonia, particularly *S. aureus* (MSSA and MRSA)*, S. pneumoniae* and *S. pyogenes.*[8,21] In a murine model of secondary pneumococcal infection following influenza, combined use of oseltamivir and antibiotics was more effective than antibiotic therapy alone in improving survival.[22,23] If careful microbiologic studies do not indicate bacterial co-infection, early cessation of antibiotic therapy may be warranted; use of prophylactic or prolonged courses of antibiotics may be associated with an increased risk of late superinfection with antimicrobic-resistant organisms, particularly in those requiring protracted ventilatory support.

Adjunctive pharmacologic therapy

The potential value of adjunctive immunomodulatory therapies for treating severe influenza is uncertain, and insufficient data are currently available to assess the possible value of available agents like systemic interferon or ribavirin that have both immunomodulatory and antiviral activities.[24]

In pneumonia patients during the 1918 pandemic, early administration of convalescent blood products appeared to be associated with increased survival.[25] Similar therapy has been used in severe illness caused by highly pathogenic avian influenza

A(H5N1) virus infection,[26,27,28] and studies in pH1N1 illness are anticipated with polyclonal antibody preparations derived from convalescent patient or vaccinee plasma and possibly with human monoclonals. Depending on plasmapheresis capacity and pandemic severity, one modelling study found that a passive-immunotherapy program would be a logistically feasible mitigation option for many developed countries.[29] In addition, preliminary findings suggest that severe illness from pH1N1 virus infection may be associated with IgG2 deficiency and that pregnancy-related reductions in IgG2 level may explain the increased severity of illness with pH1N1 virus infection in some pregnant patients.[30] The possible therapeutic role of IV immunoglobulin requires further investigation.

High-dose corticosteroids have no established role in ARDS; their use has been associated with prolonged viral shedding in seasonal influenza, increased mortality in H5N1 influenza and possibly pH1N1 virus infections,[31] and substantial risk of side effects. However, lower dose corticosteroids (0.5-2.5 mg/kg/day of methylprednisolone) may improve outcomes in non-pH1N1 ARDS[32] and septic shock[33] and have been used with oseltamivir in treating pHN1-associated acute lung injury.[34] Controlled studies are needed in influenza-associated pneumonitis.[35]

Other commonly used drugs with anti-inflammatory properties (e.g., statins, glitazones, fibrates, cyclooxygenase 2 inhibitors) have been suggested as potential treatments,[36,37,38] but data from prospective, controlled trials are currently lacking. Although beneficial in animal models of influenza,[39] salicylates are linked to Reye syndrome in children, may have been associated with increased mortality in 1918[40,41] and should be avoided.

PREVENTION AND INFECTION CONTROL

Immunization

Almost all pH1N1 isolates globally are antigenically similar to the vaccine strain, A/California/07/2009(H1N1), and multiple countries have initiated pH1N1 immunisation programmes. In the United States, the FDA has approved egg-grown, split and sub-unit vaccines, and live-attenuated monovalent pH1N1 vaccines, which are all made in the same manner as seasonal vaccines,[42] whereas in Europe the EMEA has approved a whole virus vaccine propagated on Vero cells, and two egg-grown, split and subunit vaccines that contain proprietary oil-in-water adjuvants.[43] In the United States the approved inactivated vaccines contain 15µg of hemagglutinin, whereas in Europe, doses containing 3.8 and 7.5 µg virus hemagglutinin with AS03 and MF-59, respectively, are approved.

Studies of these and other vaccines indicate that one 15 µg dose of inactivated vaccine raises protective hemagglutination inhibition (HAI) antibody levels ($\geq$1:40) in 50-96% of children aged 6 months to 17 years,[44,45,46] in 63-98% of adults 18 to 64 years, and in 79-93% of the elderly.[47,48,49] One US study found that 25-36% of children aged 6 months to 9 years responded to a single dose as early as 8-10 days.[50] A second dose is not required in older children or adults, but may be needed in young children and possibly others.[45,46] Single oil-in-water adjuvanted doses of 1.9 ug appear immunogenic in young children. Single non-adjuvanted doses of 7.5 µg appear to be immunogenic in most persons.[46,47] While MF-59 oil-in-water adjuvant augments the antibody response to inactivated pH1N1 vaccine,[48] alum was found to be ineffective as an adjuvant in studies in China.[47,49] Initial studies in the United Kingdom with non-adjuvanted whole virion

and ASO3-adjuvanted, reduced antigen (3.75 ug HA) pH1N1 vaccines indicate high immunogenicity and good vaccine effectiveness.[51]

Recent seasonal influenza vaccine may elicit antibodies that are cross-reactive to pH1N1 influenza virus in a few adults,[52] as well as broadly reactive heterosubtypic neutralizing antibodies directed against HA in some.[52a] However, available evidence is conflicting regarding a possible protective (or even adverse) effect of previous seasonal vaccination on the frequency or severity of pH1N1 illness.[53,54,55,56,56a,56b] Co-administration of inactivated seasonal and pandemic H1N1 vaccines does not appear to impair antibody response to either one,[57] and studies of sequential administration are in progress.

The HA of pH1N1 virus shares conserved antigenic epitopes with human and swine H1 viruses from the early 20th century but differs antigenically from recent seasonal H1N1 viruses, in part because of differences in glycosylation patterns.[58,59] In mice, immunization with 1918 or pH1N1, but not seasonal H1N1, virus vaccines elicits cross-neutralizing antibodies to both and provides protection against lethal pH1N1 infection,[58] as does prior infection with a classical 1976 swine H1N1 virus.[60] One neutralizing monoclonal antibody derived from a 1918 survivor shows substantial antiviral activity in mice infected with pH1N1 virus.[61] Testing of archived specimens from recipients of the A/New Jersey/76 swine influenza vaccine confirmed that the majority developed cross-reactive neutralizing antibodies to pH1N1 virus.[52]

No serious unexpected adverse events have been observed to date with pH1N1 vaccines.[62,63] Local reactogenicity (e.g., sore arm) tends to be higher with adjuvanted vaccines, and more fever and reactogenicity have been noted in children. While the safety

profile overall is comparable to that of seasonal influenza vaccine, post-vaccination safety monitoring is being undertaken to look for serious or rare events above background levels.[63,64] Anaphylaxis has been noted in about 5 per million vaccine doses distributed, which does not exceed the expected frequency after receiving other vaccines.[65] Guillain-Barré syndrome (GBS) was observed in about 1 additional case per 100,000 recipients of swine influenza vaccine in 1976, but studies of seasonal influenza vaccine conducted since then have not demonstrated a substantial increase in risk.[66,67,68] In contrast, GBS is a recognised complication of influenza,[69] and the risk of GBS is substantially greater after ILI than after vaccination.[70] The frequency of GBS following receipt of pH1N1 vaccines has been below the estimated background rate to date.[71] Administration of pH1N1 vaccine appears to be safe in HIV-infected pregnant women.[72]

The limited early availability of pH1N1 vaccines has been important in determining their impact and cost effectiveness. Even in countries with substantial numbers of early pH1N1 infections like the United Kingdom, modelling suggests that immunization of groups at higher risk of complications and deaths appears to be both beneficial and cost-effective.[73] Due to anticipated ongoing pH1N1 activity, monovalent pH1N1 vaccine should be considered for travellers to the tropics and countries in the Southern hemisphere during its seasonal influenza period. The pH1N1 virus has been recommended to replace the previously circulating seasonal H1N1 virus in the 2010 trivalent vaccine formulations for the Southern and Northern hemispheres.[74,75]

Antiviral chemoprophylaxis

While oseltamivir appears effective in preventing spread of pH1N1 virus infection among close contacts in household and outbreak settings,[76,77,78] neuraminidase inhibitors are generally not recommended for chemoprophylaxis of pH1N1 illness due to cost considerations, variable compliance related to side effects,[78,79,80] and potential for selection of resistant variants, perhaps related to emergence during subtherapeutic dosing or transmission from treated ill contacts.[81,82,83] High frequencies of gastrointestinal symptoms and headache have been reported by recipients when oseltamivir has been used for chemoprophylaxis.[78,80] Where there is risk of transmission and the likelihood of complications of infection is high, oseltamivir or zanamivir might be used for post exposure chemoprophylaxis in persons at high risk for influenza-related complications (e.g., patients with severe immunosuppression).[83] When oseltamivir resistance is a concern, inhaled zanamivir would be the preferred agent. An alternative option is close monitoring for symptoms, followed by prompt early antiviral treatment should symptoms develop.[84]

Infection control

Nosocomially acquired illness has been reported in both healthcare workers[85] and patients. Seroprevalence (HAI $\geq$ 1:40) was higher in front-line healthcare workers than other hospital staff or the general population in Taiwan (Supplementary Table 2),[86] presumably reflecting greater exposure, and several nosocomial outbreaks in hospitalized immunocompromised patient groups have been documented.[87,88,89,90] Infection control measures recommended by the WHO include Droplet and Standard Precautions among the healthcare workers (HCWs) and maintaining a minimum distance of $\geq$1 metre

between patients when providing routine care to patients infected with pH1N1 influenza and those with influenza-like symptoms.[91] Surgical masks appear to be as effective as N95 respirators for respiratory protection of HCWs during the routine care of patients hospitalized with seasonal influenza,[92,93] and in one small study were also as effective in reducing production of infectious aerosols during coughing when worn by influenza patients.[94] The incidence of nosocomial pH1N1 infections appeared to remain low in staff using surgical masks in one hospital admitting substantial numbers of pH1N1 patients.[95]

Fit-tested respirators are recommended in the United States by US CDC for healthcare workers exposed to pH1N1 patients in routine healthcare settings at present.[96] However, both CDC and WHO recommend that when performing aerosol-generating procedures (e.g. aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy), HCWs should use higher levels of infection control precautions including the use of respirators (e.g., N95 masks).[91] Because of the risks of occupational HCW exposure, transmission of pH1N1 influenzavirus from HCWs to patients, and of adverse impacts of HCW illness on healthcare delivery, HCWs are a first priority group for pH1N1 immunization.[85,91]

The optimal duration of isolation precautions for hospitalized patients is unknown; current guidelines recommend that isolation precautions be continued for minimum of 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a healthcare facility.[96] For prolonged illness (i.e. pneumonia), control measures should be used during the acute illness phase, [91] but continued requirement for ventilator or ICU support by itself does not necessitate

isolation. Severely immunocompromised persons may have prolonged viral replication, isolation should continue for the duration of influenzal illness,[96] and when feasible, depend on sequential virological monitoring.[97] Studies assessing the association of viral detection with communicability are needed.

The frequency of viremia and associated risk of transfusion-related transmission from pH1N1 virus-infected blood donors appear to be very low.[98]

Non-pharmaceutical interventions

Non-pharmaceutical measures, either individually or in combination, have been used extensively during the pH1N1 and previous pandemics, but data on their usefulness and cost-effectiveness are limited.[99] Such measures include personal protective measures like masks and hand hygiene; isolation and quarantine; traveller screening; environmental decontamination; and social distancing measures like school and worksite closures and cancellation of mass gatherings. Hand hygiene with soap and water or alcohol-based hand rub is highly effective in reducing infectious influenza A virus levels on human hands.[100] Compliance with hand hygiene and masking may have some benefit in reducing the risk of secondary illnesses in household contacts during seasonal influenza when used very early by contacts after illness onset in a household index case.[101,102]

During the 1918 pandemic, combining multiple community-based measures appeared to be effective in decreasing influenza-related deaths, but only when implemented early in the outbreak and for extended periods (at least 4 weeks).[103,104,105] Early school closures may reduce peak illness incidence and modestly decrease the number of cases.[106,107] During the current pandemic, some countries have employed

various interventions, especially school closure (generally for 1 week or less) and cancellation of mass gatherings despite the associated adverse social and economic effects.[108,109] The effectiveness of school closures and other community NPI measures in slowing the spread of pH1N1 needs to be evaluated.

Animal-Human Interface Issues

Infected humans have also been implicated in transmitting pH1N1 virus to swine, turkeys, and occasionally household pets including cats, ferrets, and dogs.[110] Swine are highly susceptible to pH1N1 virus infection, and experimentally infected swine may shed pH1N1 virus from the respiratory tract up to 10 days.[111] Although most avian species appear resistant to experimental pH1N1 virus infection,[112,113] the known susceptibility of swine and domestic poultry to other influenza viruses indicates that close monitoring is warranted to detect emergence of novel strains. One instance of a reassortment between pH1N1 virus and a swine influenza virus has been reported to date.[114] Virus is not detectable in meat from experimentally infected swine,[115] so that pork harvested from pH1N1 virus-infected swine does not pose a risk to humans for pH1N1 virus infection.[116]

EPIDEMIOLOGICAL NOTE

The source of pH1N1 virus and location where initial transmission to and among humans occurred is currently unknown. The earliest epidemiological evidence of 2009 pandemic influenza A (H1N1) virus activity was reported from the community of La Gloria, Veracruz, Mexico in March 2009. It has been hypothesized that this might have been linked to persons working with or otherwise exposed to pigs at farming operations

in the state of Veracruz.[117,118,119] It was noted that: “an increase in the reported incidence of respiratory diseases was noted during March 2009 at the town of La Gloria, in the south-eastern state of Veracruz, Mexico. So far, this is the first community in which a case of novel influenza A H1N1 virus has been identified. Further cases were rapidly detected in other areas of Mexico and elsewhere."[117] It is possible that pandemic influenza activity could have started before March 2009 in southern Mexico. Beginning in late March, increases in acute respiratory illness and severe lower respiratory tract disease occurred in Mexico City and other areas of Mexico.[9,117,120,121,122,123] The earliest confirmed pH1N1 cases detected in the U.S. had illness onset at the end of March 2009,[124,125] and other early cases were subsequently detected among persons in southern states bordering Mexico or epidemiologically linked to travel to Mexico in April. Similarly, the early cases in Canada were linked to Mexico travel,[126] with subsequent spread to contacts, including cases of severe lower respiratory tract disease.[13]

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Supplementary Table 1. Common genetic markers for antiviral resistance, virulence, or transmission in pandemic H1N1 and other influenza viruses.

Protein	Amino acid	Motif	Description	Pandemic (H1N1) Influenzavirus 2009
HA*	222 (225 in H3 numbering system)	D→G	Present in avian H5N1 and some 1918 H1N1 isolates; associated with altered receptor specificity (increased binding to α2,3-linked receptors) and increased binding to cells of the lower respiratory tract. Also observed in egg-isolates of swine H1N1 viruses.	Increased frequency of detection (possibly also D→N) in fatal pH1N1 cases in multiple countries (up to about 20% to date),[127,127a] perhaps related to emergence during lower respiratory tract replication. Also found in uncomplicated illnesses. Effects on virulence and transmission to be determined.[128] Viruses lacking this mutation are also capable of causing deep lung infections.
PB2	271	T→A	T271A associated with enhanced polymerase activity in mammalian cells.[129]	All PB2 sequences from pH1N1 viruses contain alanine at position 271, indicative of prior adaptation to mammalian hosts.

PB2	627	E→K	E627K associated with replication at 33°C, and perhaps increased pathogenicity and transmission (avian to human) of H5N1 virus[130,131]	2 isolates from the Netherlands reported in public databases with this change were not associated with unusual pathogenicity or transmission. When mutation introduced into pH1N1 virus, no major effects on replication in murine or ferret models or on pathogenesis.[132]
PB2	Serine at 590 + arginine at 591		SR polymorphism observed in triple reassortant swine H1N1 viruses with E627, and introduction of this polymorphism into the PB2 subunit of a primary avian isolate also increased polymerase activity and viral replication in human and porcine cells.[133]	pH1N1 virus has acquired second-site suppressor mutations in its PB2 polymerase subunit that convey enhanced polymerase activity in human cells.[133]
PB2	701	D→N	D701N may compensate for the lack of E627K for transmission of avian viruses[131]	None detected in pH1N1 to date. When mutation introduced into pH1N1 virus, no major effects on replication in murine or ferret models or on pathogenesis.[132]

PB1-F2			PB1-F2 associated with increased pneumonia severity in animal models; truncation or absence of PB1-F2 has been associated with attenuating effect in mice and reduced replication in cells	All viruses analyzed to date are truncated at 11 amino acids and lack functional PB1-F2. Pandemic H1N1 viruses purposefully mutated to allow expression of full-length PB1-F2 did not show increased virulence in animal models.[134]
NA	275	H→Y	Resistance to oseltamivir and reduced susceptibility peramivir; present in seasonal H1N1 viruses from 2008 onwards.[135]	Detected in > 265 viruses worldwide (about 1-2% of tested) most often after treatment, with approximately 1/3 of these from immunocompromised hosts.[128] Several clusters in healthcare settings and otherwise healthy contacts but no sustained community transmission to date.[136,137]
M2	31	S→N	Resistance to adamantanes; present in seasonal H3N2 and some seasonal H1N1 viruses	Present in nearly all viruses examined to date

NS1	227-230 PDZ domain	X-S/T-X-V	Viruses containing PDZ domains from the 1918 H1N1 and H5N1 viruses demonstrated increased virulence in infected mice.[138]	All viruses analyzed to date are truncated at 219 amino acids and therefore lacking the PDZ domain. Extension of NS1 to 230 amino acids has no impact on virus replication in human or swine cells and minimal effects on replication, pathogenicity and transmission in mouse and ferret models.[139]
NS1	217	K→E	Abolishes binding to host Crk/CrkL signaling adapters	Restoration of Crk/CrkL binding has no impact on virus replication in human or swine cells and minimal effects on replication, pathogenicity and transmission in animal models.[139]
NS1	92	D→E	D92E shift in NS1 protein may contribute to increased virulence of H5N1 viruses	2 viruses from New York have a D→G mutation; no severity information available

*Note: Only 31% of B cell epitopes present in human H1N1 strains are conserved in the pH1N1 virus, including only 17% conserved in the HA, whereas more CD4 T cell (41%) and CD8 T-cell (69%) epitopes are conserved.[140] The HA of pH1N1 virus shares

conserved antigenic epitopes with 1918 pandemic virus and swine H1 viruses from the early 20th century, particularly within the Sa antigenic site, but differs antigenically from recent seasonal H1N1 viruses, in part because of lack of glycosylation sites present in seasonal H1N1viruses.[58,59]

Note: While no reassortment with seasonal influenza viruses has been recognized to date, detection of a swine H1N1 virus with a gene derived from the pH1N1 virus has been recently reported from Hong Kong SAR.[114]

Supplementary Table 2. Results of representative studies of pH1N1 antibody seroprevalence

Study Population	Findings	Assay	Titer cutoff [Virus]
US residents born between 1880 and 2004; sera collected in 1971 and 2002 through February 2009[52]	Birth 1910-1929: 100% ≥1:80 (n = 11) Birth before 1950: 34% ≥1:80 (n = 115) Birth after 1980: 4% ≥1:40 (n = 107)	MN	1:40 [A/CA/04/09 (H1N1)]
US residents aged ≥25 years, recipients of split A/NJ/76 (H1N1) vaccine; sera collected in 1976 [52]	63% with cross-reactive titer of 1:160 (n = 83)	MN	1:80 [A/CA/04/09 (H1N1)]
Persons born between 1897 and 1959; sera collected 1999 [1]	Birth 1897-1917: 53% ≥1:32 (n = 49)	MN	1:32 [A/CA/04/09 (H1N1)]
Persons born between 1909-2005; sera collected in 2004-2005[141]	Birth 1909-1919: 55.6% (n = 27) Birth 1920-1929: 21.2% (n = 104) Birth 1930-1939: 1.6% (n = 125) Birth 1940-1949: 0% (n = 116) Birth 1950-1969: 0% (n = 119)	HI	1:40 [A/Finland/554/09 (H1N1)]

England residents aged 0 to >80 years; sera collected in 2008 or early 2009 [142]	Age ≥80 years: 47% (n = 166) Age 75-79 years: 17.6% (n = 187) Age 65-74 years: 25.1% (n = 167) Age 50-64 years: 18.5% (n = 65) Age 25-49 years: 9.5% (n = 168) Age 15-24 years: 12.7% (n = 110) Age 5-14 years: 4.3% (n = 163) Age 0-4 years: 2.8% (n = 143)	MN	1:40 [A/Eng/195/09 (H1N1]
England residents in London and West Midlands aged 0 to ≥65 years; difference between baseline sera (2008 or early 2009) and sera collected in September 2009 [142]	*Sero-incidence* Age <5 years: 21.3% (n = 26) Age 5-14 years: 42% (n = 35) Age 15-24 years: 20.6% (n = 21) Age 25-44 years: 6.2% (n = 53)	HI	1:32 [A/Eng/195/09 (H1N1]
US residents in Pittsburgh aged 0-89 years; sera collected November to December	Age 0-9 years: 28% (n = 88) Age 10-19 years: 45% (n = 96)	HI	1:40 [A/CA/07/09 (H1N1)]

2009[143]	Age 20-29 years: 20% (n = 89) Age 30-39 years: 14% (n = 81) Age 40-49 years: 18% (n = 100) Age 50-59 years: 22% (n = 96) Age 60-69 years: 13% (n = 100) Age 70-79 years: 5% (n = 100) Age 80-89 years: 26% (n = 96)		
Taiwan health care workers, mean age 36.9 years; controls mean age 52 years; sera collected from October to November 2009[86]	Infectious disease doctors, inpatient nurses and Emergency Room staff: 30.8% (n = 120) General clinicians, laboratory and administrative staff: 12.6% (n = 175) Controls (general physical exam patients): 7% (n = 244)	HI	1:40 [A/Taiwan/07/T1338/09 (H1N1)]

MN = Microneutralization assay; HI = Hemagglutinin inhibition assay

Note: Seroprevalence data not included from Nougairède A, *et al.,* 2010[144]; Chen H *et al.*, 2009[218]; Chen MIC *et al.*, 2010[355]; and Tang JW *et al.*, 2010[354].

Supplementary Table 3. Comparison of representative admission laboratory study results in patients who survived or died following hospitalization with pandemic H1N1 influenzavirus illness.

Admission laboratory finding	Perez-Padilla *et al.*, 2009[120] (N=18)				Kumar *et al.*, 2009[13] (N=168)				Dominguez-Cherit *et al.*, 2009[9] (N=58)+			
	Survivors (n=11)		Non-survivors (n=7)		Survivors (n=139)		Non-survivors (n=29)		Survivors (n=34)		Non-survivors (n=24)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Leukocyte, /mm^3	7.23 (mean)	5.66 (SD)	5.3 (mean)	2.1 (SD)	6.7	(3.8-12.1)	6.9	(3.7-9.5)	9.5 (mean)	5.5 (SD)	10.6 (mean)	6.6 (SD)
Creatine kinase, U/L	189	(58-1249)	514	(175-2156)	255	(104-1117)	221	(42-455)	121	(5-231)	1059	(652-2449)*
Creatinine, mg/dL	0.94	(0.22-1.26)	1.04	(0.49-4.59)	0.71	(0.46-1.01)	0.97	(0.58-2.33)*	0.9	(0.67-1.1)	1.4	(1.1-3.1)*
PaO2/FiO2	164	(87-	53	(46-	124	(80-	85	(67-	120	(62-	70	(51-

		250)		107)*		181)		166)		161)		105)*

Values are presented as median and (IQR) interquartile range with exception of leukocyte counts, some of which are expressed as mean (standard deviation)

+Includes suspected and laboratory proven cases of pH1N1

*Statistically significant difference ($P < 0.05$) for comparison of survivors and non-survivors

Supplementary Table 4. Representative studies of rapid antigen diagnostic test sensitivity for pandemic H1N1 2009 and seasonal influenza viruses

RIDT Kit	Patient group	Specimen type	Influenza A virus type	No. of specimens positive by RIDT/ no. positive by RT-PCR (%)	No. of specimens positive by RIDT/ no. of specimens by culture (%)
Binax Now Influenza A&B (Binax, Inc., Scarborough, Maine, USA)[145]	Not stated	NP swabs and OP swabs*	pH1N1 2009	18/45 (40)	
			Seasonal H1N1	3/5 (60)	
			Seasonal H3N2	12/15 (80)	
Directigen EZ Flu A+B (Becton, Dickinson and Company; Sparks,	Not stated	NP and OP swabs	pH1N1 2009	21/43 (49)	
			Seasonal H1N1	3/4 (75)	
			Seasonal H3N2	10/12 (83)	

MD, USA) [145]					
Binax Now Influenza A&B[146]	Children	Nasal wash or swab, sputum specimens	pH1N1 2009	1285/2880 (45)	1590/2880 (55)
Binax Now Influenza A&B[147]	Children	NP swabs	pH1N1 2009	66/107 (62)	
Binax Now Influenza A&B[148]	Children, young adults	NP specimens	pH1N1 2009	23/60 (38)	
		Tracheal aspirate or BAL		82/140 (58)	84/140 (60)
Quidel QuickVue Influenza A+B (Quidel Corporation, San Diego, CA, USA) [145]	Not stated	NP and OP swabs	pH1N1 2009	31/45 (69)	
			Seasonal H1N1	4/5 (80)	
			Seasonal H3N2	12/15 (80)	

QuickVue Influenza A+B (Quidel)[149]	University students, outpatient	Throat swab	Seasonal A or B	14/74 (19)	
			Seasonal A or B		12/49 (24.5)
	Children and adults	Deep nasal swab	Seasonal A or B	10/31 (32)	
			Seasonal A or B		11/32 (34)
	Elementary school students	Nasal swab	Seasonal A or B		28/105 (27)
QuickVue Influenza A+B (Quidel)[150]	Not stated	Not stated	pH1N1 2009	20/39 (51)	
	Not stated		Seasonal H1N1	12/19 (63)	
	Not stated		Seasonal H3N2	6/19 (31)	
Directigen EZ Flu A+B[148]	Children, young adults	NP specimens	pH1N1 2009	28/60 (47)	
QuickVue Influenza	Hospitalized	Upper	pH1N1 2009	5/20 (25)	

A+B (Quidel)[151]		respiratory tract			
QuickVue Influenza A+B (Quidel)[152]	Pediatric outpatients	Nasal swab	pH1N1 2009	89/142 (63)	

* The original specimens provided largely by local state health laboratories.

Abbreviations: RIDT, rapid influenza diagnostic test

Supplementary Table 5. Comparative pharmacology of intravenous and oral neuraminidase inhibitors [153,154,155,156,157]

	Route	Usual adult dose	Mean plasma Cmax (ng/ml)	Mean plasma Cmin (ng/ml)	Mean plasma AUC (ng*hr/ml)	Elimination	Plasma T1/2 (hr)	Vdss	Ratio of IC50 values for H1N1 Y275/ H275
Peramivir*	IV	600 mg daily	43,804	70 (predicted)*	82,800 (0→24 hrs) (predicted)*	Renal	7.7-20.8	22 L	≥ 80
Zanamivir	IV	600 mg twice daily	32,577 -39,712	340-353	66,450 (0→12 hrs)	Renal	1.8-2.1	16L	1-2
Oseltamivir	PO[+]	150 mg twice daily	383-599	279-282	2,941 -4,904 (0→12 hrs)	Renal	6.3-9.0	23-26L	≥300

*Predicted from studies administering up to 8 mg/kg doses

[+]Intravenous oseltamivir is also currently in clinical development

Supplementary Table 5 (continued)

	Possible adverse events	Recommended Dose Adjustments			
		Renal insufficiency (CrC1)	Hepatic insufficiency	Children	Elderly
Peramivir§	Diarrhea, CNS effects (including depression, anxiety, confusion, altered insomnia, somnolence), decreased PMN counts	<50 ml/min	No	6-10 mg/kg depending on age (birth – 17 years)§	No#
Zanamivir	Aerosolized: bronchospasm; allergic-	<80ml/min	No	TBD for weight <38kg	No

	like reactions (including oropharyngeal edema, serious skin rashes, and anaphylaxis); dizziness				
Oseltamivir	Nausea, emesis; anaphylaxis; serious skin reactions (including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme); delirium, abnormal behaviour	<30 ml/min	No (mild-moderate)	Weight-based for <40kg; age- and weight-based for < 24 months (see reference 83)	No

§No pediatric pharmacology or clinical trials data published to date. Dose depend on age (birth to 17 yrs)

#Drug exposure 26% higher based on plasma AUC in those ≥65years old

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362:1708-19.

SUPPLEMENTARY MATERIALS (12 April 2010)

CLINICAL MANAGEMENT

Investigational Antivirals

Other investigational agents in clinical development including the polymerase inhibitor favipiravir (T-705), the topical neuraminidase inhibitor laninamivir (CS-8958), and the influenza virus receptor-destroying sialidase DAS181 are active in murine models of pH1N1 virus infection.[1,2] Intranasal interferon is effective for reducing transmission when used for treating experimentally infected guinea pigs and for prevention in guinea pigs exposed to pH1N1 virus-infected animals,[3] but was ineffective for prophylaxis of seasonal influenza in humans.[4,5,6] Combinations of oseltamivir with ribavirin and amantadine are reported to show greater *in vitro* inhibition of pH1N1 viruses than single agents or oseltamivir and ribavirin together, despite pH1N1 virus resistance to adamantanes, and combinations of oseltamivir and other NAIs (peramivir, zanamivir) show additive to antagonistic interactions depending on the concentrations tested.[7] The possible clinical relevance of such in vitro observations remains to be determined.

Supportive Care

Close monitoring of oxygen saturation with pulse oximetry for any patient in respiratory distress combined with early administration of supplemental oxygen is critical to correct hypoxemia.[8] Most elements of intensive care for patients with severe complications of pH1N1 virus infection are similar to those for any critically ill patient,

although many pH1N1 patients manifest persistent hypoxemia and require prolonged (medians, 1-3 weeks) ventilatory support.[9,10,11,12,13,14] While severe pH1N1 cases have isolated single organ failure in most cases, shock, renal failure, and other organ dysfunction occur. Renal replacement therapy has been required in 10% or more of ICU patients.[14a]

Many patients with progressive pneumonitis require intubation within 24 hours of hospitalization, and non-invasive ventilatory support is usually ineffective.[12,13] Standard initial pressure and volume limited lung protective ventilatory strategies are appropriate,[15] with high frequency oscillation (HFO) for children.[16,17] Controlled mandatory ventilation is least useful in severe cases, whereas pressure-cycled modes including pressure support at very high levels (25-35 cm), pressure control with inverse ratio, airway pressure release ventilation and HFO has been used with apparent benefit in some patients.[17a]

For patients with refractory hypoxemia, some centres have reported benefit from controlled diuresis early in the course of disease.[17b] Prone positioning may be helpful but extremely difficult to perform due to illness severity and obesity in many patients. In highly resourced settings, severe hypoxemia may be reduced by advanced respiratory support including nitric oxide at 5-40 ppm, HFO, and/or extracorporeal membrane oxygenation (ECMO).[13] ECMO was associated with 21% mortality in one pH1N1 case series,[18] and one controlled trial in non-pH1N1 ARDS reported improved survival with ECMO.[19] Independent predictors of mortality among ventilated adult ICU patients with pH1N1 virus infection in Argentina included APACHE II score, lowest PaO_2/FIO_2,

inotropic use, hemodialysis, prone positioning, and pneumonic co-infection with *S. pneumoniae.*[20]

Antibiotic Therapy

Initial antibiotic therapy based on national guidelines and local antimicrobial susceptibility patterns should cover pathogens associated with community-acquired pneumonia, particularly *S. aureus* (MSSA and MRSA)*, S. pneumoniae* and *S. pyogenes.*[8,21] In a murine model of secondary pneumococcal infection following influenza, combined use of oseltamivir and antibiotics was more effective than antibiotic therapy alone in improving survival.[22,23] If careful microbiologic studies do not indicate bacterial co-infection, early cessation of antibiotic therapy may be warranted; use of prophylactic or prolonged courses of antibiotics may be associated with an increased risk of late superinfection with antimicrobic-resistant organisms, particularly in those requiring protracted ventilatory support.

Adjunctive pharmacologic therapy

The potential value of adjunctive immunomodulatory therapies for treating severe influenza is uncertain, and insufficient data are currently available to assess the possible value of available agents like systemic interferon or ribavirin that have both immunomodulatory and antiviral activities.[24]

In pneumonia patients during the 1918 pandemic, early administration of convalescent blood products appeared to be associated with increased survival.[25] Similar therapy has been used in severe illness caused by highly pathogenic avian influenza

A(H5N1) virus infection,[26,27,28] and studies in pH1N1 illness are anticipated with polyclonal antibody preparations derived from convalescent patient or vaccinee plasma and possibly with human monoclonals. Depending on plasmapheresis capacity and pandemic severity, one modelling study found that a passive-immunotherapy program would be a logistically feasible mitigation option for many developed countries.[29] In addition, preliminary findings suggest that severe illness from pH1N1 virus infection may be associated with IgG2 deficiency and that pregnancy-related reductions in IgG2 level may explain the increased severity of illness with pH1N1 virus infection in some pregnant patients.[30] The possible therapeutic role of IV immunoglobulin requires further investigation.

High-dose corticosteroids have no established role in ARDS; their use has been associated with prolonged viral shedding in seasonal influenza, increased mortality in H5N1 influenza and possibly pH1N1 virus infections,[31] and substantial risk of side effects. However, lower dose corticosteroids (0.5-2.5 mg/kg/day of methylprednisolone) may improve outcomes in non-pH1N1 ARDS[32] and septic shock[33] and have been used with oseltamivir in treating pHN1-associated acute lung injury.[34] Controlled studies are needed in influenza-associated pneumonitis.[35]

Other commonly used drugs with anti-inflammatory properties (e.g., statins, glitazones, fibrates, cyclooxygenase 2 inhibitors) have been suggested as potential treatments,[36,37,38] but data from prospective, controlled trials are currently lacking. Although beneficial in animal models of influenza,[39] salicylates are linked to Reye syndrome in children, may have been associated with increased mortality in 1918[40,41] and should be avoided.

PREVENTION AND INFECTION CONTROL

Immunization

Almost all pH1N1 isolates globally are antigenically similar to the vaccine strain, A/California/07/2009(H1N1), and multiple countries have initiated pH1N1 immunisation programmes. In the United States, the FDA has approved egg-grown, split and sub-unit vaccines, and live-attenuated monovalent pH1N1 vaccines, which are all made in the same manner as seasonal vaccines,[42] whereas in Europe the EMEA has approved a whole virus vaccine propagated on Vero cells, and two egg-grown, split and subunit vaccines that contain proprietary oil-in-water adjuvants.[43] In the United States the approved inactivated vaccines contain 15µg of hemagglutinin, whereas in Europe, doses containing 3.8 and 7.5 µg virus hemagglutinin with AS03 and MF-59, respectively, are approved.

Studies of these and other vaccines indicate that one 15 µg dose of inactivated vaccine raises protective hemagglutination inhibition (HAI) antibody levels ($\geq$1:40) in 50-96% of children aged 6 months to 17 years,[44,45,46] in 63-98% of adults 18 to 64 years, and in 79-93% of the elderly.[47,48,49] One US study found that 25-36% of children aged 6 months to 9 years responded to a single dose as early as 8-10 days.[50] A second dose is not required in older children or adults, but may be needed in young children and possibly others.[45,46] Single oil-in-water adjuvanted doses of 1.9 ug appear immunogenic in young children. Single non-adjuvanted doses of 7.5 µg appear to be immunogenic in most persons.[46,47] While MF-59 oil-in-water adjuvant augments the antibody response to inactivated pH1N1 vaccine,[48] alum was found to be ineffective as an adjuvant in studies in China.[47,49] Initial studies in the United Kingdom with non-adjuvanted whole virion

and ASO3-adjuvanted, reduced antigen (3.75 ug HA) pH1N1 vaccines indicate high immunogenicity and good vaccine effectiveness.[51]

Recent seasonal influenza vaccine may elicit antibodies that are cross-reactive to pH1N1 influenza virus in a few adults,[52] as well as broadly reactive heterosubtypic neutralizing antibodies directed against HA in some.[52a] However, available evidence is conflicting regarding a possible protective (or even adverse) effect of previous seasonal vaccination on the frequency or severity of pH1N1 illness.[53,54,55,56,56a,56b] Co-administration of inactivated seasonal and pandemic H1N1 vaccines does not appear to impair antibody response to either one,[57] and studies of sequential administration are in progress.

The HA of pH1N1 virus shares conserved antigenic epitopes with human and swine H1 viruses from the early 20th century but differs antigenically from recent seasonal H1N1 viruses, in part because of differences in glycosylation patterns.[58,59] In mice, immunization with 1918 or pH1N1, but not seasonal H1N1, virus vaccines elicits cross-neutralizing antibodies to both and provides protection against lethal pH1N1 infection,[58] as does prior infection with a classical 1976 swine H1N1 virus.[60] One neutralizing monoclonal antibody derived from a 1918 survivor shows substantial antiviral activity in mice infected with pH1N1 virus.[61] Testing of archived specimens from recipients of the A/New Jersey/76 swine influenza vaccine confirmed that the majority developed cross-reactive neutralizing antibodies to pH1N1 virus.[52]

No serious unexpected adverse events have been observed to date with pH1N1 vaccines.[62,63] Local reactogenicity (e.g., sore arm) tends to be higher with adjuvanted vaccines, and more fever and reactogenicity have been noted in children. While the safety

profile overall is comparable to that of seasonal influenza vaccine, post-vaccination safety monitoring is being undertaken to look for serious or rare events above background levels.[63,64] Anaphylaxis has been noted in about 5 per million vaccine doses distributed, which does not exceed the expected frequency after receiving other vaccines.[65] Guillain-Barré syndrome (GBS) was observed in about 1 additional case per 100,000 recipients of swine influenza vaccine in 1976, but studies of seasonal influenza vaccine conducted since then have not demonstrated a substantial increase in risk.[66,67,68] In contrast, GBS is a recognised complication of influenza,[69] and the risk of GBS is substantially greater after ILI than after vaccination.[70] The frequency of GBS following receipt of pH1N1 vaccines has been below the estimated background rate to date.[71] Administration of pH1N1 vaccine appears to be safe in HIV-infected pregnant women.[72]

The limited early availability of pH1N1 vaccines has been important in determining their impact and cost effectiveness. Even in countries with substantial numbers of early pH1N1 infections like the United Kingdom, modelling suggests that immunization of groups at higher risk of complications and deaths appears to be both beneficial and cost-effective.[73] Due to anticipated ongoing pH1N1 activity, monovalent pH1N1 vaccine should be considered for travellers to the tropics and countries in the Southern hemisphere during its seasonal influenza period. The pH1N1 virus has been recommended to replace the previously circulating seasonal H1N1 virus in the 2010 trivalent vaccine formulations for the Southern and Northern hemispheres.[74,75]

Antiviral chemoprophylaxis

While oseltamivir appears effective in preventing spread of pH1N1 virus infection among close contacts in household and outbreak settings,[76,77,78] neuraminidase inhibitors are generally not recommended for chemoprophylaxis of pH1N1 illness due to cost considerations, variable compliance related to side effects,[78,79,80] and potential for selection of resistant variants, perhaps related to emergence during subtherapeutic dosing or transmission from treated ill contacts.[81,82,83] High frequencies of gastrointestinal symptoms and headache have been reported by recipients when oseltamivir has been used for chemoprophylaxis.[78,80] Where there is risk of transmission and the likelihood of complications of infection is high, oseltamivir or zanamivir might be used for post exposure chemoprophylaxis in persons at high risk for influenza-related complications (e.g., patients with severe immunosuppression).[83] When oseltamivir resistance is a concern, inhaled zanamivir would be the preferred agent. An alternative option is close monitoring for symptoms, followed by prompt early antiviral treatment should symptoms develop.[84]

Infection control

Nosocomially acquired illness has been reported in both healthcare workers[85] and patients. Seroprevalence (HAI $\geq$ 1:40) was higher in front-line healthcare workers than other hospital staff or the general population in Taiwan (Supplementary Table 2),[86] presumably reflecting greater exposure, and several nosocomial outbreaks in hospitalized immunocompromised patient groups have been documented.[87,88,89,90] Infection control measures recommended by the WHO include Droplet and Standard Precautions among the healthcare workers (HCWs) and maintaining a minimum distance of $\geq$1 metre

between patients when providing routine care to patients infected with pH1N1 influenza and those with influenza-like symptoms.[91] Surgical masks appear to be as effective as N95 respirators for respiratory protection of HCWs during the routine care of patients hospitalized with seasonal influenza,[92,93] and in one small study were also as effective in reducing production of infectious aerosols during coughing when worn by influenza patients.[94] The incidence of nosocomial pH1N1 infections appeared to remain low in staff using surgical masks in one hospital admitting substantial numbers of pH1N1 patients.[95]

Fit-tested respirators are recommended in the United States by US CDC for healthcare workers exposed to pH1N1 patients in routine healthcare settings at present.[96] However, both CDC and WHO recommend that when performing aerosol-generating procedures (e.g. aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy), HCWs should use higher levels of infection control precautions including the use of respirators (e.g., N95 masks).[91] Because of the risks of occupational HCW exposure, transmission of pH1N1 influenzavirus from HCWs to patients, and of adverse impacts of HCW illness on healthcare delivery, HCWs are a first priority group for pH1N1 immunization.[85,91]

The optimal duration of isolation precautions for hospitalized patients is unknown; current guidelines recommend that isolation precautions be continued for minimum of 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a healthcare facility.[96] For prolonged illness (i.e. pneumonia), control measures should be used during the acute illness phase, [91] but continued requirement for ventilator or ICU support by itself does not necessitate

isolation. Severely immunocompromised persons may have prolonged viral replication, isolation should continue for the duration of influenzal illness,[96] and when feasible, depend on sequential virological monitoring.[97] Studies assessing the association of viral detection with communicability are needed.

The frequency of viremia and associated risk of transfusion-related transmission from pH1N1 virus-infected blood donors appear to be very low.[98]

Non-pharmaceutical interventions

Non-pharmaceutical measures, either individually or in combination, have been used extensively during the pH1N1 and previous pandemics, but data on their usefulness and cost-effectiveness are limited.[99] Such measures include personal protective measures like masks and hand hygiene; isolation and quarantine; traveller screening; environmental decontamination; and social distancing measures like school and worksite closures and cancellation of mass gatherings. Hand hygiene with soap and water or alcohol-based hand rub is highly effective in reducing infectious influenza A virus levels on human hands.[100] Compliance with hand hygiene and masking may have some benefit in reducing the risk of secondary illnesses in household contacts during seasonal influenza when used very early by contacts after illness onset in a household index case.[101,102]

During the 1918 pandemic, combining multiple community-based measures appeared to be effective in decreasing influenza-related deaths, but only when implemented early in the outbreak and for extended periods (at least 4 weeks).[103,104,105] Early school closures may reduce peak illness incidence and modestly decrease the number of cases.[106,107] During the current pandemic, some countries have employed

various interventions, especially school closure (generally for 1 week or less) and cancellation of mass gatherings despite the associated adverse social and economic effects.[108,109] The effectiveness of school closures and other community NPI measures in slowing the spread of pH1N1 needs to be evaluated.

Animal-Human Interface Issues

Infected humans have also been implicated in transmitting pH1N1 virus to swine, turkeys, and occasionally household pets including cats, ferrets, and dogs.[110] Swine are highly susceptible to pH1N1 virus infection, and experimentally infected swine may shed pH1N1 virus from the respiratory tract up to 10 days.[111] Although most avian species appear resistant to experimental pH1N1 virus infection,[112,113] the known susceptibility of swine and domestic poultry to other influenza viruses indicates that close monitoring is warranted to detect emergence of novel strains. One instance of a reassortment between pH1N1 virus and a swine influenza virus has been reported to date.[114] Virus is not detectable in meat from experimentally infected swine,[115] so that pork harvested from pH1N1 virus-infected swine does not pose a risk to humans for pH1N1 virus infection.[116]

EPIDEMIOLOGICAL NOTE

The source of pH1N1 virus and location where initial transmission to and among humans occurred is currently unknown. The earliest epidemiological evidence of 2009 pandemic influenza A (H1N1) virus activity was reported from the community of La Gloria, Veracruz, Mexico in March 2009. It has been hypothesized that this might have been linked to persons working with or otherwise exposed to pigs at farming operations

in the state of Veracruz.[117,118,119] It was noted that: “an increase in the reported incidence of respiratory diseases was noted during March 2009 at the town of La Gloria, in the south-eastern state of Veracruz, Mexico. So far, this is the first community in which a case of novel influenza A H1N1 virus has been identified. Further cases were rapidly detected in other areas of Mexico and elsewhere."[117] It is possible that pandemic influenza activity could have started before March 2009 in southern Mexico. Beginning in late March, increases in acute respiratory illness and severe lower respiratory tract disease occurred in Mexico City and other areas of Mexico.[9,117,120,121,122,123] The earliest confirmed pH1N1 cases detected in the U.S. had illness onset at the end of March 2009,[124,125] and other early cases were subsequently detected among persons in southern states bordering Mexico or epidemiologically linked to travel to Mexico in April. Similarly, the early cases in Canada were linked to Mexico travel,[126] with subsequent spread to contacts, including cases of severe lower respiratory tract disease.[13]

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Supplementary Table 1. Common genetic markers for antiviral resistance, virulence, or transmission in pandemic H1N1 and other influenza viruses.

Protein	Amino acid	Motif	Description	Pandemic (H1N1) Influenzavirus 2009
HA*	222 (225 in H3 numbering system)	D→G	Present in avian H5N1 and some 1918 H1N1 isolates; associated with altered receptor specificity (increased binding to α2,3-linked receptors) and increased binding to cells of the lower respiratory tract. Also observed in egg-isolates of swine H1N1 viruses.	Increased frequency of detection (possibly also D→N) in fatal pH1N1 cases in multiple countries (up to about 20% to date),[127,127a] perhaps related to emergence during lower respiratory tract replication. Also found in uncomplicated illnesses. Effects on virulence and transmission to be determined.[128] Viruses lacking this mutation are also capable of causing deep lung infections.
PB2	271	T→A	T271A associated with enhanced polymerase activity in mammalian cells.[129]	All PB2 sequences from pH1N1 viruses contain alanine at position 271, indicative of prior adaptation to mammalian hosts.

PB2	627	E→K	E627K associated with replication at 33°C, and perhaps increased pathogenicity and transmission (avian to human) of H5N1 virus[130,131]	2 isolates from the Netherlands reported in public databases with this change were not associated with unusual pathogenicity or transmission. When mutation introduced into pH1N1 virus, no major effects on replication in murine or ferret models or on pathogenesis.[132]
PB2	Serine at 590 + arginine at 591		SR polymorphism observed in triple reassortant swine H1N1 viruses with E627, and introduction of this polymorphism into the PB2 subunit of a primary avian isolate also increased polymerase activity and viral replication in human and porcine cells.[133]	pH1N1 virus has acquired second-site suppressor mutations in its PB2 polymerase subunit that convey enhanced polymerase activity in human cells.[133]
PB2	701	D→N	D701N may compensate for the lack of E627K for transmission of avian viruses[131]	None detected in pH1N1 to date. When mutation introduced into pH1N1 virus, no major effects on replication in murine or ferret models or on pathogenesis.[132]

PB1-F2			PB1-F2 associated with increased pneumonia severity in animal models; truncation or absence of PB1-F2 has been associated with attenuating effect in mice and reduced replication in cells	All viruses analyzed to date are truncated at 11 amino acids and lack functional PB1-F2. Pandemic H1N1 viruses purposefully mutated to allow expression of full-length PB1-F2 did not show increased virulence in animal models.[134]
NA	275	H→Y	Resistance to oseltamivir and reduced susceptibility peramivir; present in seasonal H1N1 viruses from 2008 onwards.[135]	Detected in > 265 viruses worldwide (about 1-2% of tested) most often after treatment, with approximately 1/3 of these from immunocompromised hosts.[128] Several clusters in healthcare settings and otherwise healthy contacts but no sustained community transmission to date.[136,137]
M2	31	S→N	Resistance to adamantanes; present in seasonal H3N2 and some seasonal H1N1 viruses	Present in nearly all viruses examined to date

NS1	227-230 PDZ domain	X-S/T-X-V	Viruses containing PDZ domains from the 1918 H1N1 and H5N1 viruses demonstrated increased virulence in infected mice.[138]	All viruses analyzed to date are truncated at 219 amino acids and therefore lacking the PDZ domain. Extension of NS1 to 230 amino acids has no impact on virus replication in human or swine cells and minimal effects on replication, pathogenicity and transmission in mouse and ferret models.[139]
NS1	217	K→E	Abolishes binding to host Crk/CrkL signaling adapters	Restoration of Crk/CrkL binding has no impact on virus replication in human or swine cells and minimal effects on replication, pathogenicity and transmission in animal models.[139]
NS1	92	D→E	D92E shift in NS1 protein may contribute to increased virulence of H5N1 viruses	2 viruses from New York have a D→G mutation; no severity information available

*Note: Only 31% of B cell epitopes present in human H1N1 strains are conserved in the pH1N1 virus, including only 17% conserved in the HA, whereas more CD4 T cell (41%) and CD8 T-cell (69%) epitopes are conserved.[140] The HA of pH1N1 virus shares

conserved antigenic epitopes with 1918 pandemic virus and swine H1 viruses from the early 20th century, particularly within the Sa antigenic site, but differs antigenically from recent seasonal H1N1 viruses, in part because of lack of glycosylation sites present in seasonal H1N1viruses.[58,59]

Note: While no reassortment with seasonal influenza viruses has been recognized to date, detection of a swine H1N1 virus with a gene derived from the pH1N1 virus has been recently reported from Hong Kong SAR.[114]

Supplementary Table 2. Results of representative studies of pH1N1 antibody seroprevalence

Study Population	Findings	Assay	Titer cutoff [Virus]
US residents born between 1880 and 2004; sera collected in 1971 and 2002 through February 2009[52]	Birth 1910-1929: 100% ≥1:80 (n = 11) Birth before 1950: 34% ≥1:80 (n = 115) Birth after 1980: 4% ≥1:40 (n = 107)	MN	1:40 [A/CA/04/09 (H1N1)]
US residents aged ≥25 years, recipients of split A/NJ/76 (H1N1) vaccine; sera collected in 1976 [52]	63% with cross-reactive titer of 1:160 (n = 83)	MN	1:80 [A/CA/04/09 (H1N1)]
Persons born between 1897 and 1959; sera collected 1999 [1]	Birth 1897-1917: 53% ≥1:32 (n = 49)	MN	1:32 [A/CA/04/09 (H1N1)]
Persons born between 1909-2005; sera collected in 2004-2005[141]	Birth 1909-1919: 55.6% (n = 27) Birth 1920-1929: 21.2% (n = 104) Birth 1930-1939: 1.6% (n = 125) Birth 1940-1949: 0% (n = 116) Birth 1950-1969: 0% (n = 119)	HI	1:40 [A/Finland/554/09 (H1N1)]

England residents aged 0 to >80 years; sera collected in 2008 or early 2009 [142]	Age ≥80 years: 47% (n = 166) Age 75-79 years: 17.6% (n = 187) Age 65-74 years: 25.1% (n = 167) Age 50-64 years: 18.5% (n = 65) Age 25-49 years: 9.5% (n = 168) Age 15-24 years: 12.7% (n = 110) Age 5-14 years: 4.3% (n = 163) Age 0-4 years: 2.8% (n = 143)	MN	1:40 [A/Eng/195/09 (H1N1]
England residents in London and West Midlands aged 0 to ≥65 years; difference between baseline sera (2008 or early 2009) and sera collected in September 2009 [142]	*Sero-incidence* Age <5 years: 21.3% (n = 26) Age 5-14 years: 42% (n = 35) Age 15-24 years: 20.6% (n = 21) Age 25-44 years: 6.2% (n = 53)	HI	1:32 [A/Eng/195/09 (H1N1]
US residents in Pittsburgh aged 0-89 years; sera collected November to December	Age 0-9 years: 28% (n = 88) Age 10-19 years: 45% (n = 96)	HI	1:40 [A/CA/07/09 (H1N1)]

2009[143]	Age 20-29 years: 20% (n = 89) Age 30-39 years: 14% (n = 81) Age 40-49 years: 18% (n = 100) Age 50-59 years: 22% (n = 96) Age 60-69 years: 13% (n = 100) Age 70-79 years: 5% (n = 100) Age 80-89 years: 26% (n = 96)		
Taiwan health care workers, mean age 36.9 years; controls mean age 52 years; sera collected from October to November 2009[86]	Infectious disease doctors, inpatient nurses and Emergency Room staff: 30.8% (n = 120) General clinicians, laboratory and administrative staff: 12.6% (n = 175) Controls (general physical exam patients): 7% (n = 244)	HI	1:40 [A/Taiwan/07/T1338/09 (H1N1)]

MN = Microneutralization assay; HI = Hemagglutinin inhibition assay

Note: Seroprevalence data not included from Nougairède A, *et al.,* 2010[144]; Chen H *et al.*, 2009[218]; Chen MIC *et al.*, 2010[355]; and Tang JW *et al.*, 2010[354].

Supplementary Table 3. Comparison of representative admission laboratory study results in patients who survived or died following hospitalization with pandemic H1N1 influenzavirus illness.

Admission laboratory finding	Perez-Padilla *et al.*, 2009[120] (N=18)				Kumar *et al.*, 2009[13] (N=168)				Dominguez-Cherit *et al.*, 2009[9] (N=58)+			
	Survivors (n=11)		Non-survivors (n=7)		Survivors (n=139)		Non-survivors (n=29)		Survivors (n=34)		Non-survivors (n=24)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Leukocyte, /mm^3	7.23 (mean)	5.66 (SD)	5.3 (mean)	2.1 (SD)	6.7	(3.8-12.1)	6.9	(3.7-9.5)	9.5 (mean)	5.5 (SD)	10.6 (mean)	6.6 (SD)
Creatine kinase, U/L	189	(58-1249)	514	(175-2156)	255	(104-1117)	221	(42-455)	121	(5-231)	1059	(652-2449)*
Creatinine, mg/dL	0.94	(0.22-1.26)	1.04	(0.49-4.59)	0.71	(0.46-1.01)	0.97	(0.58-2.33)*	0.9	(0.67-1.1)	1.4	(1.1-3.1)*
PaO2/FiO2	164	(87-	53	(46-	124	(80-	85	(67-	120	(62-	70	(51-

		250)		107)*		181)		166)		161)		105)*

Values are presented as median and (IQR) interquartile range with exception of leukocyte counts, some of which are expressed as mean (standard deviation)

+Includes suspected and laboratory proven cases of pH1N1

*Statistically significant difference ($P < 0.05$) for comparison of survivors and non-survivors

Supplementary Table 4. Representative studies of rapid antigen diagnostic test sensitivity for pandemic H1N1 2009 and seasonal influenza viruses

RIDT Kit	Patient group	Specimen type	Influenza A virus type	No. of specimens positive by RIDT/ no. positive by RT-PCR (%)	No. of specimens positive by RIDT/ no. of specimens by culture (%)
Binax Now Influenza A&B (Binax, Inc., Scarborough, Maine, USA)[145]	Not stated	NP swabs and OP swabs*	pH1N1 2009	18/45 (40)	
			Seasonal H1N1	3/5 (60)	
			Seasonal H3N2	12/15 (80)	
Directigen EZ Flu A+B (Becton, Dickinson and Company; Sparks,	Not stated	NP and OP swabs	pH1N1 2009	21/43 (49)	
			Seasonal H1N1	3/4 (75)	
			Seasonal H3N2	10/12 (83)	

MD, USA) [145]					
Binax Now Influenza A&B[146]	Children	Nasal wash or swab, sputum specimens	pH1N1 2009	1285/2880 (45)	1590/2880 (55)
Binax Now Influenza A&B[147]	Children	NP swabs	pH1N1 2009	66/107 (62)	
Binax Now Influenza A&B[148]	Children, young adults	NP specimens	pH1N1 2009	23/60 (38)	
		Tracheal aspirate or BAL		82/140 (58)	84/140 (60)
Quidel QuickVue Influenza A+B (Quidel Corporation, San Diego, CA, USA) [145]	Not stated	NP and OP swabs	pH1N1 2009	31/45 (69)	
			Seasonal H1N1	4/5 (80)	
			Seasonal H3N2	12/15 (80)	

QuickVue Influenza A+B (Quidel)[149]	University students, outpatient	Throat swab	Seasonal A or B	14/74 (19)	
			Seasonal A or B		12/49 (24.5)
	Children and adults	Deep nasal swab	Seasonal A or B	10/31 (32)	
			Seasonal A or B		11/32 (34)
	Elementary school students	Nasal swab	Seasonal A or B		28/105 (27)
QuickVue Influenza A+B (Quidel)[150]	Not stated	Not stated	pH1N1 2009	20/39 (51)	
	Not stated		Seasonal H1N1	12/19 (63)	
	Not stated		Seasonal H3N2	6/19 (31)	
Directigen EZ Flu A+B[148]	Children, young adults	NP specimens	pH1N1 2009	28/60 (47)	
QuickVue Influenza	Hospitalized	Upper	pH1N1 2009	5/20 (25)	

A+B (Quidel)[151]		respiratory tract			
QuickVue Influenza A+B (Quidel)[152]	Pediatric outpatients	Nasal swab	pH1N1 2009	89/142 (63)	

* The original specimens provided largely by local state health laboratories.

Abbreviations: RIDT, rapid influenza diagnostic test

Supplementary Table 5. Comparative pharmacology of intravenous and oral neuraminidase inhibitors [153,154,155,156,157]

	Route	Usual adult dose	Mean plasma Cmax (ng/ml)	Mean plasma Cmin (ng/ml)	Mean plasma AUC (ng*hr/ml)	Elimination	Plasma T1/2 (hr)	Vdss	Ratio of IC50 values for H1N1 Y275/ H275
Peramivir*	IV	600 mg daily	43,804	70 (predicted)*	82,800 (0→24 hrs) (predicted)*	Renal	7.7-20.8	22 L	≥ 80
Zanamivir	IV	600 mg twice daily	32,577 -39,712	340-353	66,450 (0→12 hrs)	Renal	1.8-2.1	16L	1-2
Oseltamivir	PO[+]	150 mg twice daily	383-599	279-282	2,941 -4,904 (0→12 hrs)	Renal	6.3-9.0	23-26L	≥300

*Predicted from studies administering up to 8 mg/kg doses

[+]Intravenous oseltamivir is also currently in clinical development

Supplementary Table 5 (continued)

	Possible adverse events	Recommended Dose Adjustments			
		Renal insufficiency (CrC1)	Hepatic insufficiency	Children	Elderly
Peramivir§	Diarrhea, CNS effects (including depression, anxiety, confusion, altered insomnia, somnolence), decreased PMN counts	<50 ml/min	No	6-10 mg/kg depending on age (birth – 17 years)§	No#
Zanamivir	Aerosolized: bronchospasm; allergic-	<80ml/min	No	TBD for weight <38kg	No

	like reactions (including oropharyngeal edema, serious skin rashes, and anaphylaxis); dizziness				
Oseltamivir	Nausea, emesis; anaphylaxis; serious skin reactions (including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme); delirium, abnormal behaviour	<30 ml/min	No (mild-moderate)	Weight-based for <40kg; age- and weight-based for < 24 months (see reference 83)	No

§No pediatric pharmacology or clinical trials data published to date. Dose depend on age (birth to 17 yrs)

#Drug exposure 26% higher based on plasma AUC in those ≥65years old