Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST Recent Advances in Chest Medicine

Clinical Management of Pandemic 2009 Influenza A(H1N1) Infection

David S. Hui, MD, FCCP; Nelson Lee, MD; and Paul K. S. Chan, MD

Antiviral therapy and vaccination are important strategies for controlling pandemic 2009 influenza A(H1N1) but efficacy depends on the timing of administration and is often limited by supply shortage. Patients with dyspnea, tachypnea, evidence of hypoxemia, and pulmonary infiltrates on chest radiograph should be hospitalized. Patients with severe illness or underlying medical conditions that increase the risk of more severe disease should be treated with oseltamivir or zanamivir as soon as possible, without waiting for the results of laboratory tests. Lung-protective ventilation strategy with a low tidal volume and adequate pressure, in addition to a conservative fluid management approach, is recommended when treating adult patients with ARDS. Extracorporeal membrane oxygenation has emerged as an important rescue therapy for critically ill patients. Use of systemic steroids was associated with delayed viral clearance in severe acute respiratory syndrome and H3N2 infection. Low-dose corticosteroids may be considered in the treatment of refractory septic shock. Passive immunotherapy in the form of convalescent plasma or hyperimmune globulin may be explored as rescue therapy. More data are needed to explore the potential role of IV gamma globulin and other drugs with immunomodulating properties, such as statins, gemfibrozil, and *N*-acetyl-cysteine. Health-care workers must apply strict standard and droplet precautions when dealing with suspected and confirmed case and upgrade to airborne precautions when performing aerosol-generating procedures. Nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, good community hygiene, and restrictions on travel are useful measures in controlling an influenza pandemic at its early phase.

CHEST 2010; 137(4):916–925

Abbreviations: ECMO = extracorporeal membrane oxygenation; HCW = health-care worker; IMV = invasive mechanical ventilation; MRSA = methicillin-resistant *Staphylococcus aureus*; NAC = *N*-acetyl-L-cysteine; NPPV = noninvasive positive pressure ventilation; pandemic A(H1N1) = pandemic 2009 influenza A(H1N1); ROS = reactive oxygen species; RT-PCR = reverse transcription-polymerase chain reaction; SARS = severe acute respiratory syndrome; WHO = World Health Organization

Influenza A virus belongs to the genus *Orthomyxovirus* under the family Orthomyxoviridae. The enveloped virion contains eight segments of single, negative-stranded RNA genome, encoding the surface glycoproteins of hemagglutinin and neuraminidase, RNA polymerase (PA, PB1, PB2), nucleoprotein, matrix protein, and nonstructural protein. There are 16 hemagglutinin subtypes and nine neuraminidase subtypes based on the antigenic characteristics. Introduction of a new subtype into humans can result in a large-scale pandemic with high morbidity and mortality due to the naïve immunity and the absence of an effective vaccine in the initial phase of outbreak. Three influenza pandemics occurred in the 20th century. The most severe influenza pandemic of "Spanish flu" A(H1N1) occurred in 1918 to 1919, with a global mortality of 20 to 25 million. It was estimated that 50% of

Manuscript received October 3, 2009; revision accepted December 12, 2009.

Affiliations: From the Department of Medicine and Therapeutics (Drs Hui and Lee), the Stanley Ho Center for Emerging Infectious Diseases, School of Public Health & Primary Care (Drs Hui, Lee, and Chan), and the Department of Microbiology (Dr Chan), The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.

Correspondence to: David S Hui, MD, FCCP, Division of Respiratory Medicine, The Chinese University of Hong Kong, 9/F, Prince of Wales Hospital, 30-32 Ngan Shing St, Shatin, New Territories, Hong Kong; e-mail: dschui@cuhk.edu.hk

DOI: 10.1378/chest.09-2344

the global population became infected, of whom half suffered clinical illnesses. The A(H2N2) pandemic that occurred in 1957 to 1958 caused about 70,000 deaths in the United States. In 1968, another new type A(H3N2) emerged and remains in circulation today.[1,2]

Pandemic 2009 influenza A(H1N1) [A(H1N1)] is a new strain of influenza virus that was first identified in Mexico and the United States in March and April 2009, respectively. The pandemic A(H1N1) virus originated from the triple-reassortment swine influenza (H1) virus circulating in North American pigs.[3,4] Complete genome sequencing has shown that the known molecular markers of pathogenicity (PB1-F2 and nonstructural-1 proteins) are not expressed in the pandemic A(H1N1) virus.[5] Animal studies have shown that the novel influenza virus caused increased morbidity, replicated to higher titers in lung tissue, and was recovered from the intestinal tract of intranasally inoculated ferrets in contrast to seasonal influenza H1N1 virus.[6-8] This may explain why the novel virus is relatively more pathogenic than seasonal influenza viruses in its capacity to invade the lower respiratory tract and cause rapidly progressive pneumonia in humans because of our lack of background immunity to the former. Within several weeks from onset, the novel virus has spread throughout the world through international air travel and resulted in an influenza pandemic.[9] The World Health Organization (WHO) has raised the level of influenza pandemic alert from phase 5 to phase 6 since June 11, 2009.[10]

As of November 29, 2009, there have been > 622,482 laboratory-confirmed cases of pandemic A(H1N1) and 8,768 deaths in 207 countries and territories reported to the WHO. As more and more countries have stopped counting individual cases, particularly of milder illness, the case count is significantly lower than the actual number of cases that have occurred.[11]

Clinical and Laboratory Features of Severe Cases

The majority of patients with pandemic A(H1N1) infection develop mild upper respiratory tract symptoms similar to seasonal influenza, but gastrointestinal symptoms seem more common in the former. In a study of 642 confirmed cases during the early outbreak in the United States in April 2009, 60% of patients were ≤ 18 years of age. Among those with available data, 18% had history of recent travel to Mexico, whereas 16% were identified from school outbreaks. The most common presenting symptoms were fever (94%), cough (92%), and sore throat (66%); 25% of patients had diarrhea, and 25% had vomiting. Of the 399 patients for whom hospitalization status was known, 36 (9%) required hospitalization and two died.[12] In a study of 863 confirmed cases in Ontario, Canada, cough, fever, sore throat, and gastrointestinal symptoms were reported in 92%, 91%, 41%, and 24% of patients, respectively, with a hospitalization rate of 3.6% and a case fatality ratio of 0.2%.[13]

Patients with more severe disease present with fever, cough, dyspnea or respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia (Figs 1*A-C*). Other common findings were an increased creatinine kinase level and lymphopenia.[14] The WHO has outlined the warning signs for more severe disease as listed in Table 1.[15] Although severe disease may occur in otherwise well and young subjects, there are often risk factors for developing more severe disease (Table 2).[14,16-18]

In contrast to seasonal influenza, most severe pandemic A(H1N1) disease and its related mortality have occurred among children and adults aged < 60 years, whereas about 40% of patients who have required hospitalization or died were previously healthy.[16-18] The number of ICU admissions due to pandemic A(H1N1) infection was 15 times the number due to viral pneumonitis in recent years in Australia and New Zealand.[17] The elderly (> 65 years) are less frequently infected by the novel virus,[16-19] probably because of some pre-existing cross-reacting immunity against the virus due to their past exposure to previous circulating seasonal influenza A(H1N1) strains similar to the current pandemic A(H1N1) virus.[20] However, it is controversial if the seasonal influenza vaccine antigen components confer any cross-immunity against the pandemic strain.[20,21]

Autopsy findings have shown three distinct pulmonary histologic patterns: diffuse alveolar damage, necrotizing bronchiolitis, and diffuse alveolar damage with intense alveolar hemorrhage. There is also evidence of ongoing pulmonary aberrant immune response.[22] Pulmonary emboli were noted, whereas secondary bacterial or fungal pneumonia were reported in 7/50 (14%) fatal cases in California.[23] A fatal case with coinfection with community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) occurred in a Filipino sailor who died in Hong Kong.[24] In a study of 77 American patients with fatal cases of confirmed pandemic A(H1N1) infection,[25] evidence of concurrent bacterial infection was found in 22 (29%) patients, including 10 with *Streptococcus pneumoniae*, six with *Streptococcus pyogenes*, seven with *S aureus*, two with *Streptococcus mitis*, and one with *Haemophilus influenzae*; four cases involved multiple pathogens. The median age of the 22 patients was 31 years and median duration of illness was 6 days. These findings confirm that bacterial lung infections are occurring among patients with fatal cases of pandemic A(H1N1) infection and underscore both the need for early recognition/treatment of bacterial pneumonia in patients with influenza and the

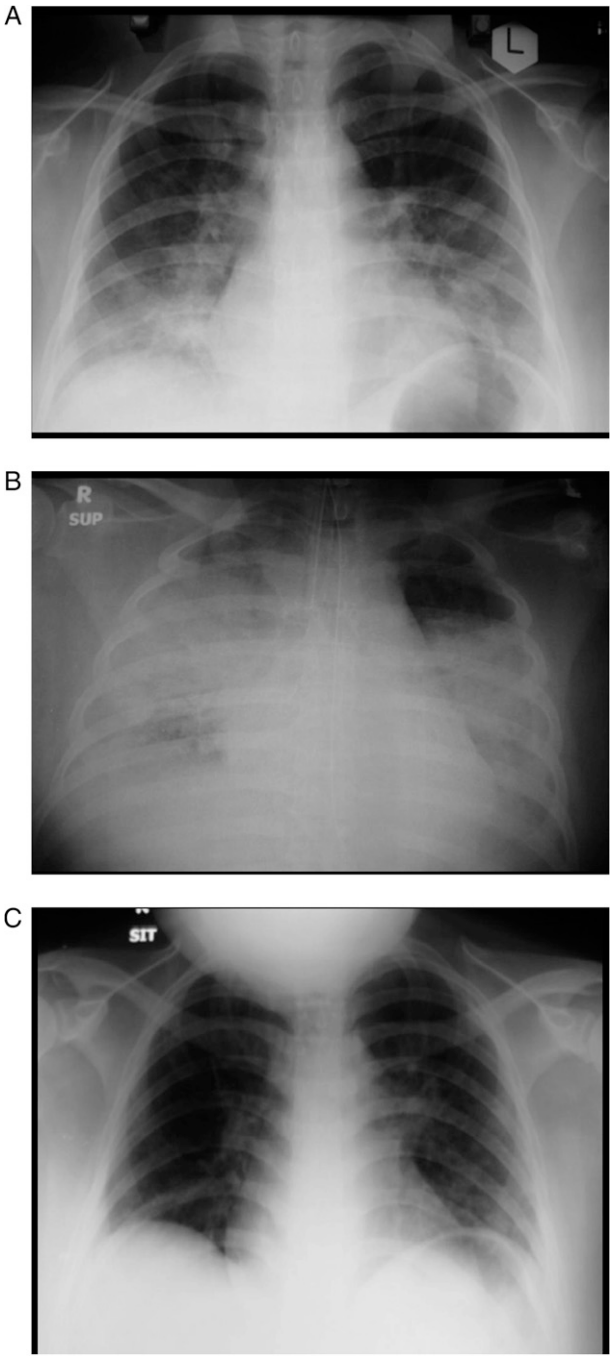

FIGURE 1. (*A*) Chest radiograph of an obese, 23-year-old woman (BMI 31 kg/m^2). She had influenza symptom onset on July 8, 2009, and was treated by a general practitioner with antibiotics. A chest radiograph taken on July 15, 2009, showed bilateral mid and lower zone patchy infiltrates. Reverse transcription-polymerase chain reaction (RT-PCR) from the nasopharyngeal aspirate was positive for the pandemic A(H1N1) virus. Oseltamivir 150 mg bid was started on July 15, 2009. (*B*) Despite treatment with high-dose oseltamivir and supplemental oxygen, her condition deteriorated, and a chest radiograph taken on July 18, 2009, showed bilateral and extensive consolidation. She required invasive mechanical ventilation (IMV) on July 18, 2009, with lung-protective ventilation strategy and conservative fluid management. (*C*) Her condition improved following intensive care support and high-dose oseltamivir for 10 days. She was extubated on July 24, 2009. Chest radiograph taken on July 29, 2009, showed marked clearing of the lung consolidation.

importance of pneumococcal vaccination for persons at increased risk for pneumococcal pneumonia.[25] The indications for hospitalization are listed in Table 3.[26]

Diagnostic Tests

Nasal swabs with nasal secretions (from the anterior turbinate area) or nasopharyngeal aspirates or swabs are appropriate specimens for detecting human influenza A and B. Although the rapid influenza diagnostic tests were capable of detecting novel A(H1N1) virus from respiratory specimens containing high levels of virus, the overall sensitivity was low (40%-69%) among all specimens tested and declined substantially as virus levels decreased. Patients with illnesses compatible with pandemic A(H1N1) virus infection but with negative rapid influenza diagnostic test results should be treated empirically based on the level of clinical suspicion, underlying medical conditions, severity of illness, and risk for complications. If a more definitive determination of infection with influenza virus is required, testing with real-time reverse transcription-polymerase chain reaction (RT-PCR) or virus isolation should be performed.[27] In patients who require invasive mechanical ventilation (IMV), tracheal aspirates may offer higher diagnostic yield than nasopharyngeal flocked swab (Fig 2). Sequential sampling is important because it increases opportunities for positive diagnosis and facilitates understanding of viral load/clearance during illness course, in addition to monitoring development of antiviral resistance.

Antiviral Therapy

The pandemic virus is currently susceptible to the neuraminidase inhibitors, but resistant to the matrix protein-2 inhibitors. Most patients infected with the pandemic virus experience typical influenza symptoms and fully recover within a week, even without any form of medical treatment. Healthy patients with uncomplicated illness need not be treated with antivirals. For patients who initially present with severe illness or whose condition begins to deteriorate, treatment with oseltamivir should commence as soon as possible and antiviral treatment should be provided even if started later than 48 h. If oseltamivir is unavailable or cannot be used for any reason, zanamivir may be given. This recommendation applies to all patient groups, including pregnant women, and all age groups, including young children and infants.[15] The Food and Drug Administration in the United States has approved emergency use of intravenous peramivir for treatment of severe cases,[28] whereas zanamivir dry powder should not be administered by nebulization as the

Table 1—*Warning Signs Indicating More Severe Disease*[15]

Dyspnea, either during physical activity or while resting
Cyanosis
Bloody or colored sputum
Chest pain
Altered mental status
High fever that persists beyond 3 d
Hypotension
In children, danger signs include tachypnea or dyspnea, drowsiness, and little or no desire to play

lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.[29]

For patients with underlying medical conditions that increase the risk of more severe disease, the WHO recommends treatment with either oseltamivir or zanamivir as soon as possible after symptom onset, without waiting for the results of laboratory tests. About 30% to 40% of severe cases globally have occurred in previously healthy children and adults, usually under the age of 50 years. Some of these patients experience a sudden and very rapid deterioration in their clinical condition, usually on day 5 or 6 following the onset of symptoms. Clinical deterioration is characterized by primary viral pneumonia and failure of multiple organs, including the heart, kidneys, and liver. These patients require management in the ICU. In cases of severe or deteriorating illness, clinicians may consider using higher doses of oseltamivir and for a longer duration (eg, 150 mg bid for 10 days for adults) than is normally prescribed.[15,30]

Cases of oseltamivir-resistant viruses continue to be sporadic and infrequent, with no evidence that oseltamivir-resistant pandemic A(H1N1) viruses are circulating within communities or worldwide. All of these viruses show the same H275Y (N1 nomenclature) mutation that confers resistance to the antiviral oseltamivir, but not to the antiviral zanamivir. Thus zanamivir remains a treatment option in symptomatic patients with severe or deteriorating illness due to oseltamivir-resistant virus.[31]

Table 2—*Risk Factors for Developing More Severe Disease*[14,16-18]

Chronic respiratory diseases (eg, asthma, COPD, bronchiectasis, lung surgery)
Obesity
Pregnancy
Smoking
Diabetes mellitus
Chronic cardiovascular diseases
Renal diseases
Immunosuppression (such as blood disorders, malignancy)
Delay in presentation to hospital (and hence delay in initiating antiviral therapy)

Table 3—*Indications for Hospital Admission*[26]

Patients with influenza symptoms should be hospitalized if there is evidence of: hypoxemia ($Spo_2 < 95\%$), tachypnea (respiratory rate > 24 breaths/min), or pulmonary infiltrates on chest radiograph.
Patients should be referred for ICU assessment if: Fio_2 of > 0.5 or oxygen at a rate of > 10 L/min is required to maintain the Spo_2 at 92%.

Spo_2 = oxygen saturation.

The risk of resistance is considered higher in patients with severely compromised or suppressed immune systems who have prolonged illness, have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication. The risk of resistance is also considered higher in people who receive oseltamivir for postexposure prophylaxis following exposure to another person with influenza and who then develop illness despite taking oseltamivir. In general, it is not recommended to use antiviral drugs for prophylactic purposes. An alternative option is close monitoring for symptoms in people who have had exposure to an infected person and are at a higher risk of developing severe or complicated illness, followed by prompt early antiviral treatment should symptoms develop.[30,31]

Respiratory Support for Critically Ill Patients

About 1% to 10% of patients with clinical illness due to the novel infection have required hospitalization and the overall case fatality ratio has been estimated as < 0.5%.[19] Rapidly progressive respiratory failure is relatively common and about 10% to 30% of hospitalized patients have required ICU admission.[30] IMV, with a lung-protective ventilation strategy, is recommended as the initial approach for managing patients with pandemic A(H1N1) infection complicated by ARDS.[26,30] The recommendation is based on the ARDSNet trial demonstrating a relative risk reduction of mortality by 22% in patients with ARDS ventilated with the lower tidal volume (eg, goal of maximum tidal volume 6 mL/kg of predicted body weight with plateau pressures up to maximum 30 cm H_2O).[32] Furthermore, it is prudent to adopt a conservative fluid management approach for patients with ARDS/acute lung injury, as this has been shown to increase ventilator-free days and improve oxygenation when compared with a fluid liberal strategy.[33]

In ICUs where expertise and technology are available, extracorporeal membrane oxygenation (ECMO), high-frequency oscillation ventilation, prone positioning, and inhaled nitric oxide have been reported as useful rescue therapies for critically ill patients.[17,18,34]

The median duration for IMV was 8 days; 12% of the ventilated patients with severe respiratory failure in Australia and New Zealand received ECMO support, with a survival rate of 70% in this subgroup.[17,34] The overall ICU mortality rate for the critically ill cases was close to 17%.[17,18] Factors that were independently associated with death in the hospital included requirement of IMV at ICU admission, any coexisting condition, and older age.[17]

Noninvasive positive pressure ventilation (NPPV) was applied to a small number of critically ill patients with pandemic A(H1N1) infection complicated by respiratory failure, but most patients subsequently required IMV support.[26,35] NPPV is generally not recommended for patients with the novel influenza infection complicated by pneumonia and ARDS. NPPV temporarily improves oxygenation and reduces the work of breathing, but does not necessarily alter the course of the disease. The need for NPPV is an indication of severe disease and the likelihood of IMV.[26] In addition, hemodynamic instability and multiorgan failure are contraindications to application of NPPV. The WHO interim guidelines on prevention and control of acute respiratory diseases in health care have included NPPV among those aerosol-generating procedures in which there is possibly increased risk of respiratory pathogen transmission.[36] Low-dose heparin should be started prophylactically for critically ill patients who require ICU treatment in view of the reports of pulmonary embolism, especially among the critically ill obese patients with pandemic A(H1N1) infection.[23]

Systemic Corticosteroids

High-dose corticosteroids have not been shown to be beneficial in ARDS and septic shock unrelated to A(H1N1) virus infection in reducing mortality. However, stress-dose corticosteroids (hydrocortisone 200-300 mg/d) may be beneficial in improving hospital mortality and morbidity outcomes.[37,38] Although low-dose corticosteroids may be considered in the management of refractory septic shock, the precise role of systemic steroids in the setting of ARDS and refractory shock due to severe influenza pneumonitis requires further investigation as metaanalyses to date have mainly derived from data related to bacterial-induced

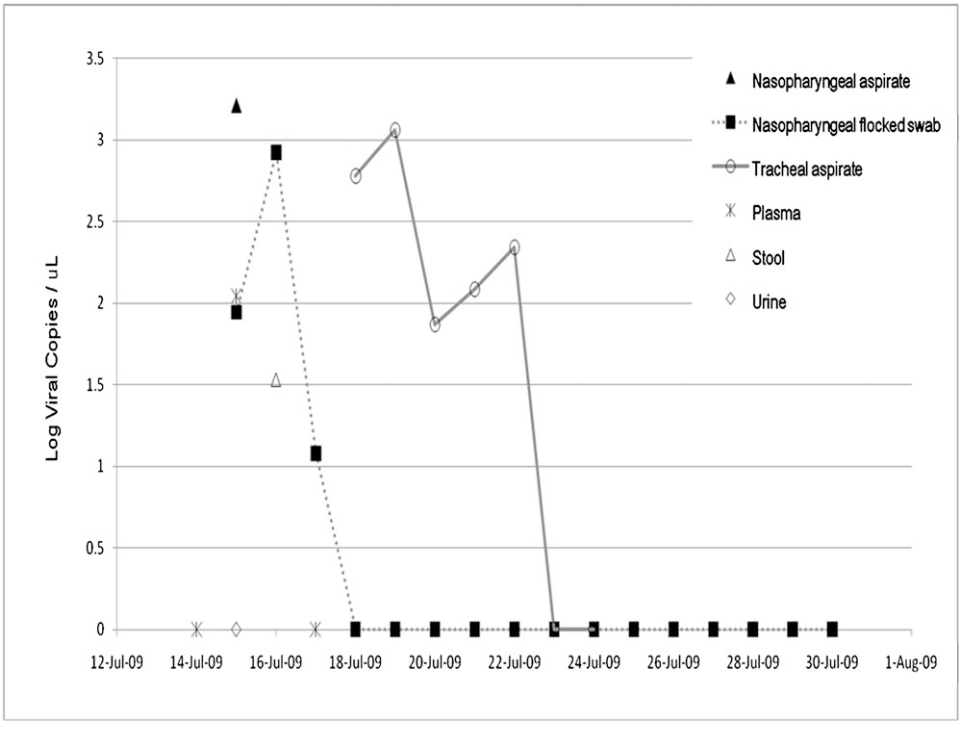

Figure 2. Virus-shedding profile of the same 23-year-old obese woman as shown in Figure 1 with pandemic A(H1N1) infection. Although the concentration of virus shed from the upper respiratory tract decreased after a few days of antiviral therapy, very high viral loads were detected from the lower respiratory tract specimens (tracheal aspirates) from July 18-22, 2009. Viral copy numbers were determined by real-time RT-PCR targeting the matrix protein gene. Specimens with undetectable viral copy number (lower detection limit = 62.6 viral copies/μL) were plotted at zero. Dotted line represents virus concentrations detected from upper respiratory tract specimens, and solid line represents virus concentrations detected from lower respiratory tract specimens. See Figure 1 legend for definition of abbreviation.

sepsis,[37,38] and data specific for pandemic A(H1N1) are limited.[39]

It is important to use systemic corticosteroids with caution in the treatment of respiratory viral diseases. Early use of corticosteroids might prolong viral replication in severe acute respiratory syndrome (SARS)[40] and H3N2 influenza.[41] In addition, prolonged use of systemic corticosteroids in SARS led to severe adverse effects, including fatal disseminated *Aspergillus* infection[42] and osteonecrosis.[43] During the SARS period in the ICU, the use of systemic steroids was associated with an increase in the rate of isolation of MRSA, *Stenotrophomonas* and *Candida* species. The ventilator-associated pneumonia rate was high, at 36.5 episodes per 1,000 ventilator-days, and 47% of episodes were caused by MRSA. The MRSA acquisition rate also increased from 3.53% during the pre-SARS period to 25.30% during the SARS period.[44] The use of systemic steroids for acute exacerbation of COPD due to pandemic A(H1N1) infection may potentially prolong viral shedding (Fig 3).

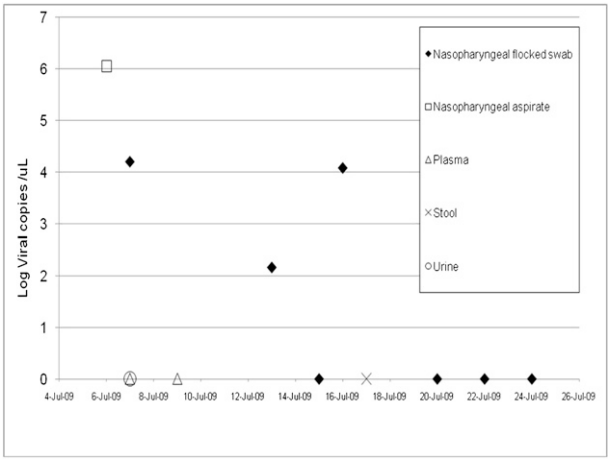

FIGURE 3. Virus-shedding profile of a 68-year-old man who was hospitalized with acute exacerbation of COPD on July 6, 2009, with a 2-day history of cough, fever, and increased dyspnea. His chest radiograph showed no consolidation. He was given prednisolone 30 mg daily for 10 days and amoxicillin-clavulanate 1 g bid for acute exacerbation of COPD. RT-PCR from his nasopharyngeal aspirate taken on July 6, 2009, was positive for the pandemic A(H1N1) virus. Oseltamivir 75 mg bid was started on July 7, 2009, for 5 days. He developed hypercapnic respiratory failure on July 8, 2009, and required noninvasive positive pressure ventilation (NPPV) support for 2 days in a negative pressure isolation room. His nasopharyngeal flocked swab was still positive by RT-PCR on July 16, 2009, although clinically he was well. The use of systemic steroid for COPD might have prolonged his viral shedding. He was discharged from hospital well on July 26, 2009. Viral copy numbers were determined by real-time RT-PCR targeting the matrix protein gene. Specimens with undetectable viral copy number (lower detection limit = 62.6 viral copies/μL) were plotted at zero. See Figure 1 legend for definition of abbreviation.

Passive Immunotherapy

A metaanalysis has suggested that early administration of convalescent blood products might have reduced the risk for death in patients with Spanish influenza pneumonia during the 1918 pandemic.[45] Convalescent plasma was used as rescue therapy with seemingly favorable response in a 31-year-old male patient in severe A(H5N1) infection complicated by multiorgan failure despite treatment with oseltamivir,[46] although it is difficult to judge the efficacy of convalescent plasma without any randomized controlled study. There is, however, experimental evidence in animal models that administration of anti-H5N1-specific antibodies in the form of neutralizing monoclonal antibodies or polyclonal sera (convalescent or postimmunization) is effective in treating influenza A(H5N1) disease.[47,48] Thus passive immunotherapy, including in the form of hyperimmune globulin made from convalescent plasma, is a potential option for treatment of pandemic A(H1N1) infection.

Other Immunomodulating Agents

Statins

High viral load and the resulting intense inflammatory response have been hypothesized as causing the organ damage and severe morbidity/mortality of A(H5N1) disease.[49] Cytokine dysregulation has also been invoked in the pathogenesis of sepsis and septic shock.[50,51] Statins have antiinflammatory and immunomodulatory effects (eg, by repressing induction of major histocompatibility complex-II by interferon-γ and subsequent T-lymphocyte activation).[52] Statins have been proposed to play a potential role for treatment and prophylaxis of pandemic influenza based on observational studies showing the survival benefits in patients receiving statins who developed bacteremia, sepsis, or pneumonia.[53]

In H5N1-, H3N2-, and H1N1-infected BALB/c mice, 50 μg statin/200 μg caffeine effectively ameliorated lung damage and inhibited viral replication and was at least as effective as oseltamivir and ribavirin. The statins/caffeine combination also appeared to be more effective when administered preventatively rather than as treatment. These findings provide justification for further research into this novel antiviral formulation.[54]

IV Ig

IV Ig may be considered as a treatment option for its immunomodulating effects in influenza with active systemic inflammation.[55] IV Ig was used for treatment of SARS, but there were thromboembolic events, such

as pulmonary embolism and ischemic stroke, despite use of prophylactic low-molecular-weight heparin.[56-58] Thus, it is important to monitor for the complications of IV Ig, especially vascular thrombotic events.

N-*acetyl-L-cysteine*

Production of reactive oxygen species (ROS) has been shown to contribute to pulmonary damage caused by influenza virus infection.[59] Different sources of ROS have been suggested in influenza A virus-infected lungs. Leukocytes may be activated and primed by influenza A virus infection and produce ROS.[60] Moreover, increased xanthine oxidase levels were found in influenza A virus-infected lungs.[60] Epithelial cells of the lungs may also be a source of ROS since influenza A virus infection induced oxidant stress response in cultured airway epithelial cells.[61] The antioxidant *N*-acetyl-L-cysteine (NAC) has been shown to inhibit replication of seasonal human influenza A viruses. NAC inhibits H5N1 replication and H5N1-induced production of proinflammatory molecules.[62] Therefore, antioxidants like NAC represent a potential additional treatment option that could be considered in the case of severe influenza infection. Other compounds with immunomodulating properties, such as macrolides, gemfibrozil, glitazone,[53] and nutritional supplements,[63] have been proposed as adjunct treatments, but these would require further investigation with controlled clinical trials.

Prevention and Infection Control Aspects

There are some infection control lessons from SARS that have important clinical implications for infection control against human influenza pandemic. A case-control study involving 124 medical wards in 26 hospitals in Guangzhou and Hong Kong has identified six independent risk factors of super-spreading nosocomial outbreaks of SARS: minimum distance between beds < 1 m, performance of resuscitation, staff working while experience symptoms, and SARS patients requiring oxygen therapy or NPPV, whereas availability of washing or changing facilities for staff was a protective factor.[64] Good hand and respiratory hygiene in 2003 led to significant reduction of common respiratory viral infections in the community in Hong Kong.[65]

Several measures are recommended by the WHO in the context of pandemic A(H1N1) and other epidemics. These include maintaining standard and droplet precautions among the health-care workers (HCWs) at all levels of health care, emphasizing respiratory etiquette and hand hygiene, cohorting, adequate room ventilation, and separating a minimum distance of ≥ 1 m between patients when providing routine care to patients infected with pandemic H1N1 influenza and those with influenza-like symptoms.[30,66] Recent data suggest that surgical masks are as effective as N95 masks for respiratory protection of HCWs in the routine care of hospitalized patients during seasonal influenza.[67,68] It is also important to limit the number of HCWs/family members/visitors exposed to the patient with pandemic A(H1N1), in addition to implementing triage, early recognition, and reporting of pandemic A(H1N1) infection. In addition, it is important to monitor health of HCWs exposed to patients with pandemic A(H1N1), whereas HCWs with symptoms should stay at home. Vulnerable groups at high risk for complications of pandemic A(H1N1) infection should carefully follow recommended infection-control measures. In addition, alternatives such as reassignment to other duties should be considered. Antiviral prophylaxis should follow local policy.[66]

When performing aerosol-generating procedures (eg, aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy), HCWs should be aware that these procedures have been associated with increased risk of infection transmission and should upgrade to airborne infection control precautions, including the use of N95 mask (Table 4).[66] It is important to note that substantial exposure to exhaled air occurs within 0.4-m and 1-m radius of patients receiving oxygen therapy via Hudson mask and during application of NPPV, respectively.[69-71] Geographically targeted nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, and restrictions on travel, are useful measures in controlling an influenza pandemic at its early phase.[72]

Pandemic vaccine is an important strategy for control of pandemic A(H1N1) disease but the efficacy of this modality is limited by shortage of supply due to limited production capacity. If vaccines were available soon enough, it has been estimated that vaccination of children, followed by adults, reaching 70% overall coverage, in addition to high-risk and essential workforce groups, could mitigate a severe epidemic.[73]

Table 4—*Airborne Precautions To Be Followed When Performing Aerosol-Generating Procedures*[66]

Wear a facial particulate respirator (eg, EU FFP2, US NIOSH-certified N95), eye protection (ie, goggles or a face shield); a clean, nonsterile, long-sleeved gown; and gloves (some of these procedures require sterile gloves)
Perform procedures in an adequately ventilated room (> 12 air changes per h)
Avoid permitting unnecessary individuals into the room
Perform hand hygiene before and after patient contact and after removal of personal protective equipment

EU FFP2 = European Union Filtering Face-Piece Class 2; NIOSH = National Institute for Occupational Safety and Health.

Table 5—*Priority Groups for Receiving the Pandemic A(H1N1) Vaccine as Recommended by the US Centers for Disease Control and Prevention*[74]

Pregnant women
Household contacts of infants younger than 6 mo
Health-care and emergency services personnel
Individuals between 6 mo and 24 y
Those aged 25 y or older with underlying conditions that put them at high risk of complications from influenza

The priority groups to receive the pandemic vaccine are listed in Table 5.[74] Because the pandemic virus is new, both nonclinical and clinical trials are being conducted to gain essential information on immune response and safety. Outcomes of trials completed to date suggest that pandemic vaccines are as safe as seasonal influenza vaccines. The WHO advises all countries administering pandemic vaccines to conduct intensive monitoring for safety and to report adverse events.[75]

In summary, antiviral agents and pandemic vaccines are important modalities in the control of a pandemic, but their efficacy is limited by timing of administration and supply. Oxygen therapy and NPPV should be applied in health-care facilities with good ventilation and respiratory protection for the HCWs, but most patients with severe respiratory failure will require IMV. A lung-protective ventilation strategy and a conservative fluid management approach are recommended for patients with ARDS. Rescue therapies, including ECMO, may be considered only after application of standard ICU management practices. Low-dose systemic steroids may be considered for patients with refractory septic shock. The role of passive immunotherapy and immunomodulating agents, such as IV Ig, statins, gemfibrozil, and NAC, requires further investigations. Nonpharmacologic measures, such as early case isolation, household quarantine, school/workplace closure, good community hygiene, and restrictions on travel, are useful measures in controlling an influenza pandemic during the early phase.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Hui DS, Chan PK. Viral pneumonia. In: Laurent GJ, Shapiro SD, eds. *Encyclopaedia of Respiratory Medicine*. Amsterdam, The Netherlands: Elsevier; 2006:456-466.
2. Smith GJ, Bahl J, Vijaykrishna D, et al. Dating the emergence of pandemic influenza viruses. *Proc Natl Acad Sci U S A*. 2009; 106(28):11709-11712.
3. Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. *N Engl J Med*. 2009;361(2):115-119.
4. Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005-2009. *N Engl J Med*. 2009;360(25):2616-2625.
5. Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science*. 2009;325(5937):197-201.
6. Maines TR, Jayaraman A, Belser JA, et al. Transmission and pathogenesis of swine-origin 2009 A(H1N1) influenza viruses in ferrets and mice. *Science*. 2009;325(5939):484-487.
7. Munster VJ, de Wit E, van den Brand JM, et al. Pathogenesis and transmission of swine-origin 2009 A(H1N1) influenza virus in ferrets. *Science*. 2009;325(5939):481-483.
8. Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature*. 2009; 460(7258):1021-1025.
9. Khan K, Arino J, Hu W, et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med*. 2009;361(2):212-214.
10. World Health Organization. What is phase 6? http://www.who.int/csr/disease/swineflu/frequently_asked_questions/levels_pandemic_alert/en/index.html. Accessed Sept 20, 2009.
11. World Health Organization. Pandemic (H1N1) 2009—update 77. http://www.who.int/csr/don/2009_12_04/en/index.html. Accessed Dec 8, 2009.
12. Dawood FS, Jain S, Finelli L, et al; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med*. 2009;360(25):2605-2615.
13. World Health Organization. Epidemiological summary of pandemic influenza A (H1N1) 2009 virus—Ontario, Canada, June 2009. *Wkly Epidemiol Rec*. 2009;84(47):485-491.
14. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al; INER Working Group on Influenza. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med*. 2009;361(7):680-689.
15. World Health Organization. Recommended use of antivirals. Pandemic (H1N1) 2009 briefing note 8. http://www.who.int/csr/disease/swineflu/notes/h1n1_use_antivirals_20090820/en/index.html. Accessed September 1, 2009.
16. Jain S, Kamimoto L, Bramley AM, et al; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20): 1935-1944.
17. Webb SA, Pettilä V, Seppelt I, et al; ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med*. 2009;361(20): 1925-1934.
18. Kumar A, Zarychanski R, Pinto R, et al; Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA*. 2009;302(17):1872-1879.
19. World Health Organization. Human infection with pandemic A (H1N1) 2009 influenza virus: clinical observations in hospitalized patients, Americas, July 2009 update. *Weekly Epidemiological Record on Pandemic H1N1 2009*. 2009;84(30):305-308.
20. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009;361(20):1945-1952.
21. Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. *BMJ*. 2009;339:b3928.
22. Mauad T, Hajjar LA, Callegari GD, et al. Lung pathology in

fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med*. 2010;181(1):72-79.
23. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(27):749-752.
24. Cheng VC, Lau YK, Lee KL, et al. Fatal co-infection with swine origin influenza virus A/H1N1 and community-acquired methicillin-resistant Staphylococcus aureus. *J Infect*. 2009; 59(5):366-370.
25. Centers for Disease Control and Prevention (CDC). Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A(H1N1)—United States, May-August 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(38): 1071-1074.
26. Kaufman MA, Duke GJ, McGain F, et al. Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza). *Med J Aust*. 2009;191(3):154-156.
27. Centers for Disease Control and Prevention (CDC). Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) virus—United States, 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(30):826-829.
28. Birnkrant D, Cox E. The emergency use authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med*. 2009;361(23):2204-2207.
29. GlaxoSmithKline (GSK) and FDA alert. Relenza (zanamivir) inhalation powder. http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm186081.htm. Accessed October 10, 2009.
30. World Health Organization. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf. Accessed November 15, 2009.
31. World Health Organization. Antiviral use and the risk of drug resistance. Pandemic (H1N1) 2009 briefing note 12. http://www.who.int/csr/disease/swineflu/notes/h1n1_antiviral_use_20090925/en/index.html. Accessed October 2, 2009.
32. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
33. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
34. Davies A, Jones D, Bailey M, et al; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302(17):1888-1895.
35. Rello J, Rodríguez A, Ibañez P, et al; H1N1 SEMICYUC Working Group. Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1) in Spain. *Crit Care*. 2009;13(5):R148.
36. World Health Organization. Infection and control of epidemic- and pandemic-prone acute respiratory diseases in health care. WHO interim guidelines. World Health Organization, 2007. http://www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/. Accessed Mar 19, 2009.
37. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301(22):2362-2375.
38. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2009;37(5):1594-1603.
39. Quispe-Laime AM, Bracco JD, Barberio PA, et al. H1N1 influenza A virus-associated acute lung injury: response to combination oseltamivir and prolonged corticosteroid treatment. *Intensive Care Med*. 2010;36(1):33-41.
40. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31(4): 304-309.
41. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. 2009;200(4):492-500.
42. Wang H, Ding Y, Li X, Yang L, Zhang W, Kang W. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med*. 2003;349(5):507-508.
43. Griffith JF, Antonio GE, Kumta SM, et al. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. *Radiology*. 2005;235(1): 168-175.
44. Yap FH, Gomersall CD, Fung KS, et al. Increase in methicillin-resistant Staphylococcus aureus acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome. *Clin Infect Dis*. 2004;39(4):511-516.
45. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med*. 2006; 145(8):599-609.
46. Zhou B, Zhong NS, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med*. 2007;357(14):1450-1451.
47. Lu J, Guo Z, Pan X, et al. Passive immunotherapy for influenza A H5N1 virus infection with equine hyperimmune globulin F(ab′)2 in mice. *Respir Res*. 2006;7:43.
48. Hanson BJ, Boon AC, Lim AP, Webb A, Ooi EE, Webby RJ. Passive immunoprophylaxis and therapy with humanized monoclonal antibody specific for influenza A H5 hemagglutinin in mice. *Respir Res*. 2006;7:126.
49. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med*. 2006;12(10):1203-1207.
50. Dinarello CA. Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. *Chest*. 1997;112(6 suppl):321S-329S.
51. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest*. 1997;112(1): 235-243.
52. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med*. 2000;6(12): 1399-1402.
53. Fedson DS. Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work. *Influenza Other Respi Viruses*. 2009;3(4):129-142.
54. Liu Z, Guo Z, Wang G, et al. Evaluation of the efficacy and safety of a statin/caffeine combination against H5N1, H3N2 and H1N1 virus infection in BALB/c mice. *Eur J Pharm Sci*. 2009;38(3):215-223.
55. Clinical management of human infection with avian influenza A (H5N1) virus. WHO updated advice 15 Aug 2007. http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html. Accessed Dec 18, 2007.
56. Lew TW, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA*. 2003;290(3):374-380.
57. Chong PY, Chui P, Ling AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med*. 2004;128(2):195-204.

58. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol*. 2004;251(10):1227-1231.
59. Han SN, Meydani SN. Antioxidants, cytokines, and influenza infection in aged mice and elderly humans. *J Infect Dis*. 2000;182(Suppl 1):S74-S80.
60. Akaike T, Ando M, Oda T, et al. Dependence on O2-generation by xanthine oxidase of pathogenesis of influenza virus infection in mice. *J Clin Invest*. 1990;85(3):739-745.
61. Knobil K, Choi AM, Weigand GW, Jacoby DB. Role of oxidants in influenza virus-induced gene expression. *Am J Physiol*. 1998;274(1 Pt 1):L134-L142.
62. Geiler J, Michaelis M, Naczk P, et al. *N*-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. *Biochem Pharmacol*. 2010;79(3):413-420.
63. Friel H, Lederman H. A nutritional supplement formula for influenza A (H5N1) infection in humans. *Med Hypotheses*. 2006;67(3):578-587.
64. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis*. 2007;44(8):1017-1025.
65. Lo JY, Tsang TH, Leung YH, Yeung EY, Wu T, Lim WW. Respiratory infections during SARS outbreak, Hong Kong, 2003. *Emerg Infect Dis*. 2005;11(11):1738-1741.
66. World Health Organization. Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses. Interim guidance. June 25, 2009 (originally published April 29, 2009). http://www.who.int/csr/resources/publications/swineflu/swineinfincont/en/index.html. Accessed Sept 28, 2009.
67. Loeb M, Dafoe N, Mahony J, et al. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. *JAMA*. 2009;302(17):1865-1871.
68. Johnson DF, Druce JD, Birch C, Grayson ML. A quantitative assessment of the efficacy of surgical and N95 masks to filter influenza virus in patients with acute influenza infection. *Clin Infect Dis*. 2009;49(2):275-277.
69. Hui DS, Chow BK, Ng SS, et al. Exhaled air dispersion distances during noninvasive ventilation via different Respironics face masks. *Chest*. 2009;136(4):998-1005.
70. Hui DS, Chow BK, Chu LC, et al. Exhaled air and aerosolized droplet dispersion during application of a jet nebulizer. *Chest*. 2009;135(3):648-654.
71. Hui DS, Hall SD, Chan MT, et al. Exhaled air dispersion during oxygen delivery via a simple oxygen mask. *Chest*. 2007;132(2):540-546.
72. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. *Nature*. 2006;442(7101):448-452.
73. Yang Y, Sugimoto JD, Halloran ME, et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science*. 2009;326(5953):729-733.
74. National Center for Immunization and Respiratory Diseases. CDC; Centers for Disease Control and Prevention (CDC). Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep*. 2009;58(RR-10):1-8.
75. World Health Organization. Experts advise WHO on pandemic vaccine policies and strategies. Pandemic (H1N1) 2009 briefing note 14. http://www.who.int/csr/disease/swineflu/notes/briefing_20091030/en/index.html. Accessed November 26, 2009.