

REVIEW ARTICLE

Pandemic 2009 H1N1 Influenza A: Clinical Review

Nawal Salahuddin*

Introduction:

Pandemic infection is described as ‘sustained, worldwide, community transmission’ of an infective organism. We are currently in the midst of a pandemic caused by a new strain of the Influenza A virus; the 2009 H1N1 subtype.

The first reports came in April 2009, when the Centres for Disease Control and Prevention (CDC) reported isolation of a new strain [1] that was causing severe respiratory illness across Mexico and California. [2, 3] Cases continued to be reported across the summer; at a time when Influenza usually does not occur. By June 2009, 74 countries across the world had reported cases of 2009 H1N1 Influenza and the World Health Organization (WHO) officially declared it as pandemic. [4] As of January 2010, the WHO has had reports of confirmed cases of pandemic influenza H1N1 2009, with at least 15174 deaths, from over 209 countries and overseas territories. [5] Individual cases are now no longer being counted and so it is likely that the actual incidence is much higher.

This review is an update of current knowledge about the 2009 Influenza pandemic, with special reference to issues pertaining to the pulmonary physician. To identify relevant literature, a Medline search for the terms; *H1N1, Influenza, epidemiology, treatment, and vaccination* were conducted.

Virology:

There are three types of Influenza viruses; A, B and C. They are further subtyped by their cell surface glycoproteins; Hemagglutinin (**H**) and Neuraminidase (**N**). Influenza viruses develop genetic diversity by antigenic *shifts* and *drifts*. Antigenic drifts are caused by small and frequent changes on the H and N glycoproteins, whilst shifts occur due to the introduction of a new subtype to which there is no previous exposure in the population. Antigenic shifts lead to seasonal influenza and require minor variations in the vaccine. Drifts are responsible for epidemics and pandemics. So far over 16 H (1-16) and 9 N (1-9) antigenic strains have been isolated. The circulating subtypes change every year; the 2009 *seasonal* Influenza subtype was a H3N2, which is distinct from the *pandemic* influenza H1N1. The current H1N1 Influenza virus is a new virus that contains gene segments from three separate sources; avian, swine and human. [6,7]

*Associate Professor, Aga Khan University, Karachi

The first described Influenza pandemic occurred in 1918; known as the 'Spanish Flu' it killed between 50 million to 100 million people globally. In 1957, the emergence of the H2N2 subtype caused the 'Asian flu' pandemic which caused 2 million deaths worldwide. The 'Hong Kong Flu' of 1968 was a H3N2 virus that resulted in 1 million deaths across the globe.

Pathogenesis:

Respiratory infection starts with the inhalation of infected droplets. Once the Influenza virus is inhaled into the respiratory tract, it binds to receptors on columnar epithelial cells. The seasonal Influenza virus, H5N1 typically binds to receptor types a2-6 which are located in the nose and throat, however the 2009 H1N1 however can also infect cells with receptor types a2-3, which are located deep in the lungs.

Once cell membrane binding has occurred, the virus is able to move intracellularly where it replicates and budding virions are released to infect adjacent cells. Virus-induced apoptosis leads to epithelial cell death. [8, 9, 10] High levels of viral replication and resultant cytokine dysregulation [11, 12, and 13] lead to progressive parenchymal injury in the lower respiratory tract [14] with the development of respiratory failure and ARDS. Autopsy findings have shown three distinct pulmonary histological patterns: diffuse alveolar damage (DAD), necrotizing bronchiolitis, and intense alveolar haemorrhage. Pulmonary emboli have been also identified with secondary bacterial or fungal pneumonia in 7 out of 50 (14%) fatal cases in California. [15]

Epidemiology:

Like seasonal Influenza, 2009 H1N1 Influenza is spread by large particle droplets, which remain suspended in air for short periods of time and require close contact (< 6 ft) between the source and recipient. [16] Transmission by contact with contaminated fomites and surfaces is also considered possible. The incubation period is between 1 and 7 days, again similar to seasonal influenza.[17,18] In infected individuals, viral shedding begins 1 day prior to symptom onset and continues until symptoms resolve. Recent data demonstrate viral shedding occurs in 80% patients' for 5 days, 40% for 7 days and 10% may still shed the virus up to 10 days post-symptom development. [19] The duration of viral shedding can continue for up to 10 days in children and adolescents and may continue for weeks in the immune suppressed individuals. [20-22]

About 1-10% 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%. [23] In contrast to seasonal Influenza, most cases of severe disease and mortality have occurred in younger adults and children; 40% of those hospitalized or who died were previously healthy individuals. In these, the age group 5 – 59 years accounted for 87% of the deaths (usually account for 17%) and 71% of the cases of severe pneumonia (usually account for 32%). [24-28]

It is possible that the elderly have continued to be less severely infected with the 2009 H1N1 virus due to the development of partial immunity from exposure to the 1957 pandemic virus (which was an H1N1 strain).

Clinical Presentation:

An Influenza-like illness (ILI) is defined as fever (temperature > 37.8° C or 100° F) and either cough or a sore throat in the absence of any other known cause. [29] Analyses of outbreaks have confirmed that the clinical manifestations due to infection with the 2009 H1N1 are similar to those caused by seasonal Influenza virus. [30, 31]

Most cases developed mild upper respiratory tract symptoms; sore throat (82%), cough (98%), rhinorrhea (82%), accompanied by fever (96%), headache (82%), myalgias and chills (80%). Fewer patients reported nausea (55%), diarrhoea (48%), stomach aches (36%) or joint pains (46%). [32] In patients presenting with mild illness, hospitalization rate and case fatality ratio have been low at 3.6% and 0.2%. [33] Patients who require hospitalization are more likely to have chronic medical conditions, especially asthma, COPD, diabetes, immune suppression, cardiac disease, obesity or pregnancy. [32] These individuals typically present with fever, cough, dyspnoea, gastrointestinal symptoms and abnormal chest radiographs. Most are typically discharged.

Patients who develop severe disease present with rapidly progressive respiratory failure / ARDS characterized by patchy alveolar opacities on chest radiograph, severe hypoxemia [33], elevated serum LDH, CPK, lymphopenia and multi organ dysfunction. [35] In a review of 168 critically ill patients admitted to a Canadian ICU, the mean age of patients was 32 years. Median time of onset of illness and hospitalization was 4 days. [36] Overall mortality rate was 17%. All these patients were severely hypoxic at presentation and mortality correlated with severity of organ dysfunction. In critically ill patients admitted to ICUs in Mexico and Spain, a greater risk of acute respiratory failure / ARDS was reported amongst the morbidly obese (BMI > 30 kg/m²). [37,38] In the ANZAC area, the number of intensive care unit (ICU) admissions due to pandemic (H1N1) 2009 infection was 15 times the number usually due to viral pneumonitis. [39] Mortality has mostly occurred due to progressive respiratory failure / ARDS or secondary bacterial infection. In a study of 77 American patients with fatal cases of confirmed pandemic (H1N1) 2009 infection, [40] concurrent bacterial infection was found in 22(29%) patients, including 10 caused by *Streptococcus pneumoniae*, 6 with *Streptococcus pyogenes*, 7 with *Staphylococcus aureus*, 2 with *Streptococcus mitis*, 1 with *Haemophilus influenzae* whereas 4 cases involved multiple pathogens. The median age of these 22 patients was 31 years and median duration of illness was 6 days. A fatal case with co-infection with community-acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) occurred in a Filipino sailor who died in Hong Kong. [41] Classically bacterial infection has developed at 4 -14 days after Influenza. [42]

These findings confirm that bacterial lung infections occur amongst patients with fatal cases of pandemic (H1N1) 2009 infection and underscore both the need for early

recognition/treatment of bacterial pneumonia in patients with influenza and the importance of pneumococcal vaccination for persons at increased risk.

Complications with novel H1N1 are similar to seasonal Influenza; these include exacerbations of underlying respiratory illness; upper (sinusitis, otitis media) and lower respiratory (bronchiolitis, asthma exacerbation, pneumonia), neurologic (encephalitis, seizures), cardiac (pericarditis, myocarditis), musculoskeletal (rhabdomyositis) and secondary bacterial infections with sepsis. [42]

Diagnosis:

Testing methods include 1/ Rapid Influenza Diagnostic Tests (RIDT) which detect influenza viral nucleoprotein antigen and can provide results in 30 minutes. The testing does not discriminate between viral subtypes (H1 v/s H3) and therefore is only useful for screening with an inherent sensitivity between 10 – 70%. 2/ Real time reverse transcriptase polymerase chain reaction (RT-PCR) which is a confirmatory test and discriminates between seasonal H1N1 or H3N1 and novel 2009 H1N1 Influenza A virus with a sensitivity of 87%.

Nasopharyngeal, oropharyngeal swabs or nasal aspirates, endotracheal aspirates, bronchial washings or bronchoalveolar lavage can be sent for testing. Swabs should be made from inert materials; with plastic or aluminium shafts and synthetic tips). Samples must be transported in viral culture medium, cooled and stored at 4° C for no longer than 4 days.[43]

Treatment:

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 an uncomplicated febrile illness, who are at low risk of severe disease are unlikely to derive any substantial benefit from drug therapy ; duration of illness is estimated to be reduced by 1 day, so are not recommended to receive antivirals.

For patients with an influenza-like illness requiring hospitalization, those with risk factors for progression (see Table 1) or patients who initially present with severe illness or whose condition begins to deteriorate, treatment with the neuraminidase inhibitors; Oseltamivir or Zanamivir, is recommended. Treatment should ideally be started within 48 hours of symptom onset, but has been reported effective even when delayed. The recommended dosage and duration of therapy are given in Table 3. This recommendation applies to all patient groups, including pregnant women, and all age groups, including young children and infants. [44]

For patients with underlying medical conditions that increase the risk of more severe disease, WHO recommends treatment as soon as possible after symptom onset, without waiting for the results of laboratory tests. About 30-40% 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 ICU. In cases of severe or deteriorating illness,

clinicians may consider using higher doses of Oseltamivir and for a longer duration (e.g. 150mg bid for 10 days for adults) than is normally prescribed. [45, 46]

Cases of Oseltamivir-resistant viruses continue to be sporadic and infrequent, with no evidence that Oseltamivir-resistant pandemic 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.

Post exposure chemoprophylaxis can be considered for health care workers and high risk groups who have been in close contact within the past 48 hours with a case of confirmed or suspected H1N1 Influenza. Duration of prophylaxis is usually for 10 days. Individuals must be counselled that they can still develop Influenza despite receiving prophylactic therapy and should seek medical care if influenza-like symptoms develop. Reliable individuals can be given the option of foregoing prophylaxis and recommended to report if symptoms develop.

Pregnant women are at a high risk of developing severe illness or complications with influenza. Prophylactic therapy is strongly recommended for any pregnant woman in close contact with a case of suspected or confirmed novel H1N1. Both drugs are Category C (controlled human data is not available) but are still advised in pregnancy. The recommended duration of prophylaxis is 10 days of either oral Oseltamivir or inhaled Zanamivir, with a preference for Zanamivir due to its limited systemic absorption. [46]

Rapidly progressive respiratory failure is relatively common and about 10-30% of hospitalized patients have required ICU admission. The overall ICU mortality rate for the critically ill cases was close to 17% [47, 48] whereas factors that were independently associated with death in the hospital included requirement of Invasive mechanical ventilation at ICU admission, any coexisting condition, and older age. [47]

Invasive mechanical ventilation (IMV), with a lung-protective ventilation strategy, is recommended as the initial approach for managing patients with pandemic H1N1 infection complicated by acute respiratory distress syndrome (ARDS). [49,50] The recommendation is based on the ARDS Net trial demonstrating a relative risk reduction of mortality by 22% in patients with ARDS ventilated with the lower tidal volume (e.g. goal of maximum total volume 6 ml/kg of predicted body weight with plateau pressures up to maximum 30 cmH₂O).[51] Furthermore, it is prudent to adopt a conservative fluid management approach for patients with ARDS /acute lung injury(ALI), as this has been shown to increase ventilator-free days and improve oxygenation when compared with a fluid liberal strategy.[52]

Non-invasive positive pressure ventilation (NPPV) was applied to a small number of critically ill patients with pandemic H1N1 infection complicated by respiratory failure but most patients subsequently required IMV support. NPPV is generally not recommended for patients with the novel influenza infection complicated by pneumonia and ARDS. [47, 48] 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. In addition; hemodynamic instability and multi-organ failure are contra-indications to application of NPPV. The WHO interim guidelines on prevention and control of acute respiratory diseases in healthcare have included NPPV among those aerosol-generating procedures in which there is possibly increased risk of respiratory pathogen transmission. 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 (H1N1) 2009 infection.

Vaccination/ Prevention:

Since 2009 H1N1 is a new viral subtype, there is no protection conferred by previous influenza vaccines. A new vaccine has been developed and is available in some areas. Due to limited vaccine stocks, the Centres for Disease Control and Prevention Advisory Committee on Immunization Practices have identified highest-priority groups to receive the vaccine based on their risks for severe disease and mortality. These include pregnant women, caregivers for children < 6 months, health care workers in direct contact with cases, children 6 months – 4 years and aged 5 – 18 years at high risk for influenza- related complications. A single dose is considered adequate for adults and children > 9 years.

Emphasis on preventive practices to limit the spread of infection is likely to have the highest impact. In health care surroundings, standard isolation procedures including nonsterile gloves for any patient contact and gowns and eye shields are recommended for any activity requiring contact with respiratory secretions or infectious materials. Regular surgical face masks are considered adequate protection for most patient contact, although fitted N 95 masks are recommended for aerosol-generating procedures (see Table 5). Aerosol-generating procedures should be carried out in a negative pressure room with as few as possible personnel present. Finally, all health care workers are recommended to receive both the seasonal and pandemic influenza vaccines.

Conclusion:

2009 H1N1 is a new virus that has caused a pandemic. It has tended to be as virulent as the seasonal Influenza subtypes but with higher attack rates in younger age groups. Drug therapy with neuraminidase inhibitors is effective in reducing the duration and severity of illness. Vaccines have been developed, but limited availability has led to prioritization for certain high risk groups.

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Tables

Table 1: Risk factors for developing severe disease [44, 45]

Risk Factors For Developing Severe Disease
Chronic respiratory disease(e.g.; Asthma, COPD, Bronchiectasis)
Obesity
Pregnancy
Smoking
Diabetes mellitus
Chronic Cardiovascular disease
Chronic Renal disease
Malignancy
Delay in initiating antiviral therapy

Table 2: Warning signs for clinicians which may signal progression to severe disease (reference 46)

Warning Signs Indicating More Severe Disease
Dyspnea
Cyanosis
Coloured sputum
Haemoptysis
Chest pain
Altered mental status
Fever that persists beyond 3 days
Hypotension

Table 3: Antiviral recommendations for 2009 H1N1 Influenza (reference 46)

	Treatment	Chemoprophylaxis
Oseltamivir		
Adults	75-mg capsule twice daily for 5 d	75mg once daily
Children >12 mo, weight (kg)		
<15	60 mg/d, divided into 2 doses	30 mg once daily
15-23	90 mg/d, divided into 2 doses	45 mg once daily
24-40	120 mg/d, divided into 2 doses	60 mg once daily
>40	150 mg/d, divided into 2 doses	75 mg once daily
Zanamivir		
Adults	Two 5-mg inhalations (10 mg total) twice daily	Two 5-mg inhalations (10 mg total) once daily
Children	Two 5-mg inhalations (10 mg total) twice daily	Two 5-mg inhalations (10 mg total) once daily

Table 4: Aerosol-generating procedures (from the Centres for Disease Control and Prevention)

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