A clinician's guide to 2009 H1N1 influenza

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Emergence of 2009 H1N1 influenza

Beginning in late March 2009, outbreaks of respiratory illness were noted in several areas of Mexico, with reports of high mortality rates amongst previously well, young adults.[1] Concurrently, the Centers for Disease Control and Prevention (CDC) in the US identified a novel influenza A virus of swine origin in samples taken from two children presenting with influenza-like illness in southern California.[2,3] On April 23, this same novel influenza virus, termed 2009 H1N1, was identified amongst the clusters of patients suffering from severe respiratory illness in Mexico.[1] By the end of April, 97 confirmed cases had been reported in Mexico; 1 week later, almost 2000 cases had been identified in 21 countries in five continents.[1,4] On June 11, with rapidly escalating case numbers and evidence of sustained transmission in several regions, the World Health Organization raised the pandemic alert level to 6, declaring the emergence of the first global influenza pandemic for more than 40 years.[5]

Influenza A viruses

Influenza A viruses cause regular seasonal epidemics throughout much of the world and were responsible for several pandemics during the twentieth century.[6] Each pandemic occurred following the emergence of a novel virus against which there was little or no pre-existing immunity in the human population.[7] Novel influenza A viral strains are formed through reassortment events, in which sections of genetic material are exchanged between distinct viruses co-infecting a single organism.[8] The ability of influenza viruses to circulate amongst avian, swine, and human populations provides a huge reservoir of infection in which such reassortment events can occur.[7–8] The main antigenic determinant of influenza A is the haemagglutinin (H) protein, present in the outer shell of the virus, of which there are 16 subtypes. Reassortment of haemagglutinin subtypes is responsible for the so-called 'antigenic shifts' underlying influenza pandemics.[8]

2009 H1N1 influenza A is a triple reassorted virus containing a previously unseen combination of gene segments from North American and Eurasian swine influenza lineages.[2] The haemagglutinin subtype 1 (i.e. H1) protein is sufficiently distinct from that present in human seasonal H1 viruses to result in negligible serological cross-reactivity between 2009 H1N1 and seasonal H1N1.[7, 9]

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There have been previous reports of isolated human infection with triple reassorted swine origin influenza A viruses, but in contrast to 2009 H1N1, efficient human-to-human transmission has not occurred.[10,11] This reflects the ability of 2009 H1N1, in similar fashion to seasonal influenza H1N1 and previous pandemic influenza viruses, to replicate efficiently within the epithelium of the upper respiratory tract and produce infectious respiratory droplets. In animal models of infection, 2009 H1N1 also shows features of a highly pathogenic influenza virus in that it is also able to induce pathological changes within lower respiratory tract structures, which may explain the pneumonic presentations of some individuals with 2009 H1N1 infection.[8,12–14]

Early case reports

Case descriptions of 2009 H1N1 in Mexican patients in the early weeks of the pandemic prompted fears of a highly virulent virus with significant mortality rates among infected individuals.[1] Gømez-Gømez *et al* described a hospitalised cohort of 50 adults with suspected influenza virus-related pneumonia during the initial 2009 H1N1 outbreak in which one-third of patients required mechanical ventilation. However, in this series only 11 individuals had 2009 H1N1 confirmed on reverse transcription-polymerase chain reaction (RT-PCR) of respiratory tract secretions.[15] Another study from Mexico described a cohort of 18 patients hospitalised with pneumonia and confirmed 2009 H1N1, in which more than half developed acute respiratory distress syndrome requiring mechanical ventilation and almost 40% died.[16]

Large case series

As the number of 2009 H1N1 infections rose throughout the world, further large case series in many countries were described.[17–21] In China, in the early weeks of the pandemic, all patients with confirmed 2009 H1N1 were quarantined in hospital. In the 426 patients identified in one series, the most common symptoms were fever (67.4%) and cough (69.5%), followed by sore throat (36.6%) and rhinorrhoea (23.7%). Pneumonic changes on chest radiography were seen in only 5% of patients. All 426 recovered and were discharged home.[17] Similarly, no severe disease was observed in a cohort of 126 individuals with confirmed 2009 H1N1 diagnosed during an outbreak at a New York high school, although, in addition to typical influenza symptoms, nausea (46%), vomiting (17%), and diarrhoea (26%) were frequently reported.[18]

In contrast to the early reports, it has therefore become apparent that symptomatic infection with 2009 H1N1, whilst highly transmissible, results in a mild self-limiting

illness in the majority of individuals. Moreover, serological surveys suggest that a significant proportion of infections are asymptomatic.[22–24] Cohort studies of hospitalised patients with 2009 H1N1 have helped to define the features of severe infection and to identify those individuals at risk.[25–34] Reported hospitalisation rates for 2009 H1N1 infection range from 1 to 10%.[2,18,35-38] On presentation, many patients are dyspnoeic, as well as displaying typical features of fever and cough.[16,31,34] Atypical presentations such as acute exacerbations of chronic obstructive pulmonary disease (COPD) and encephalitis, chest pain, and refractory shock in children have also been observed. Notably, up to 30% of patients are afebrile at presentation.[2,9,17,25,26,29,34,39] Pneumonic changes, typically bilateral pulmonary infiltrates, are commonly seen on chest radiography.[15,31,34,40,41] In the majority of individuals these probably represent primary viral pneumonia since the incidence of confirmed concurrent bacterial infection is low.[15,31,34,36,42] Even with intense investigation in ultimately fatal cases, concurrent bacterial infection has only been detected in 30%. Approximately 40–70% of hospitalised individuals have underlying medical conditions, with asthma, COPD, chronic cardiovascular disease and immunocompromise being common.[25–28,30,31,33,34,43] Obesity and pregnancy are also recognised as independent risk factors for severe disease.[27,31,32,34,44–46] Fifteen to thirty per cent (15–30%) of patients require mechanical ventilation and overall in-hospital mortality rate is approximately 10%.[2,15,16,25,30–32,34,36,43,46]

Risk groups and mortality rates

Epidemiological studies have highlighted important differences in the pattern of infection and disease caused by 2009 H1N1 compared with seasonal influenza. Both hospitalisation rates and mortality rates for seasonal H1N1 are highest in infants and adults over 65 years.[31,37,47–50] In contrast, infections with 2009 H1N1 are less common in adults over 65 years; presumably due to some pre-existing cross-reactivity immunity induced by past exposure to previous influenza viruses.[23,24,51,52] Accordingly, hospitalisation rates are relatively lower in this group and are variably reported as highest in infants, children, or young adults. Mortality rates for 2009 H1N1 however, remain highest in older adults (>65 years) at approximately 1000 per 100 000 cases, with overall mortality rates estimated at 11–66 per 100 000 cases.[43,53]

Diagnostic methods and diagnostic mistakes

Reverse transcription-polymerase chain reaction (RT-PCR) testing to detect virus in respiratory tract secretions is the recommended means to confirm or exclude 2009 H1N1 infection.[54–55] Whilst attractive in terms of reduced cost and need for laboratory facilities, rapid influenza antigen diagnostic tests have poor sensitivity in detecting 2009 H1N1 infection.[56–60] Some clinicians advocate the routine testing of all patients with co-morbidities putting them at increased risk of complicated infection who present acutely to health services.[9,28,31] However, vigilance must be maintained and alternative diagnoses always considered – delays in the diagnosis of conditions such as meningococcal meningitis, primary HIV infection, and *Plasmodium falciparum* malaria following an initial presumptive diagnosis of 2009 H1N1 have been reported.[61,62]

Antiviral drug treatment

Neuraminidase inhibitors and M2 inhibitors (adamantanes) have been developed to treat influenza A infection. 2009 H1N1 influenza is susceptible to neuraminidase inhibitors but intrinsically resistant to M2 inhibitors.[36] Three neuraminidase inhibitors are now available: oseltamivir, an orally administered medication, is the most commonly used; zanamivir, an inhaled drug with limited systemic absorption; and recently, the parenterally administered, peramivir, has been granted Emergency Use Authorisation for the treatment of severely unwell, hospitalised patients.[63]

In controlled trials, early treatment of patients with uncomplicated seasonal influenza with oseltamivir resulted in reduced severity and duration of symptoms compared to placebo.[64] Observational studies of hospitalised patients with seasonal influenza show decreased mortality amongst patients treated with oseltamivir.[64–66] No controlled trials of neuraminidase inhibitors in the treatment of 2009 H1N1 have been completed, but data from recently reported observational studies support their use. Amongst patients hospitalised with 2009 H1N1 infection, initiation of neuraminidase inhibitors within 48 hours of onset of symptoms is independently associated with a reduction in the risk of death or admission to intensive care.[34,67,68] The CDC recommends immediate, empirical treatment with oseltamivir or zanamivir for patients with suspected 2009 H1N1 infection who have severe, complicated, or progressive illness or who are hospitalised, or for those at increased risk of developing severe disease. Treatment may be considered for patients with mild, uncomplicated illness and without risk factors for severe disease if they present within 48 hours of symptom onset.[69] Twice daily, oral oseltamivir for five days is the most commonly used regimen, although some clinicians advocate a 10-day course at higher dosing for critically ill patients.[69] Parenteral zanamivir or peramivir in critically ill patients may also be beneficial.[70,71]

Sporadic cases of resistance to oseltamivir due to the H275Y mutation in the viral neuraminidase gene have been reported.[53,72,73] Resistant isolates have been more commonly found in immunocompromised patients, perhaps resulting from previous use of low-dose post exposure prophylaxis and therefore some clinicians recommend the use of zanamivir as first line agent in treating 2009 H1N1 in this patient group.[36,71,74]

Prevention of transmission

The prevention of onward transmission of 2009 H1N1 is a vital consideration in managing hospitalised patients. Person-to person-transmission occurs via respiratory

droplet spread and direct cutaneous contact with an infectious patient or fomite with subsequent self-inoculation.[69] It is recommended that patients are admitted to a single-bedded isolation room, visitor access limited as much as possible, and the practices of cough etiquette and regular hand hygiene emphasised. Healthcare staff should use appropriate personal protective equipment when caring for patients, including disposable gloves and aprons, respiratory and eye protection. Particular care should be exercised when the patient is undergoing aerosol-producing procedures such as airway suction, sputum induction, and bronchoscopy.[75] Current guidelines recommend that the use of antiviral chemoprophylaxis is restricted to those contacts of confirmed patients who are at increased risk of developing severe complicatations of influenza.[69] Vaccination is the most effective way to control the spread of influenza and limit associated illness and death. Several safe and immunogenic 2009 H1N1 vaccines have been produced and mass vaccination programmes are underway in some countries, although the challenge of providing adequate vaccine supply to resource-poor countries is concerning.[76–79]

Global impact and future waves

Following the declaration of the flu pandemic, waves of 2009 H1N1 transmission spread across the globe, peaking first in the temperate southern hemisphere, followed by the tropics and the temperate northern hemisphere. At the time of writing, more than 211 countries have reported confirmed cases of 2009 H1N1 including more than 15,000 deaths.[80] Whilst compared with seasonal influenza a relatively greater proportion of fatal cases have occurred amongst young adults, the high rates of morbidity and mortality reported in the early descriptions of 2009 H1N1 have thankfully not been widely observed. However, 2009 H1N1 virus continues to be the predominant influenza virus circulating worldwide and intense global surveillance attention now is turning to predict its potential impact in future transmission waves.[81] However it is in the tropics, where, with perennial influenza transmission the potential for reassortment events and the emergence of a more virulent virus is arguably greatest, that surveillance systems are weak or absent.[82] The low number of 2009 H1N1 infections reported from many African countries in the last year reflects the limitations in diagnostic capability rather than the absence of disease.[83] Moreover, the impact of co-infection with HIV on 2009 H1N1 is largely unknown, but disease severity is likely to be worsened and transmission could possibly be enhanced. It is in these areas therefore that intense vigilance is required amongst healthcare staff to observe any new features of this emerging pathogen.

Readers with concerns about 2009 H1N1 outbreak in Africa are advised to consult the following sources of information:

- Pandemic (H1N1) 2009 section of the World Health Organization website (http://www.who.int/csr/disease/swineflu/en/).
- H1N1 Information for Health Care Providers section of the Centers for Disease Control and Prevention website (http://www.cdc.gov/h1n1flu/clinicians/).

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