

A clinician's guide to 2009 H1N1 influenza

S Aston

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}

Stephen Aston, Liverpool School of Tropical Medicine, Liverpool, UK. Correspondence to: Respiratory Infection Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK.
Email: S.J.Aston@liverpool.ac.uk

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 Gómez-Gómez *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 complications 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/>).

References

1. Outbreak of swine-origin influenza A (H1N1) virus infection – Mexico, March–April 2009. *Morb Mortal Wkly Rep* 2009; 58: 467–70.
2. Dawood, FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 360: 2605–15.
3. Swine influenza A (H1N1) infection in two children – Southern California, March–April 2009. *Morb Mortal Wkly Rep* 2009; 58: 400–2.
4. Update: novel influenza A (H1N1) virus infections – worldwide, May 6, 2009. *Morb Mortal Wkly Rep* 2009; 58: 453–8.
5. Timeline: Swine flu. *Nature* 2009. <http://www.nature.com/news/2009/090429/full/news.2009.416.html>.
6. Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature* 2009; 460: 1021–5.
7. Ciacchi-Zanella JR, Vincent AL, Prickett JR, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 2009; 325: 197–201.
8. Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. *Nature* 2009; 459: 931–9.
9. Liu W, et al. Characteristics derived from outbreaks of pandemic influenza A (H1N1) 2009 virus. *Clin Infect Dis* 2010; 50: 622–3.
10. Shinde V, Bridges CB, Bannerman K, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med* 2009; 360: 2616–25.
11. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. *Clin Infect Dis* 2007; 44: 1084–8.
12. 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: 484–7.
13. 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: 481–3.
14. Yang Y, Sugimoto JD, Halloran ME, et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science* 2009; 326: 729–33.
15. Gómez-Gómez A, Magaña-Aquino M, García-Sepúlveda C, et al. Severe pneumonia associated with pandemic (H1N1) 2009 outbreak, San Luis Potosi, Mexico. *Emerg Infect Dis* 2010; 16: 27–34.
16. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 361: 680–9.
17. Cao, B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009; 361: 2507–17.
18. Lessler J, Reich NG, Cummings DA, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. *N Engl J Med* 2009; 361: 2628–36.
19. BinSaeed AA. Characteristics of pandemic influenza A (H1N1) infection in patients presenting to a university hospital in Riyadh, Saudi Arabia. *Ann Saudi Med* 2010; 30: 59–62.
20. AlMazroa MA, Memish ZA, AlWadey AM. Pandemic influenza A (H1N1) in Saudi Arabia: description of the first one hundred cases. *Ann Saudi Med* 2010; 30: 11–4.
21. Tsalik EL, Hendershot EF, Sangvai DG, et al. Clinical presentation and response to treatment of novel influenza A H1N1 in a university-based summer camp population. *J Clin Virol* 2010; 47: 79–81.
22. Yang J, Yang F, Huang F, et al. Subclinical infection with the novel influenza A (H1N1) virus. *Clin Infect Dis* 2009; 49: 1622–3.
23. Reed C, Katz JM. Serological surveys for 2009 pandemic influenza A H1N1. *Lancet* 2010 [E pub ahead of print].
24. Miller E, Hoschler K, Hardelid P. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* 2010 [E pub ahead of print].
25. O’Riordan S, Barton, M, Yau, Y, et al. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *CMAJ* 2010; 182: 39–44.
26. Lister P, Reynolds F, Parslow R, et al. Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. *Lancet* 2009; 374: 605–7.
27. Fuhrman C, Bonmarin I, Paty AC, et al. Severe hospitalised 2009 pandemic influenza A(H1N1) cases in France, 1 July–15 November 2009. *Euro Surveill* 2010; 15.
28. Hackett S, Patel J, Ratnaraja N, et al. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. *Lancet* 2009; 374: 605–7.
29. Klein NC, Chak A, Chengot M, et al. Fatal case of pneumonia

- associated with pandemic (H1N1) 2009 in HIV-positive patient. *Emerg Infect Dis* 2010; 16: 149–50.
30. Lacombe PJ, Moloney SE, Schmidt PA. Pandemic (H1N1) 2009: A clinical spectrum in the general paediatric population. *Arch Dis Child* 2009; 16: 149–50.
 31. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA* 2009; 302: 1896–902.
 32. Scriven J, McEwen R, Mistry S, et al. Swine flu: a Birmingham experience. *Clin Med* 2009; 9: 534–8.
 33. Gautret P, Parola P, Brouqui P. Risk factors for H1N1 influenza complications in 2009 Hajj pilgrims. *Lancet* 2010; 375: 199–200.
 34. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009; 361: 1935–44.
 35. De Angelis D, Lipsitch M, Presanis AM, et al., The severity of pandemic H1N1 influenza in the United States, April–July 2009. *PLoS Curr Influenza*, 2009; RRN1042.
 36. Hui DS, Lee N, Chan PK. Clinical management of pandemic (H1N1) infection. *Chest* 2009.
 37. Kamigaki T, Oshitani H. Epidemiological characteristics and low case fatality rate of pandemic (H1N1) 2009 in Japan. *PLoS Curr Influenza* 2009; RRN1139.
 38. Presanis AM, De Angelis D, Hagy A, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. *PLoS Med* 2009; 6: e1000207.
 39. Wiebe C, Reslerova M, Komenda, et al. Atypical clinical presentation of H1N1 influenza in a dialysis patient. *Lancet* 2009; 374: 1300.
 40. Lee EYA, McAdam J, Chaudry G, et al. Swine-origin influenza A (H1N1) viral infection in children: initial chest radiographic findings. *Radiology*, 2009.
 41. Ajlan AM, Quiney B, Nicolaou S, et al. Swine-origin influenza A (H1N1) viral infection: radiographic and CT findings. *Am J Roentgenol* 2009; 193: 1494–9.
 42. Ellis C. Antibacterial agents in patients with swine flu. *Int J Antimicrob Agents* 2009; 34: 622.
 43. Donaldson LJ, Rutter PD, Ellis BM, et al., Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. *BMJ* 2009; 339: b5213.
 44. Rasmussen SA, Jamieson DJ, Macfarlane K. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; 374: 451–8.
 45. Hewagama S, Walker SP, Stuart RL, et al. 2009 H1N1 Influenza A and pregnancy outcomes in Victoria, Australia. *Clin Infect Dis* 2010.
 46. Kumar AZ, Pinto R. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009; 302: 1872–9.
 47. Ong AK, Chen MI, Lin L, et al., Improving the clinical diagnosis of influenza – a comparative analysis of new influenza A (H1N1) cases. *PLoS One* 2009; 4: e8453.
 48. Patients hospitalized with 2009 pandemic influenza A (H1N1) – New York City, May 2009. *Morb Mortal Wkly Rep* 2010; 58: 1436–40.
 49. Bansal S, Pourbohloul B, Grenfell B, Meyers LA. The shifting demographic landscape of influenza. *PLoS Curr Influenza*, 2009; RRN1047.
 50. Kelly H, Grant K, Williams S, Smith D. H1N1 swine origin influenza infection in the United States and Europe in 2009 may be similar to H1N1 seasonal influenza infection in two Australian states in 2007 and 2008. *Influenza Other Respi Viruses*, 2009; 3: 183–8.
 51. 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: 1945–52.
 52. Fisman DN, Savage R, Gubbay J, et al. Older age and a reduced likelihood of 2009 H1N1 virus infection. *N Engl J Med* 2009; 361: 2000–1.
 53. *Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave*. Health Protection Agency, 2009.
 54. Kubo T, Agoh M, Mai LQ, et al. Development of reverse transcription-loop-mediated isothermal amplification assay for pandemic (H1N1) 2009 virus as a novel molecular based testing for pandemic influenza even in resource limited settings. *J Clin Microbiol* 2010.
 55. Biere B, Schweiger B, Nitsche A. Influenza A H1N1 diagnostics: the first, the fastest, and the most reliable. *Lancet Infect Dis* 2009; 9: 721–2.
 56. Herzum I, Lutz T, Koch F, Geisel R, Gehrt A. Diagnostic performance of rapid influenza antigen assays in patients infected with the new influenza A (H1N1) virus. *Clin Chem Lab Med* 2010; 48: 53–6.
 57. Drexler JF Helmer A, Kirberg H, et al., Poor clinical sensitivity of rapid antigen test for influenza A pandemic (H1N1) 2009 virus. *Emerg Infect Dis* 2009; 15: 1662–4.
 58. Uyeki T. Diagnostic testing for 2009 pandemic influenza A (H1N1) virus infection in hospitalized patients. *N Engl J Med* 2009; 361: e114.
 59. Cunha BA, Pherez FM, Strollo S. Swine influenza (H1N1): Diagnostic dilemmas early in the pandemic. *Scand J Infect Dis* 2009; 1–3.
 60. Blyth CC, Iredell JR, Dwyer DE. Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 361: 2493.
 61. Houlihan CF Patel S, Price DA, et al. A/H1N1 flu pandemic. Life threatening infections labelled swine flu. *BMJ* 2010; 340: c137.
 62. Dosekun O, Kober C, Richardson D, et al. It's not all swine flu... are we missing opportunities to diagnose primary HIV infection in patients with flu symptoms? *Int J STD AIDS* 2010; 21: 145–6.
 63. Birnkrant D, Cox E. The Emergency Use Authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med* 2009; 361: 2204–7.
 64. Jefferson T, Jones M, Doshi P, et al., Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009; 339: b5106.
 65. Lee N, Cockram CS, Chan PK, et al. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clin Infect Dis* 2008; 46: 1323–4.
 66. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007; 45: 1568–75.
 67. Uyeki T. Antiviral treatment for patients hospitalized with 2009 pandemic influenza A (H1N1). *N Engl J Med* 2009; 361: e110.
 68. Weber JT, Nicoll A, Bridges CB, et al. The truth about Tamiflu? Neuraminidase inhibitors in pandemic A/H1N1 flu. *BMJ* 2010; 340: c130.
 69. *Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season*. Centers for Disease Control and Prevention, 2009.
 70. Kidd I, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 2009; 374: 1036.
 71. Gaur AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. *N Engl J Med* 2010; 362: 88–9.
 72. Le QM, Wertheim HF, Tran ND, et al. A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza. *N Engl J Med* 2010; 362: 86–7.
 73. Kawai N, Ikematsu H, Hirotsu N, et al. Clinical effectiveness of oseltamivir and zanamivir for treatment of influenza A virus subtype H1N1 with the H274Y mutation: a Japanese, multicenter study of the 2007–2008 and 2008–2009 influenza seasons. *Clin Infect Dis* 2009; 49: 1828–35.
 74. Baz M, Abed Y, Papenburg J, et al. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. *N Engl J Med* 2009; 361: 2296–7.
 75. *Pandemic (H1N1) 2009 influenza: a summary of guidance for infection control in healthcare settings*. Department of Health and Health Protection Agency, 2009.
 76. Plennevaux E, Sheldon E, Blatter M, et al. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010; 375: 41–8.
 77. Liang XF, Wang HQ, Wang JZ, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2010; 375: 56–66.
 78. Vajo Z, Tamas F, Sinka L, et al. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009–10 influenza season: a multicentre, randomised controlled trial. *Lancet* 2010; 375: 49–55.
 79. Yamada T. Poverty, wealth, and access to pandemic influenza vaccines. *N Engl J Med* 2009; 361: 1129–31.
 80. *Pandemic (H1N1) 2009 – update 86*. World Health Organization, 5 February 2009. Available at: http://www.who.int/csr/don/2010_02_5/en/index.html
 81. Update: novel influenza A (H1N1) virus infection – Mexico, March–May, 2009. *Morb Mortal Wkly Rep* 2009; 58: 585–9.
 82. Butler D. Swine flu attention turns to the tropics. *Nature* 2009; 459: 490–1.
 83. Enserink M. Swine flu outbreak. Worries about Africa as pandemic marches on. *Science* 2009; 325: 662.