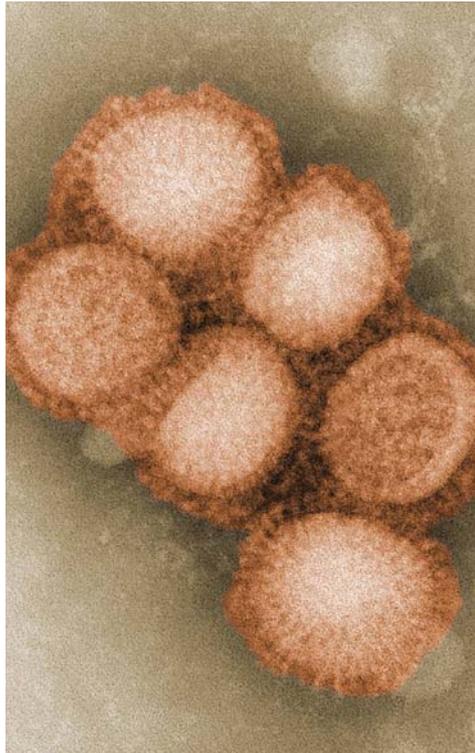


# Anatomy of a pandemic: influenza A (H1N1) 2009



## Abstract

The H1N1 2009 influenza A virus has reached pandemic status and is currently infecting hundreds of thousands of people, spreading efficiently since being isolated in Mexico in April 2009. In this review, the current pandemic state of H1N1 will be discussed along with the symptoms and severity of illness caused by the virus and how they compare to previous pandemics. A number of diagnostic tests are available for the rapid detection of the H1N1 2009 infection and are discussed, along with management of infection and the emergence of antiviral resistance. A vaccine has currently been licensed for use against the H1N1 2009 virus and its effectiveness will be addressed, along with prevention measures that should be taken to hinder further spread of the virus.

**Keywords:** Influenza A virus, H1N1 subtype, disease outbreaks, influenza, human, virus replication, virus shedding, influenza vaccines, oseltamivir, zanamivir.

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## Introduction

Influenza A viruses have long caused human pandemics. The current pandemic virus is a direct descendent of the influenza A H1N1 outbreak of 1918 (the 'Spanish flu'), which killed an estimated 50 million people worldwide.<sup>1</sup> In April 2009, a novel triple-reassortment swine-origin influenza A virus was isolated from a patient in Mexico, and quickly spread worldwide. This is the first influenza A virus pandemic since the H3N2 Hong Kong influenza outbreak of 1968, which killed an estimated one to two million people.<sup>1</sup> As of November 15, 2009, 206 countries have reported 6,770 deaths due to H1N1 2009 to the World Health Organisation (WHO).<sup>2</sup> In contrast, seasonal influenza A epidemics result in three to five million severe infections worldwide, with 250,000-500,000 deaths annually.<sup>3</sup> Ireland has reported 3,914 confirmed cases, with 16 deaths due to H1N1 2009 as of November 14, 2009.<sup>4</sup>

The current influenza outbreak has been classified as phase 6 by the WHO, indicating that the virus has reached full pandemic status and has the capability to cause sustained outbreaks in populations across the globe. All WHO pandemic phases are illustrated in **Figure 1**.<sup>5</sup> H1N1 2009 infections had been steadily increasing worldwide until reaching a peak in late October 2009. Decreases in infection indices were observed in many countries throughout November, with the amount of hospitalised cases of H1N1 2009 decreasing by 50% in Ireland.<sup>4,1</sup> Although the drop in influenza cases may appear to indicate that the worst of the pandemic has passed, this may in fact be due to the natural progression of the pandemic. Influenza pandemics typically progress in waves, and a decrease in the amount of cases may indicate the end of a wave of infections, with potentially more outbreaks to come.<sup>6</sup>

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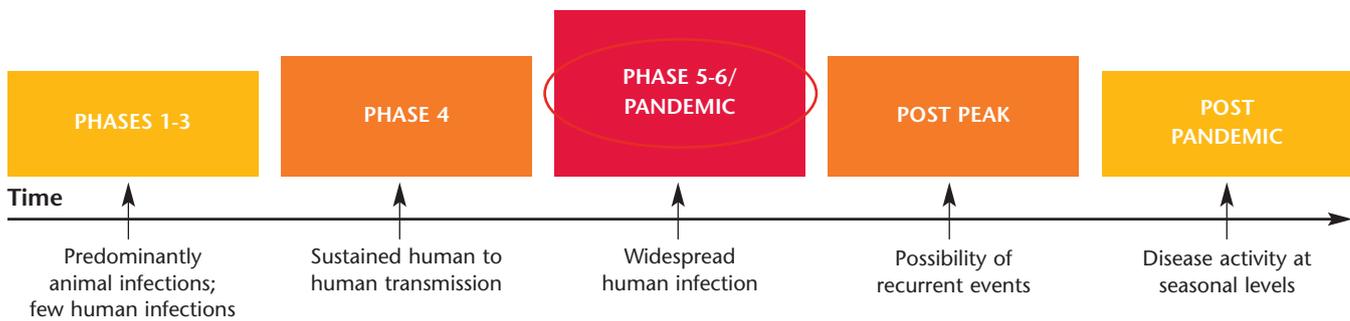


FIGURE 1: Pandemic influenza phases. Source: WHO.

### Influenza A virus

Influenza viruses are classified by their core proteins as influenza A, B, or C.<sup>1</sup> Influenza A is a negative sense RNA orthomyxovirus containing eight genetic segments, which code for 10 different proteins<sup>7</sup> (Table 1).<sup>1,8-10</sup> Influenza A is further classified by the surface antigens haemagglutinin (H) and neuraminidase (N). Sixteen H and nine N alleles exist, coding for 144 possible unique surface antigen combinations.<sup>11</sup> In addition, mutations in the influenza genome can result in antigenic drift, introducing new viral subtypes into the population and altering the pathogenicity of individual virus strains.

When two viral subtypes co-infect the same host, genetic shift can occur. Genetic shift results from the swapping of one or both genomic segments encoding H and N between two different influenza subtypes. Pigs are frequently infected with human and avian influenza strains, and thus are thought to be prime organisms for facilitating the creation of new strains of influenza via genetic drift. In the case of H1N1 2009, the virus was originally endemic in swine and adapted to cause widespread infection in humans.<sup>12</sup> Pandemics arise when a virus undergoes genetic shift resulting in a novel H surface protein. Rapid spread through large populations occurs due to an absence of previous immunity to the new H antigen, which contributed to the 1918, 1957 and 1968 pandemics, and is implicated in the current H1N1 2009 outbreak.<sup>10</sup> An overview of previous pandemics is detailed in Table 2.<sup>11,13</sup>

### Pathogenicity of the virus

It is of great benefit to use previous pandemics as models to assess the potential of the H1N1 2009 virus for widespread infection and loss of life. Pathogenicity of viruses is often determined by the reproduction number ( $R_0$ ), which indicates the average number of infections caused by a single person with the illness. The reproduction number for H1N1 2009 is estimated to be between 1.4 and 1.6.<sup>14</sup> This is more transmissible than the seasonal influenza virus, which has a mean  $R_0$  of 1.3, and less transmissible than the 1918 pandemic, which at its peak had an estimated mean  $R_0$  of 2.0.<sup>15</sup>

Table 2: Influenza pandemics.

Year/name	Strain	Estimated deaths
1918 'Spanish flu'	H1N1	20-50 million
1957-'58 'Asian flu'	H2N2	2-4 million
1968-'69 'Hong Kong flu'	H3N2	1-2 million
1977 'Russian flu'	H1N1	0.7 million
2009 Pandemic flu	H1N1	Under review

Table 1: Influenza gene segments and functions.

Gene segment	Protein(s)	Function	Lineage
NA	Neuraminidase	Viral progeny release and spread	Eurasian swine
M	Matrix protein 1 Matrix protein 2	Structural	Eurasian swine
*HA	Haemagglutinin	Binds to sialic acid receptors on host cell surface	Classical swine
NP	Nucleoprotein	Encapsidation of viral genome	Classical swine
*NS	Non-structural protein 1 NEP	Inhibits host interferon response; inhibits apoptosis	Classical swine
*PB1, PB2, PA	Viral polymerase complex	Viral RNA replication	Swine triple reassortant
*Virulence factors			

Table 3: Diagnostic tests for H1N1 2009.

Test	Time to complete	Sensitivity	Specificity	PPV	NPV
Rapid antigen detection	15 minutes	17.8	93.6	77.4	47.9
Direct fluorescent antibody	2.5 hours	46.7	94.5	91.3	58.9
Viral cell culture	2-3 days	88.9	100	100	87.9
Polymerase chain reaction	Up to 6 hours	97.8	100	100	97.3

PPV: positive predictive value; NPV: negative predictive value.

Although the reproduction number of H1N1 2009 is closer to that of the seasonal flu virus than the devastating 1918 influenza pandemic, it carries the potential to develop mutations that could allow more efficient spread between humans, increasing its replication number.

### Symptoms of pandemic H1N1

H1N1 2009 is spread through respiratory droplets, with an incubation time of two to seven days.<sup>16</sup> This is considerably longer than the incubation time of the seasonal influenza A virus, which has been estimated at 1.4 days.<sup>17</sup> Models have shown that shedding of the virus is observed as soon as one day after infection and lasts seven days,<sup>18</sup> allowing for asymptomatic spread. Symptoms of infection are similar to symptoms of the seasonal influenza virus, including fever (94%), cough (92%) and sore throat (66%). Vomiting and diarrhoea are also present in 25% of cases, and potential faecal–oral spread of the virus must be investigated.<sup>1,16</sup> The majority of previously healthy patients who acquire H1N1 2009 will fully recover in one week.

In a study of 272 patients hospitalised with H1N1 2009 infection, 73% had underlying medical conditions, including asthma, diabetes, pregnancy, and neurological disease. Nineteen (7%) died, with a median time from onset of illness to death of 15 days.

Hospitalisations were seen more frequently in younger patients, with only 5% of admissions consisting of patients over 65 years old.<sup>19</sup> This is in contrast with seasonal influenza, in which the majority of hospitalisations occur in the elderly population and children under two years of age.<sup>20</sup>

### Diagnosis of pandemic H1N1

Many different variables contribute to making a diagnosis. Clinical suspicion based on current pandemic trends in the community must be high to cost-effectively carry out diagnostic testing. There are many techniques readily available to confirm a diagnosis, including rapid antigen testing, direct fluorescent antibody testing, polymerase chain reaction (PCR), and cell culture methods. Characteristics of each test are shown in **Table 3**.<sup>21</sup> PCR remains the most robust test for diagnosing pandemic influenza, yielding the most sensitive and specific results within a reasonable time period. Other tests may be quicker, but are much less sensitive.

### Treatment strategies

The earlier antiviral therapy is started, the more effective the treatment is at reducing influenza viral load and the duration of viral shedding.<sup>19,22</sup> Current antiviral treatments include N inhibitors (oseltamivir and zanamivir) and adamantane derivatives (amantadine and rimantidine).

Oseltamivir and zanamivir function by blocking progeny virion release from infected cells, while adamantane and its derivatives interfere with intracellular viral uncoating.<sup>23</sup> While most strains of pandemic H1N1 have remained susceptible to N inhibitors, adamantane-based drug resistance has been described and these drugs are not considered to be treatment options for acute infection.<sup>16,24</sup>

Due to its effectiveness against H1N1 2009, many countries have stockpiled vast quantities of oseltamivir to combat the global pandemic. Unfortunately, resistance to oseltamivir has recently emerged in 31 cases of H1N1 2009 infection.<sup>25</sup> Peramivir, an N inhibitor that is currently undergoing Phase 3 clinical trials, was authorised for emergency use by the Centers for Disease Control (CDC) on October 23, 2009. It has been approved for use in severe cases of H1N1 2009, which are not responsive to oseltamivir or zanamivir.<sup>26</sup>

Zanamivir has shown similar efficacy and safety to oseltamivir with no resistance reported to date, and is effective in treating oseltamivir-resistant strains.<sup>27,28</sup> Zanamivir is contraindicated in patients with chronic obstructive pulmonary disease (COPD), and is delivered using an inhaler, which is difficult to administer correctly to children and elderly patients.<sup>27</sup> Countries are now adding zanamivir to their antiviral stockpiles (which are dominated by oseltamivir stores); however, a large number of children, COPD patients, and the elderly are currently vulnerable to oseltamivir-resistant H1N1 2009.<sup>27</sup>

New research has shown that a synergy of oseltamivir, amantadine and ribavirin (a widely available antiviral drug) has a two- to 13-fold increase in antiviral activity against influenza A when compared to any two of the agents used together *in vitro*.<sup>30</sup> Additional studies of antiviral treatments for oseltamivir-resistant H1N1 must be undertaken to ensure the safety and preparedness of the general population in the event of a multidrug-resistant influenza pandemic.

## Vaccination

Vaccination continues to be the most important primary prevention measure against influenza spread.<sup>31</sup> Both live attenuated and inactivated vaccines providing protection from H1N1 2009 have been manufactured for general use, with the first batches administered to the public in early October 2009. The pandemic H1N1 vaccine is being manufactured in the same way as the annual influenza vaccine, using hen's eggs to grow both the pandemic H1N1 virus and an inactive laboratory strain. Hybrid virions containing surface proteins of the pandemic strain with an inactivated genome are isolated and become the main constituent of the inactive vaccine.<sup>32</sup> A single dose influenza H1N1 vaccine is immunogenic in adults with sufficient protective antibodies produced 14-21 days post vaccination.<sup>33</sup> Children aged six months to nine years should receive two doses of vaccine separated by 21 days to ensure sufficient production of antibodies.<sup>34</sup> Side effects are similar to those of the seasonal influenza vaccine, consisting of injection site tenderness and mild headaches. No serious adverse events have been consistently reported. However, there is widespread public concern over the vaccine's safety,<sup>35</sup> which is based on fears of rare complications from the vaccine, namely Guillain-Barré syndrome. Thus far, in the population who have been vaccinated, the incidence of Guillain-Barré syndrome has not increased over the baseline rates that are observed in the general population. This is also true for other serious medical conditions.<sup>36</sup> Careful vaccine safety surveillance must be undertaken to detect increases in adverse vaccine reactions over background incidences. Since availability of the vaccine will be limited, selected countries have initiated prioritisation schedules for vaccine recipients in the event of a vaccine shortage. The CDC has advised that populations at risk of serious complications should be vaccinated. This includes all children and young adults between the ages of six months and 24 years of age, all people between the ages of 25 and 64 who have underlying health conditions, healthcare and emergency service workers, pregnant women, and people who care for children under the age of six months.<sup>37</sup>

## Prevention and infection control

Prevention of the spread of H1N1 2009 can also be facilitated by community interventions. Simple measures such as covering coughs and sneezes, washing hands, staying home when sick, and avoiding close contact with people who are ill can have enormous effects on reducing the spread of disease. Households that initiate the use of facemasks and hand hygiene within the first 36 hours after the onset of flu-like symptoms in a family member have a reduced incidence of household transmission of influenza.<sup>38</sup> This illustrates the importance of non-medical measures for controlling infection and can also be translated to the hospital setting, where the use of facemasks, gloves and aprons is recommended when treating infected patients. The use of negative pressure rooms and fit-tested ventilators has been advised by the CDC, but may not be possible in all centres due to facility and financial limitations.<sup>30,39</sup>

## Conclusion

Past pandemics have shown that influenza A viruses have great potential to cause widespread infections and deaths worldwide. It is important to stay vigilant in the surveillance and detection of influenza strains so that future pandemics can be predicted and prevented before they reach advanced stages. While the current H1N1 2009 virus has not been as devastating as some had forecast, the capability for further, and perhaps more virulent and lethal mutations, still exists.<sup>1</sup> Vaccine production must be increased so that new pandemic strains of influenza can quickly be vaccinated against. A combination of public awareness of the pandemic threat, increased vaccine production technologies, and further development of antiviral treatments is the key to being prepared for current and future influenza pandemics.

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