



WHO Technical Consultation on the severity of disease caused by the new influenza A (H1N1) virus infections

Original short summary posted 6 May 2009. Revised full report posted May 9 2009.

On 5 May 2009 WHO convened a technical consultation via teleconference to assess current knowledge about the severity of disease caused by influenza A(H1N1) infection and the implications this might have near the start of a pandemic. WHO also sought data on the clinical spectrum and patterns of the disease and how this compares with what is seen during epidemics of seasonal influenza.

Information was provided by epidemiologists, clinicians, and virologists from Canada, Mexico, Spain, the United Kingdom, and the United States of America. These countries have the largest experience, to date, in aggressive surveillance for the disease and the detection and investigation of cases. In addition, international experts advised WHO during the consultation.

This report includes data provided by each country followed by a brief summary of the key points and considerations for interpretation. *The information should be considered preliminary as the situation is evolving and investigations are ongoing.*

COUNTRY REPORTS

Canada

The Public Health Agency of Canada

Updated information can be found at:

http://www.phac-aspc.gc.ca/alert-alerte/swine_200904-eng.php

A total of 140 laboratory-confirmed cases have been reported in Canada as of 5 May 1500 EDT. Cases continue to be reported on a daily basis. Information on date of illness onset is available for approximately 76 cases; the earliest date of onset was 13 April and the most recent was 30 April.

The majority of cases are ≤ 50 years of age with a median age of 22 years (range of 2 to 64 years). There are no cases > 65 years of age. Approximately 50% of cases are male. Of the 50 cases with known travel within 7 days of symptom onset, 45 travelled to Mexico, one to the United States and four did not specify to which country they had travelled.

No cases have died. One of the 140 laboratory-confirmed cases (a child of 10 years with no known pre-existing risk factors) required hospitalization. Systematic information on clinical illness is not yet available. Most cases had a mild influenza-like illness (ILI). Of note, among the initial cases associated with a school outbreak in Nova Scotia, it was reported that $\leq 50\%$ had fever as part of their illness. Illness was characterized by cough and/or fever with other ILI symptoms such as myalgia and rhinorrhea. Some (proportion not yet tabulated) cases reported diarrhoea.

Mexico

Dirección General de Epidemiología and the Instituto de Diagnostico y Referencia Epidemiologicos



Updated information can be found at: <http://www.dgepi.salud.gob.mx/>

Editorial note: Following the teleconference, an MMWR report was published with updated information at: <http://www.cdc.gov/mmwr/PDF/wk/mm5817.pdf>

As of 5 May, a total of 949 laboratory-confirmed cases and 42 deaths have been reported in Mexico (CDC, MMWR 2009;58:453-8). Confirmed cases have occurred in 27 of 31 Mexican States and the Federal District. The recent increase in the number of confirmed cases and deaths largely reflects laboratory testing of previously reported cases.

In addition, 11,932 suspect cases have been reported (CDC, MMWR 2009;58:453-8). A broad definition for febrile clinical respiratory illness was used that did not include laboratory testing information. Until laboratory testing is completed, it is not known how many of the suspect cases represent infection with influenza A(H1N1).

Most cases are between 5 and 44 years of age, however, cases >60 years of age have been reported. Cases are evenly distributed among males and females. Among the early cases, an unusual pattern was observed in that severe respiratory disease and pneumonia was reported in the 15-29 and 30-44 year old age groups.

Approximately 2000 cases have been hospitalized; while some cases have been laboratory confirmed, many are suspect cases for whom laboratory testing is pending. The average duration of hospitalization is 5 to 7 days. Approximately 17% of hospitalized cases required some form of mechanical ventilation. Secondary bacterial pneumonia occurred in some hospitalized patients.

On average, cases had a 13 day course of illness. Among confirmed cases for whom information was available, fever, dyspnea, cough, headache, and rhinorrhea were most commonly reported (CDC, MMWR 2009;58:453-8). In some instances resolution of fever required up to nine days.

None of the confirmed cases have had neurological signs or symptoms of illness. There are some pregnant females among the confirmed cases; however, information about their age and clinical illness are not yet available. Two cases have occurred in health care workers and investigation of these cases is ongoing. There are no data at this time that suggest health care workers are at increased risk.

Spain

Dirección General de Salud Pública y Sanidad Exterior

Ministerio de Sanidad y Consumo/Ministry of Health and Consumers' Affairs

Updated information can be found at:

<http://www.msps.es/en/servCiudadanos/alertas/gripePorcina.htm>

Spain instituted enhanced surveillance immediately after the initial cases of influenza A(H1N1) were reported in the United States. Efforts have focused on detecting travelers returning from Mexico with fever and acute respiratory symptoms. Clinical criteria include a fever of 37.5°C and onset of symptoms within 10 days of exposure.



As of May 5, a total of 57 laboratory-confirmed cases have been reported in Spain. The earliest date of illness onset was 19 April and the most recent was 30 April. No cases have experienced complications or have died.

The mean and median ages for cases are 24.2 and 23 years, respectively with a range of 19-55 years; 47% of cases were male. None of the cases include pregnant women or health care workers.

Of the 57 cases, 52 had a history of travel to an affected area and five were close contacts of confirmed cases. The incubation period for the five secondary cases ranged from 1 to 5 days with a median of 3 days.

All cases have had a mild ILI and recovered within 3 to 5 days. More than 95% reported fever and cough; approximately 50% had headache, rhinorrhea, sore throat, malaise and diarrhoea. All cases were treated with oseltamivir. Contacts of cases have been traced and given prophylaxis with oseltamivir.

Information about receipt of the 2008/2009 seasonal influenza vaccine was available for 30 of the 57 cases; 4 of 30 cases received vaccine. No cases occurred in groups for whom vaccine was recommended.

The impact on the health care system has been minimal. A total of five cases have been hospitalized. However, hospitalization was done to facilitate isolation procedures and was not related to illness severity. Most cases are now being isolated at home; personal protective equipment is provided to household members as well as prophylaxis.

Routine seasonal influenza surveillance is ongoing and to date has not detected any increase in ILI in primary care or hospitalized patients.

**United Kingdom
Health Protection Agency**

Updated information can be found at:

<http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1240732817665?p=1240732817665>

Surveillance for influenza A(H1N1) was established soon after the reports of influenza A(H1N1) in the United States and Mexico were published. Suspect cases are assessed to ensure that they have a compatible illness as well as an epidemiological link either through travel to an affected area or close contact with a probable or confirmed case. Cases that meet these criteria are tested for influenza and begun on antivirals. Patients who test positive for influenza A are classified as probable cases and confirmatory testing is then performed. Contacts of probable and confirmed cases are identified, assessed and started on antiviral prophylaxis in an effort to contain additional transmission. A local risk assessment has been performed when cases have arisen among school students or airline passengers. Close contacts in these settings are offered prophylaxis.

As of 5 May, a total of 28 laboratory-confirmed cases have been reported from throughout the United Kingdom. The earliest date of onset was 16 April and the most recent was 30 April. Additional cases are under laboratory investigation. No cases have died.



The median age is 25 years; very few cases are >40 years. Slightly more than half are female. Both the age and sex distribution, however, likely reflect that many of the cases have occurred in a school-aged population. Among cases that traveled to Mexico, two were between 40 and 50 years of age and three were >50 years.

Of the 28 cases, 18 traveled to an affected area and 10 occurred among contacts of cases. Seven of the 10 contact cases were associated with a school: two were family members of a confirmed case who had traveled to an affected area and five were other students at the school. Preliminary data from investigations of returning travelers and their close contacts have indicated that the incubation period may range from 4 to 6 days. There have been no cases in health care workers.

All of the confirmed cases had a mild illness with fever; only three of the 28 cases had diarrhoea or other gastrointestinal symptoms. Two were hospitalized out of concern for infection control issues and not severity of illness.

**United States of America
Centers for Disease Control and Prevention**

Updated information can be found at: <http://www.cdc.gov/h1n1flu/>

Editorial note: Following the teleconference, updated information was published at:
<http://www.cdc.gov/mmwr/PDF/wk/mm5817.pdf> and
<http://content.nejm.org/cgi/content/full/NEJMoa0903810?query=TOC>

As of 5 May a total of 642 laboratory-confirmed have been reported from 41 states (NEJM.org on May 7, 2009). The date of onset of illness was available for 394 patients and ranged from 28 March to 1 May. In addition more than 700 probable cases (defined as a case that meets clinical criteria and tests positive for non sub-typable influenza A) have been reported.

Among the confirmed cases, approximately 50% were male and the median age was 20 years (range 3 months to 81 years). The initial cases in the United States were associated with travel to an affected area and outbreaks in schools with subsequent transmission to household and school contacts. An increasing number of more recently reported cases do not have travel-related linkages.

Of the 399 confirmed cases for whom hospitalization information was available, 36 (9%) required hospitalization (NEJM.org on May 7, 2009). Of the 22 hospitalized patients for whom more detailed information was available, 12 had factors associated with an increased risk of complications for seasonal influenza including a chronic medical condition, pregnancy or an age of less than 5 years (NEJM.org on May 7, 2009). A primary reason for hospitalization was severe respiratory illness and not for an underlying medical condition.

Preliminary data suggest that the incubation period appears to range from 2 to 7 days (NEJM.org on May 7, 2009). A secondary attack rate of approximately 22% has been estimated based on preliminary data; higher attack rates have been observed in some school-related outbreaks.

Several key pieces of information about the H1N1 virus and its characteristics have been observed. First, all of the H1N1 viruses to date demonstrate antiviral resistance to amantadine and rimantadine but are susceptible to the neuraminidase inhibitor drugs oseltamivir and zanamivir. Second, there is no evidence currently that the virus has markers for human virulence



that have been described for the 1918 H1N1 pandemic virus and avian influenza H5N1 viruses. Third, molecular sequencing of approximately 30 viruses has found nearly 100% homology for all of the viral genes.

Table. Characteristics of reported cases of influenza A(H1N1) by country¹

Parameter	Country				
	USA	Mexico	Spain	Canada	UK
Incubation period (days)	Range 2-7 ²	NA	Median 3 Range 1-5	NA ³	Range 4-6
Age (years)	Median 20 Range 3 mo - 81yrs ²	Most cases 5-44	Mean 24 Median 23 Range 19-55	Median 22 Range 2-64	Median 25
Number of deaths	2 (0.3%) of 642 confirmed cases ²	42 of 11, 932 suspect and 949 confirmed cases ⁴	0	0	0
Prominent clinical signs	Most ILI; ⁵ diarrhoea in 82 (25%) of 323 cases; ² vomiting in 74 (25%) of 295 cases ²	ILI; secondary bacterial pneumonia in some severe cases	All mild ILI	Most ILI; some diarrhoea; some cases had cough without fever	ILI; 3 (11%) of 28 had diarrhoea or gastrointestinal symptoms
Factors predisposing to severe illness ⁶	12 (55%) of 22 hospitalized cases ²	Some cases in pregnant women	No severe cases	No severe cases	No severe cases
Hospitalization for illness	36 (9%) of 399 confirmed cases ²	~2,000 cases (many not confirmed)	0	1 (0.7%) of 140 confirmed cases	0
Community level spread	yes	yes	no	no	no
M:F ratio	51:49 ²	~50:50	47:53	~50:50	Slightly >50% of cases female

DISCUSSION

Information about the severity of disease caused by influenza A(H1N1) infection is needed to help countries effectively respond to the newly emerged virus and plan for the best use of medical and non-medical interventions. Although the data in this report are preliminary and many key questions cannot be answered at present, the teleconference provided a better understanding about this illness than was previously known.

Key points include:

- Most cases of H1N1 infection have had a mild typical influenza-like illness with fever, cough, runny nose, headache and malaise. Severe illness has been reported in Mexico

¹ Data provided during WHO technical consultation, 5 May 2009 unless otherwise noted; data are preliminary.

² <http://content.nejm.org/cgi/content/full/NEJMoa0903810?query=TOC>

³ NA= not available

⁴ <http://www.cdc.gov/mmwr/PDF/wk/mm5817.pdf>

⁵ ILI = influenza-like illness

⁶ Factors associated with an increased risk of severe seasonal influenza such as pregnancy, chronic medical conditions, very young or very old age.

and the United States, in persons who are at risk for complications of seasonal influenza, such as the very young, women who are pregnant and persons with underlying medical conditions, as well as in healthy young adults.

- The principal reason for hospitalization of cases in Mexico and the United States is severe respiratory disease. In the Mexican experience, secondary bacterial pneumonia has occurred among hospitalized cases.
- Some confirmed cases did not have fever; it is likely that there are asymptomatic and very mild cases of infection -- as occurs with seasonal epidemics of influenza.
- Some, but not all, countries reported cases that had diarrhoea. This initial finding requires further confirmation, and studies to determine if virus is shed in the faeces. If this is found, it could have significance for countries or situations in which there is inadequate sanitation.
- While all age groups have been affected, most cases are occurring in younger age groups with a median age in the mid-20's.
- The virus appears to be easily transmitted from person to person. In the United States and Mexico, community transmission has been widespread. Based on limited data, the secondary attack rate is estimated to be about 22%, but could be as high as 30% in some settings.
- Mexico experienced a large number of persons over a short period of time seeking care and hospitalization for respiratory disease. However, health care systems of other affected countries have not had a similar experience to date.
- At present, the virus is susceptible to oseltamivir (Tamiflu) and zanamivir (Relenza). In laboratory studies, there is no evidence so far that the virus has markers for human virulence that have been described for the 1918 H1N1 pandemic virus and avian influenza H5N1 viruses.

There are several important limitations about the data that must be considered. First, countries are using different surveillance methods and case definitions to detect cases; this will influence information about clinical disease. For example, case detection focused in hospitals would be expected to preferentially detect cases of H1N1 infection with more severe disease. Conversely, detection and investigation of cases in the community setting may favor finding less severe illness. Second, most countries are at an early stage of disease spread and have reported a small number of cases. The experience of Mexico and the United States suggests that only as more cases occur and infection spreads into the wider community can a more complete picture of the epidemiological and clinical characteristics of the H1N1 virus begin to be delineated. Caution must be exercised in interpreting information such as age as it may reflect patterns of travel or the occurrence of outbreaks in special settings such as schools. Third, the early estimates of important epidemiological parameters such as incubation period and attack rate have been derived from a limited number of settings such as households and schools and may not be broadly generalizable. Fourth, although Mexico and the United States have reported deaths among persons with confirmed H1N1 infection, it is too early to get a reliable estimate of the case fatality ratio. Additional studies are needed to assess risk factors for infection with the H1N1 virus as well as the severity of illness.

The situation is expected to evolve over time and bears careful watching. Although illness to date has been mainly mild, as the number of cases and the geographic spread of the virus increase a fuller picture of the virus will emerge that will likely include increased numbers of severe illness and deaths -- as occurs with influenza epidemics each year.

