National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

NCCID RAPID REVIEW

Influenza H7N9: Ten Questions and Answers for Canadian Public Health Decision-makers

May 27, 2013

Ten Questions:

1. Has a case definition been established for surveillance purposes?
2. What has been the estimated severity rate?
3. Who has been at increased risk for severe illness?
4. What has been the natural history of a typical case and the effectiveness of care and treatment?
5. What was the original source of exposure and modes of transmission of infection?
6. What are the ongoing sources of exposure and modes of transmission of infection?
7. What is known about the "epidemic curve"?
8. What geographic spread has been observed?
9. What are the opportunities and challenges for immediate surveillance in Canada?
10. What are the opportunities and challenges for effective prevention and control strategies in Canada at this time?

1. Has a case definition been established for surveillance purposes?

***Comment**: There are a variety of case definitions and indications for testing which may make it difficult to compare findings in different settings, especially if testing protocols and case classifications are not specified in a surveillance or other type of report. For example, in Europe, only patients requiring hospitalization would be tested, whereas in China and USA, any patients with influenza-like-illness could be tested and classified as a confirmed case, if lab-positive. Canadian public health officials should consider reviewing and clarifying case definitions that will be used in Canada, including severity categories, that could be used as a guide for systematic or case-based surveillance and testing.*

<u>China</u>

For investigation of human H7N9 cases in China, the **Chinese Center for Disease Control and Prevention (Chinese CDC)** has devised case definitions based on the H5N1 case definitions recommended by WHO in 2006.

A **suspected case** was defined as a person presenting with unexplained acute lower respiratory illness with fever (≥38 C) and cough, shortness of breath or difficulty breathing or infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnea), **AND**

a. Positive laboratory confirmation of an influenza A virus infection but insufficient laboratory evidence for H7N9 virus infection because of lack of specimens, **OR**

b. Epidemiologically-linked to a confirmed H7N9 case, but without any respiratory specimens available for H7N9 testing.

A **confirmed case** was defined as a patient with ILI or a suspected case with respiratory specimens that tested positive for H7N9 virus by any of the following:

a. Isolation of H7N9 virus or positive results by real-time reverse transcription polymerase chain reaction (RT-PCR) assay for H7N9, **OR**
b. A fourfold or greater rise in antibody titer forH7N9 virus based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen collected at least two weeks later.

USA

On April 5, 2013, the **US Centers for Disease Control and Prevention (US CDC)** published an interim guidance on investigating human H7N9 cases in the US. The CDC recommends the following:

A **confirmed case** is a patient with novel influenza A (H7N9) virus infection that is confirmed by CDC's Influenza Laboratory or a CDC certified public health laboratory using methods agreed upon by CDC and the Council of State and Territorial Epidemiologists (CSTE).

A **probable case** is a patient with illness compatible with influenza for whom laboratory diagnostic testing is positive for influenza A, negative for H1, negative for H1pdm09, and negative for H3 by real-time reverse transcriptase polymerase chain reaction (RT-PCR), and therefore unsubtypeable.

A **case under investigation** is defined as a patient with illness compatible with influenza meeting either of the following exposure criteria and for whom laboratory confirmation is not known or pending, or for whom test results do not provide a sufficient level of detail to confirm novel influenza A virus infection.

a. A patient who has had recent contact (within ≤ 10 days of illness onset) with a confirmed or probable case of infection with novel influenza A (H7N9) virus; **OR**
b. A patient who has had recent travel (within ≤ 10 days of illness onset) to a country where human cases of novel influenza A (H7N9) virus have recently been detected or where novel influenza A (H7N9) viruses are known to be circulating in animals (NB: Since publication of this guidance, this criterion has not changed and is limited to travellers who visited China).

Europe

Similarly, the **European Centre for Diseases Prevention and Control (ECDC)** recommends (on April 26, 2013) that individuals who fulfill both the clinical and exposure criteria should be tested for H7N9.

Clinical criteria:
A severe acute respiratory infection (SARI) with onset within the last 10 days:

a. History of fever or measured fever of ≥ 38C, **AND**
b. Cough, **AND**
c. Requiring hospitalization for clinical care purposes.

Exposure criteria:

a. Recent travel (within 10 days of illness onset) to a risk area where human cases of avian influenza A(H7N9) viruses were reported or where avian influenza A(H7N9) viruses are known to be circulating in animals, **OR**
b. Close contact with confirmed case (within 10 days of illness onset).

As such, a **confirmed case** is defined as a patient for which avian influenza A(H7N9) nucleic acid has been detected by RT-PCR according to ECDC/WHO Regional Office Guidance. There are no definitions for a probable or possible case.

Canada

Case definitions specific to human H7N9 for Canada were not found for this review.

2. What has been the estimated severity rate?

a. At last report there have been 36 deaths among 131 lab-confirmed cases (WHO May 17 update).

b. In an earlier report by the China-WHO Joint Mission, , 2/3 of the first 77 confirmed cases (in which data were available) had developed severe pneumonia and required ventilator support in intensive care units. http://www.who.int/influenza/human_animal_interface/influenza_h7n9/ChinaH7N9JointMissionReport2013u.pdf

> ***Comment:*** *Although not explicitly stated, there is an implication that about one-third of these severe cases died.*

c. On May 10, WHO reported that monitoring and testing of contacts (>2000 people) of confirmed cases has detected "few infections". http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7N9_10May13.pdf

> ***Comment:*** *It is not clear whether these "few" contacts that were "infected" were asymptomatic or ill.*

d. WHO also reported that only six H7N9 infections were detected amongst 20,000 people with mild cases.

> ***Comment:*** *It is not clear what tests were used or what the approach was to testing (e.g. number of days after onset of symptoms, etc.). "Infections" (as distinct from "colonization") usually refer to evidence of an antibody response and should imply more than only an upper respiratory tract positive swab test, but the WHO Risk Assessment (May 10) did not clarify this.*
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> ***Comment:*** *There is incomplete information about denominators such as the total number/proportion of asymptomatic contacts and milder ILI cases that have been tested with an appropriate test at the appropriate time. If there is a testing bias (either more testing or more likelihood of a positive test—because of test type, frequency, or timing) in favour of more severe cases, the case fatality rate of 32/131 = 27% may be an over-estimated indication of the true severity rate of illness associated with infection by this virus.*
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> ***Comment:*** *Although the concern about the number of cases and deaths in China during the first three months of this apparent outbreak (in comparison to H5N1) seems understandable and prudent, the major information sources have not described what proportion of the estimated total deaths in China (about 2.3 million persons in three months) are associated (endemically) with an undiagnosed acute severe respiratory illness. In other words, about one in 63,000 deaths in China as a whole has been reported to be associated with the H7N9 virus.*

3. Who has been at increased risk for severe illness?

a. Descriptions of the epidemiology of the cases have not been sub-specified by severity or death. The age range has been two to 89, with a median of 62 years for all cases (mild, severe or fatal). The prevalence of chronic ill health has been considered typical of Chinese people of this median age. There have been more than twice as many males as females. This pattern has been considered quite different from cases of H5N1 in which the median age was younger and the sex distribution more equal.

4. What has been the natural history of a typical case and the effectiveness of care and treatment?

a. Based on a history of exposure to live bird markets, the incubation period has been estimated to be seven days.

b. Early signs and symptoms were most commonly those of an influenza-like illness. Severe illness has been characterized by rapid deterioration to acute respiratory failure. Refractory hypoxemia and multiple organ failure were the major cause of death.

c. About 2/3 of the first 77 confirmed cases (in which data was available) developed severe pneumonia and required ventilator support in intensive care units.

> ***Comment:*** *Although not explicitly stated, there is an implication that about one-third of these severe cases died.*

d. Although evidence has been limited for the benefit of neuraminidase inhibitors, there has been an association of better outcomes with earlier use of antivirals and there has been some in vitro evidence of sensitivity to neuraminidase inhibitors.

5. What was the original source of exposure and modes of transmission of infection?

a. This H7N9 virus has a combination of genes not previously identified among viruses obtained (and analyzed by modern methods) from birds, humans or any other species. It has been considered an avian influenza with gene sequences from mammalian influenza viruses which has caused limited disease in poultry. Until February, 2013, there were no known cases of human illness associated with this virus.

b. There has been evidence of the presence of this virus in poultry in live bird markets, but not poultry farms. Live bird markets have been considered a possible source of human infection, consistent with the finding that more than 2/3 of the first 77 reported cases reported “some recent contact with live poultry and live poultry markets”.

> ***Comment:*** *No references have been found with a comparison or control group rate of exposure to live poultry. Nor have any references been found that describe the specific type of exposure to live poultry.*

c. There has been insufficient evidence to suggest a sustained or significant rate (if any) of human to human transmission. On May 10, WHO reported that “monitoring and testing of contacts (>2000 people) of confirmed cases has detected few infections.”

> ***Comment:*** *The type of human contact exposure has not been clear, but this suggests a very low R_0 for symptomatic illness.*

6. What are the ongoing sources of exposure and modes of transmission of infection?

a. Although at least three "family clusters" have been identified, evidence has been insufficient to conclude that person-to-person transmission has occurred.

b. According to the China-WHO joint mission which visited China from April 18-24, no new cases had been reported in Shanghai with dates of onset later than April 13, one week after the closure of the live bird markets in Shanghai on April 6th.

7. What is known about the "epidemic curve"?

a. First reported case had onset of symptoms on February 19, 2013.

Date	Cases	Deaths
February	2	2
March	30	12
April	87	7
May to date	2	0
Unknown month of onset	10	11

b. As of May 17, there had been no new laboratory-confirmed human cases to the World Health Organization since May 8, 2013, suggesting a decrease in the incidence rate of reported illnesses with positive lab tests associated with this virus. http://www.who.int/influenza/human_animal_interface/influenza_h7n9/06_ReportWebH7N9Number.pdf

Comment: *Despite the apparent "lull" in reported new cases of H7N9, it is too soon to conclude the future course of this apparently novel influenza virus. Reasonable surveillance seems prudent at this time in Canada and throughout the world.*

8. What geographic spread has been observed?

a. To date, there has been no evidence for cases having been exposed outside of China. The only case reported in another land mass (Taiwan) was believed by officials to have been exposed in mainland China. No evidence for human or animal cases outside of China have been reported, but the extent of surveillance and testing in other countries has not been described or analyzed; "absence of proof is not proof of absence".

9. What are the opportunities and challenges for immediate surveillance in Canada?

a. WHO has not advised special screening at points of entry.

b. PCR tests and serological anti-sera agents have been developed enabling testing for colonization and infection, respectively.

c. Case definitions, diagnostic protocols, and public health reporting requirements have been in place in Canada and in many countries for many years, especially since SARS, for severe acute respiratory illness in which routine diagnostic tests have been negative.

Comment: *Communication to remind appropriate clinicians of protocols for SRIs, combined with an appropriate level of systematic primary care and veterinary based sample testing, should ensure the early recognition of the presence of the H7N9 influenza virus or other new or old causes of SRIs in Canada.*

10. What are the opportunities and challenges for effective prevention and control strategies in Canada at this time?

a. At this point in time, WHO has not recommended any travel or trade restrictions.

Comment: *In addition to the surveillance policies and protocols referred to in #9 above, usual and routine hygiene practices in community and health care settings should be appropriate and sufficient for this currently and apparently distant threat. Indications do not seem to be present for significant government investment in specific vaccine development for the H7N9 influenza virus nor do indications seem to be present for enhanced use of antiviral medications in non-severe case of influenza-like-illness.*

The information here used for knowledge translation was obtained from web-posted reports by official organizations, namely WHO, the China-WHO Joint Commission on Human Infection with Avian Influenza A(H7N9) Virus Mission Report, the US Centers for Disease Control, the European Centre for Disease Prevention and Control, and the Public Health Agency of Canada. Comments are the opinion of Dr. Joel Kettner, Scientific Director, National Collaborating Centre for Infectious Diseases.

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