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ORIGINAL ARTICLE

Epidemiology of human influenza A(H7N9) infection in Hong Kong

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Abstract *Background/Purpose:* We conducted a case series study to review the epidemiology of human influenza A(H7N9) infection reported in Hong Kong.
Methods: We reviewed case records of confirmed human cases of influenza A(H7N9) infection reported in Hong Kong in the 2013—2014 winter season. We compared the median viral shedding duration and interval from illness onset to initiation of oseltamivir treatment between severe and mild cases. We estimated the incubation period of influenza A(H7N9) virus from cases with a single known date of poultry exposure.
Results: A total of 10 cases were reported and all were imported infection from Mainland China. Four patients died and the cause of death was related to influenza A(H7N9) infection in two patients. The median interval from illness onset to initiation of oseltamivir treatment for the severe cases (4.5 days) was significantly longer than the mild cases (2 days; $p = 0.025$). Severe cases had a significantly longer viral shedding duration than mild cases ($p = 0.028$). The median incubation period for cases with a single known exposure date was 4 days. Nasopharyngeal aspirate taken from the 88 close contacts of the 10 patients all tested negative for influenza A virus using reverse transcription polymerase chain reaction.
Conclusion: Delayed administration of antiviral treatment may be associated with a more severe illness for influenza A(H7N9) infection. Despite our aggressive contact tracing policy with laboratory testing of all close contacts, no secondary case was identified which implied that the potential of human-to-human transmission of the circulating influenza A(H7N9) virus remains low.

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Introduction

Human influenza A(H7N9) infection was first reported in China in March 2013.[1] Since then, >450 laboratory confirmed cases were reported to the World Health Organization.[2] These cases were reported in different provinces or municipalities in Mainland China, Taiwan, and Malaysia.[3–5]

In Hong Kong, human influenza A(H7N9) infection is a notifiable infectious disease under "Novel influenza A infection". Medical practitioners are required by law to report suspected or confirmed cases to the Centre for Health Protection (CHP) of the Department of Health. Reporting criteria with clinical and epidemiological components are in place (Table 1), and medical practitioners are required to report suspected cases that fulfil both the clinical and epidemiological criteria to the CHP for investigation. A confirmed case is defined as a patient with clinically compatible illness with either positive viral culture or molecular testing for influenza A(H7N9) virus, or a four-fold or higher rise in influenza A(H7N9) virus specific antibody titer in paired serum samples.

The CHP conducted epidemiological investigations for all reported cases. The patients and their attending doctors were interviewed using a standardized questionnaire to obtain clinical and exposure history. All reported cases were admitted to public hospital for isolation, treatment, and laboratory testing. Patients were placed under droplet, contact, and airborne precautions until the diagnosis of influenza A(H7N9) infection was refuted for suspected cases, or until three consecutive respiratory specimens tested negative for influenza A virus using reverse transcription polymerase chain reaction (RT-PCR) for confirmed cases.

We conducted contact tracing for all confirmed cases. Contacts were categorized into "close contact" or "other contact". A close contact refers to a person who had close (<1 m) unprotected contact with a case patient 1 day before, through 14 days after symptom onset. This includes healthcare workers who provided care for the patient without adequate personal protective equipment. Other contact refers to all other types of contacts who do not fulfil the definition of close contact.

All close contacts were placed under quarantine for 10 days after last exposure to the index patient. They were quarantined either at an isolation room of the public hospital or at a designated quarantine camp. Nasopharyngeal aspirate was taken from each close contact including those who were asymptomatic once quarantine commenced. They were subject to an additional 10 days of medical surveillance after the end of quarantine. For other contacts, they were placed under medical surveillance for 20 days after last exposure to the index patient. All contacts who developed fever or respiratory symptoms during the quarantine or medical surveillance period were treated as a suspected case of influenza A(H7N9) infection and were immediately transferred to a public hospital for isolation and laboratory testing.

The first case of human influenza A(H7N9) infection in Hong Kong was confirmed on 2 December 2013.[6] A total of 10 confirmed cases were reported in the winter season of 2013–2014. For the current winter season, three confirmed cases were reported from December 2014 to February 2015. We conducted a case series study to review the epidemiology of the 10 confirmed cases of human influenza A(H7N9) infection reported in the winter season of 2013–2014.

Methods

Data collection

We reviewed case records of the 10 confirmed cases of human influenza A(H7N9) infection reported in the winter season of 2013–2014. We retrieved information including demographic characteristics (age, sex, and ethnicity), past medical history, clinical presentation, details of antiviral treatment, poultry exposure history, and serial RT-PCR results for influenza A of the patients from the case records.

Definitions

In this study, we defined severe cases as patients who had developed respiratory failure or patients who died due to influenza A(H7N9) infection. Other cases were regarded as mild cases. Viral shedding duration was defined as the

Table 1 Reporting criteria for influenza A(H7N9) infection in Hong Kong

Clinical criteria:
- a person with acute respiratory illness, characterized by fever (temperature >38°C) and cough and/or sore throat; or
- a person with pneumonia; or
- a person who died of unexplained acute respiratory illness.

Epidemiological criteria—one or more of the following exposures in the 10 days prior to symptom onset:
- contact with a human case of influenza A(H7N9); or
- contact with poultry or wild birds or their remains, or to environments contaminated by their feces in countries/areas with documented avian influenza A(H7N9) infection in birds and/or humans in the past 6 months [a]; or
- consumption of raw or undercooked poultry products in countries/areas with documented avian influenza A(H7N9) infection in poultry and/or humans in the past 6 months [a]; or
- close contact with a confirmed influenza A(H7N9) infected animal other than poultry or wild birds; or
- worked in a laboratory that processes samples from persons or animals that are suspected of avian influenza infection; or
- worked in the live poultry industry.

[a] The latest list of affected areas is regularly updated and is available on the website of the Centre for Health Protection of the Department of Health. Hong Kong.

interval from the illness onset date to the date of collection of the last positive specimen from the patients. For cases with a single known date of poultry exposure, we defined the incubation period for each case as the interval between the exposure date and the illness onset date.

Data analysis

We computed the median duration of viral shedding for all 10 patients. We compared the median viral shedding duration as well as the median interval from illness onset to initiation of oseltamivir treatment between severe and mild cases. We estimated the incubation period of influenza A(H7N9) virus by computing the median incubation period for the cases with a single known exposure date. All data were entered into a spreadsheet using Microsoft Excel version 2010 (Microsoft Corporation, Redmond, Washington, United States). We used Mann-Whitney U test to compare medians and Fisher's exact test to compare proportions. We used SPSS version 14.0 (SPSS Incorporated, Delaware, United States) for all data analyses.

Results

From December 2013 to April 2014, >1800 suspected cases of influenza A(H7N9) infection were reported to the CHP. Among them, 10 cases were laboratory confirmed. Their onset date ranged from 21 November 2013 to 11 April 2014 (Figure 1). Fifty percent of the patients were male. All were Chinese except one patient who was Indonesian. The median age of the patients was 65 years (range: 5 months to 85 years). There were two pediatric patients aged 5 months and 18 months, respectively. All adult patients reported history of coexisting medical conditions. Diabetes mellitus, hypertension, coronary heart disease, and cerebrovascular disease were the most common conditions (Table 2).

Most patients presented with fever, cough, and shortness of breath. Sore throat or runny nose were uncommonly reported (Table 2). The two pediatric patients presented with a mild course of illness; one with upper respiratory tract infection and the other with febrile convulsion. All patients required hospitalization and the median interval from illness onset to hospital admission was 2 days (range: 0–6 days).

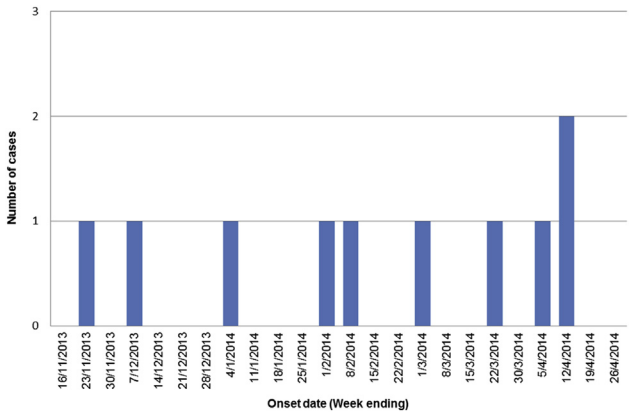

Figure 1. Onset date of the 10 confirmed cases of human influenza A(H7N9) infection in Hong Kong, 2013–2014 winter season.

Table 2 Demographic and clinical characteristics of the 10 confirmed cases of human influenza A(H7N9) infection in Hong Kong, 2013–14 winter season

Characteristic	No. of cases (%)
Male patients	5 (50)
Age (y)	
<18	2 (20)
18–64	1 (10)
≥65	7 (70)
Symptoms	
Fever	9 (90)
Cough	8 (80)
Shortness of breath	6 (60)
Runny nose	1 (10)
Sore throat	1 (10)
Coexisting medical condition	
Diabetes mellitus	6 (60)
Hypertension	6 (60)
Coronary heart disease	4 (40)
Cerebrovascular disease	4 (40)

All adult patients had pneumonia and four of them developed respiratory failure requiring mechanical ventilation and intensive care. Among them, three patients required treatment with extracorporeal membrane oxygenation (ECMO). Antiviral treatment was not given to one patient as he died soon after admission. The others were all treated with oseltamivir and three of them were also given zanamavir. The median interval from illness onset to initiation of oseltamivir treatment was 4 days (range: 0–8 days).

Overall, four patients died during hospital admission and influenza A(H7N9) infection was the cause of death in two cases. One case had developed respiratory failure requiring intensive care treatment including mechanical ventilation and ECMO therapy. Another case died approximately 10 hours following hospital admission without mechanical ventilation or intensive care. The interval from illness onset to death in these two cases was 10 days and 3 days, respectively. For the other two fatal cases, clearance of the virus was shown using RT-PCR in three sets of respiratory specimens taken weeks before their death. Their cause of death was aspiration pneumonia and ventilator-associated pneumonia, respectively. The interval from illness onset to death in these two cases was 20 days and 62 days, respectively.

Seven patients were diagnosed by detection of influenza A(H7N9) virus using RT-PCR in upper respiratory tract specimens (nasopharyngeal aspirate for 4 patients and nasopharyngeal swab for 3 patients). The remaining three patients had positive sputum specimens, while two of them had negative concurrent nasopharyngeal aspirate. Viral shedding duration ranged from 0 day to 23 days with a median of 3.5 days. In one fatal case, influenza A(H7N9) virus was detected in postmortem lung, trachea, and heart tissues using RT-PCR, while liver tissue was negative.

The four patients with respiratory failure requiring mechanical ventilation and the patient who died soon after admission were regarded as severe cases. The median

interval from illness onset to initiation of oseltamivir treatment for the severe cases (4.5 days) was significantly longer than the mild cases (2 days; $p = 0.025$). Severe cases also had a significantly longer viral shedding duration (median: 10 days, range: 2—23 days) than the mild cases (median: 1 day, range: 0—4 days; $p = 0.028$).

Our epidemiological investigations revealed that all patients contracted the infection from different cities of the Guangdong Province of China: six cases in Shenzhen and one case each in Kaiping, Shunde, Guangzhou, and Dongguan. Only two patients reported history of direct contact with poultry. They had been involved in slaughtering live chickens. Seven cases (including the 2 cases who reported history of direct contact) had history of visits to markets with live poultry stalls (Table 3). In two cases, family members of the patient had visited markets with live poultry stalls. For the remaining case, the patient only recalled history of having walked past the entrance of a market with live poultry stalls. Four patients had a single known exposure date and the median incubation period was 4 days (range: 1—7 days).

Contact tracing identified 88 close contacts for the 10 patients. The number of close contacts identified for each patient ranged from 0 to 19 (median: 8). These close contacts included 44 family members, 42 hospital contacts, a travel collateral of a patient, and a taxi driver who drove a patient to hospital. Nasopharyngeal aspirate taken from all close contacts when quarantine commenced tested negative for influenza A virus using RT-PCR. Six of these had developed fever and/or respiratory symptoms during the quarantine or medical surveillance period and repeated nasopharyngeal aspirates all tested negative for influenza A virus using RT-PCR.

We also identified a total of 924 other contacts for the 10 cases studied. The number of other contacts identified for each patient ranged from 43 to 230 (median: 80). Seventy-six of these had developed fever and/or respiratory symptoms during the medical surveillance period and nasopharyngeal aspirate taken from them all tested negative for influenza A virus using RT-PCR.

Discussion

In this report, we described the public health management of human influenza A(H7N9) infection in Hong Kong and reviewed the epidemiology of the 10 confirmed cases reported in the 2013—2014 winter season. Compared with the case series reported by Gao et al[7], the percentage of patients aged $\geq$ 65 years (70% vs 42%), with diabetes mellitus (60% vs 16%), or with coronary heart disease (40% vs 10%) was higher among our patients. By contrast, the percentage of patients that required mechanical ventilation among our cases was much lower (40% vs 86%), while the median interval from illness onset to initiation of antiviral treatment was shorter in our series (4 days vs. 7 days). It is possible that delayed antiviral treatment is associated with the development of more severe illness. Our study has also demonstrated that severe cases have a significantly longer median interval from illness onset to initiation of oseltamivir treatment than mild cases. As such, earlier administration of antiviral treatment may account for the lower complication rate among our cases compared with the study by Gao et al.[7]

In one of our cases who was complicated with respiratory and renal failure, influenza RNA was detected in respiratory specimens for up to 23 days after illness onset. To the best of our knowledge, it is probably the longest viral shedding duration reported for influenza A(H7N9) infection.[5,7—11] We also found that severe cases are associated with a significantly longer viral shedding duration. Similar viral shedding kinetics were observed for influenza A(H1N1)pdm09 infection. A recent systematic review has found that the mean duration of viral shedding generally increased with severity of clinical presentation.[12] Unfortunately, our study had a small sample size and, therefore, the finding should be interpreted with caution.

In one of the fatal cases in our study, influenza A(H7N9) RNA was detected in postmortem lung, trachea, and heart tissues using RT-PCR. The patient had a history of aortic dissection with aortic valve replacement. Findings of postmortem examination reported by local researchers revealed the presence of a thrombus over the prosthetic valve in which influenza viral antigen was detected by immunohistochemistry in isolated monocytic cells within the thrombus.[13] The presence of viral RNA in multiple organs was suggestive of a disseminated infection.

Visits to markets with live poultry stalls has been identified as a risk factor for influenza A(H7N9) infection.[14,15] In our series, 70% of cases reported history of visits to markets with live poultry stalls, which is similar to figures in other published reports which ranged from approximately 50% to 75%.[3,14—17] Unfortunately, the exact mode of transmission, whether by inhalation of contaminated droplets/aerosol or by fomite transmission, in these patients remains obscure. Further research in this aspect is urgently needed in order to formulate appropriate prevention strategies.

The median incubation period of influenza A(H7N9) infection for cases with a single known exposure reported in the literature ranged from 6 days to 7 days.[3,18—19] In our study, the median incubation period estimated from cases with a single known exposure was 4 days which was shorter than the figures reported in the case series mentioned above. However, our results are similar to the study findings of Cowling et al[16] who estimated the mean incubation period of influenza A(H7N9) virus to be 3.1 days using modelling methods.

Our epidemiological investigation identified >80 close contacts for the 10 patients. One half of these were family

Table 3 Exposure history of the 10 confirmed cases of human influenza A(H7N9) infection in Hong Kong, 2013—14 winter season

Exposure	No. of cases (%)[a]
Visited market with live poultry stalls	7 (70)
Slaughtered live chickens	2 (20)
Family member had visited market with live poultry stalls	2 (20)
Walked past the entrance of market with live poultry stalls	1 (10)

[a] One patient can have more than one type of exposure.

members of the patients who should have had prolonged face-to-face interaction with the cases. Nevertheless, nasopharyngeal aspirate taken from all these contacts tested negative for the virus. Those who had developed respiratory symptoms during the quarantine or medical surveillance period also had their nasopharyngeal aspirate tested negative for the virus. This fact adds another piece of evidence supporting the low potential of human-to-human transmission of the circulating influenza A(H7N9) virus.

In Hong Kong, we adopted an aggressive public health approach to the prevention and control of influenza A(H7N9) infection. Medical practitioners are required to report all patients that fulfil the reporting criteria to the CHP for epidemiological investigation, and laboratory diagnosis is performed for all these cases. We also conducted exhaustive contact tracing with quarantine of close contacts for each confirmed case. Currently, the virus has not yet been able to spread efficiently between humans and we are still able to cope with the resources required for this approach. However, should the virus transmission between humans become efficient and community-wide transmission established, laboratory diagnosis and epidemiological investigation of each suspected case would become impossible. At that juncture, resources should be focused on mitigation of impact of the outbreak to the community. Instead of identifying and investigation of all cases, empirical antiviral treatment for a defined target group with presumptive diagnosis of the infection should be considered, taking into account of the transmissibility and virulence of the virus as well as the availability of antiviral agents.

In conclusion, we reviewed the epidemiology of the 10 confirmed cases of human influenza A(H7N9) infection in Hong Kong reported in the 2013—2014 winter season. All cases were imported infection from Mainland China. We conducted aggressive contact tracing and quarantine measures to prevent secondary spread of the disease in Hong Kong. Our study findings suggested that delayed administration of antiviral treatment may be associated with a more severe illness for influenza A(H7N9) infection. In addition, despite our aggressive contact tracing policy with laboratory testing of all close contacts, the absence of secondary cases implied that the human-to-human transmission potential of the circulating influenza A(H7N9) virus remains low. However, on-going epidemiological surveillance is of utmost importance to detect changes in the human-to-human transmission potential of the virus such that appropriate public health control measures could be instituted in a timely manner.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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