Surveillance of avian influenza A(H7N9) virus infection in humans and detection of the first imported human case in Taiwan, 3 April to 10 May 2013

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Citation style for this article:
Lo YC, Chen WC, Huang WT, Lin YC, Liu MC, Kuo HW, Chuang JH, Yang JR, Liu MT, Wu HS, Yang CH, Chou JH, Chang FY. Surveillance of avian influenza A(H7N9) virus infection in humans and detection of the first imported human case in Taiwan, 3 April to 10 May 2013. Euro Surveill. 2013;18(20):pii=20479. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20479

Article submitted on 03 May 2013 published on 16 May 2013

On 3 April 2013, suspected and confirmed cases of influenza A(H7N9) virus infection became notifiable in the primary care sector in Taiwan, and detection of the virus became part of the surveillance of severe community-acquired pneumonia. On 24 April, the first imported case, reported through both surveillance systems, was confirmed in a man returning from China by sequencing from endotracheal aspirates after two negative throat swabs. Three of 139 contacts were ill and tested influenza A(H7N9)-negative.

The Taiwan Centers for Disease Control (TCDC) listed avian influenza A(H7N9) virus infection in humans as a nationally notifiable disease on 3 April 2013 [1], after the Chinese authorities had on 31 March 2013 announced the identification of two male influenza cases in Shanghai and one female case in Anhui with severe respiratory disease caused by an avian influenza A(H7N9) virus that had not previously been detected in humans or animals [2]. The viruses had genetic markers known to be associated with adaptation to mammalian hosts and respiratory transmission of avian influenza viruses, raising concerns about their pandemic potential [2]. The probability of introduction of this virus into Taiwan is considered high because of geographic proximity and more than 90,000 personal or business travels from Shanghai and Anhui to Taiwan per month. This report summarises Taiwan's surveillance for avian influenza A(H7N9) virus infection in humans in the period from 3 April to 10 May 2013.

Influenza surveillance in Taiwan

The National Influenza Surveillance System (NISS) in Taiwan consists of virological surveillance by sentinel primary care physicians, syndromic surveillance of influenza-like illness in emergency and outpatient departments, and surveillance of influenza with complications reported through the National Notifiable Disease Surveillance System. These surveillance activities have been described [3,4]. On 3 April 2013, the TCDC added human infection with avian influenza A(H7N9) virus into the National Notifiable Disease Surveillance System to detect suspected and confirmed cases in the primary care sector. Before 3 April 2013, specimens positive for untypeable influenza A submitted through NISS were routinely tested for influenza A(H5) by realtime RT-PCR. Since 3 April 2013, such specimens have in addition been routinely tested by RT-PCR for influenza A(H7). The TCDC has also conducted surveillance of severe community-acquired pneumonia (CAP) of unknown aetiology since 2010. We focused on these two surveillance activities in this report.

Surveillance of influenza A(H7N9) virus infection in the primary care sector

The maximal incubation period of influenza A(H7N9) was defined as seven days in the period from 3 to 25 April and was revised as 10 days on 26 April based on a recent study [5]. Contacts were defined as those who had provided care to, had been in the same place with, or had directly exposed to respiratory secretions or body fluids of a case since the day before illness onset of the case.

A suspected influenza A(H7N9) case was defined as a person with onset of pneumonia or fever (≥38 oC) with cough within the maximal incubation period of at least one the following exposures: (i) contact with a confirmed case; (ii) travel to provinces or cities in China where human infections with the avian influenza A(H7N9) virus have been reported; (iii) exposure to human, animal or environmental specimens or laboratory samples that are suspected or confirmed to contain the influenza A(H7N9) virus. A case was confirmed if tested positive for the influenza A(H7N9) virus by RT-PCR and/or culture at TCDC.

Physicians were required to report suspected cases to their local health departments within 24 h of identification and to submit nasopharyngeal or oropharyngeal swabs of all suspected cases to TCDC for influenza

testing. Local public health professionals verified case characteristics including presenting symptoms, dates of illness onset, underlying medical conditions, and exposure to poultry based on the physicians' reports and interviews with the patients or their parents.

Contact persons were identified through interviews with patients and their family and through hospital records. All contacts were interviewed for dates and mode of the exposure as well as and protective measures, and followed up daily for fever and respiratory symptoms during the maximal incubation period after last exposure.

Surveillance of influenza A(H7N9) virus in severe pneumonia of unknown aetiology

Surveillance of severe CAP of unknown aetiology has been established in Taiwan since 2010. Physicians from 29 hospitals (including 13 tertiary referral hospitals) were requested to submit respiratory specimens from CAP patients with respiratory failure for whom no aetiologic pathogen had been identified through general clinical investigations. Submitted specimens were tested for viruses using a specifically designed multiplex PCR panel targeting influenza A(H1N1), A(H3N2) and B viruses, parainfluenza viruses 1–3, adenovirus, respiratory syncytial virus (A and B), human bocavirus, human coronavirus (229E, NL63, OC43, and HKU1), enterovirus, rhinovirus, human metapneumovirus, parvovirus B19, and viruses of the human Herpesviridae. Since 3 April, influenza A(H7) virus has been incorporated into the multiplex PCR panel as a supplementary target for all cases of severe CAP of unknown aetiology. Retrospective testing of influenza A(H7) virus was also conducted on stored samples from cases of severe CAP of unknown aetiology reported from 1 January to 2 April 2013.

Laboratory testing of influenza A(H7N9) virus

Viral culture was performed on respiratory specimens using Madin Darby canine kidney cells. The RT-PCR for influenza A and B viruses and subtyping of human influenza A(H1N1) and A(H3N2) have been described before [6]. Subtyping of influenza A(H7N9) viruses was conducted with the protocol provided by the World Health Organization Collaborating Center for Reference and Research on Influenza [7].

Case description

In the period from 3 April to 10 May, TCDC was notified of 358 suspected human cases of avian influenza A(H7N9) virus infection and 41 cases of severe CAP of unknown aetiology, including one confirmed case reported through both of the surveillance systems. Of the 357 suspected cases that tested negative for influenza A(H7), 49 tested positive for influenza A(H1N1), 29 tested positive for influenza A(H3N2), and five tested positive for influenza B. Of the 88 cases of severe CAP of unknown aetiology reported in the period from 1 January to 10 May, 47 cases were negative in all tests, 16 were positive for influenza virus (13A(H1N1) , two A(H3N2), and one A(H7N9)), and 25 were positive for other viruses (details not presented because the review of the medical records is still outstanding). None of the specimens submitted through other NISS surveillance activities from 3 April to 10 May tested positive for influenza A(H7) viruses.

The confirmed case occurred in a man in his 50s who returned from Jiangsu Province, China on 9 April. The clinical course has been described in details elsewhere [8]. The patient experienced fever and general malaise without respiratory symptoms on 12 April, first sought medical attention on 16 April because of high fever (40 oC) and mild sore throat, and was reported as a suspected influenza A(H7N9) case on 16 April. A throat swab collected on 16 April tested negative for influenza A(H7N9) virus by RT-PCR. Right lower lobe interstitial pneumonia developed on 18 April and progressed to bilateral lower lung consolidation and respiratory failure on 20 April. The patient was reported to TCDC on 21 April as severe pneumonia of unknown aetiology and a throat swab was collected and submitted to TCDC on the same day for testing by RT-PCR; this sample was negative for influenza A(H7N9) virus. Endotracheal aspirates collected on 20 April tested positive for influenza A on 22 April and were subtyped as influenza A(H7N9) in the evening of 23 April at a university research laboratory. On 24 April, influenza A(H7N9) virus infection was confirmed by positive influenza A(H7N9) RT-PCR and sequencing at the TCDC National Influenza Center on endotracheal aspirates collected in the late evening of 23 April. As of 10 May, the patient had made a good recovery; mechanical ventilation had been removed.

All of 139 contact persons of this case, including three family contacts, 26 casual contacts (colleagues and friends), and 110 healthcare workers, were followed up for 10 days after last exposure. Three healthcare workers at the intensive care unit experienced respiratory symptoms within two to three days after providing routine nursing care to the patient, using N95 respirators, goggles, gloves and protective clothing. Throat swabs collected from all three symptomatic contacts on April 24 tested negative for influenza A(H7N9) virus by RT-PCR. Further epidemiological and laboratory investigations of this confirmed case and close contacts are ongoing.

Discussion

This first human influenza A(H7N9) case outside China provided important lessons on public health surveillance and detection of human influenza A(H7N9) cases. Firstly, influenza A(H7N9) RT-PCR was negative on two throat swabs collected on Day 4 and Day 9 after illness onset, but was positive on endotracheal aspirates collected on Day 8 after onset. The findings are consistent with a recent study based on four cases, that indicated sputum specimens were more likely to test influenza A(H7N9)-positive than throat swabs [9]. As a result, TCDC revised the sampling guidance on 26

April to include sputum, endotracheal aspirates and other lower airway specimens, in addition to pharyngeal swabs, as recommended specimens for collection in suspected reported influenza A(H7N9) cases with productive cough, pneumonia or other complications. TCDC also recommended that physicians submit follow-up respiratory specimens in suspected influenza A(H7N9) cases with progressive disease after initially negative test results.

Secondly, the patient presented with fever but no cough. Although the presenting symptoms did not meet our case definitions, his clinician decided to report the case based on recent travel in eastern China and fever with sore throat, and the reporting was accepted by our surveillance system. The case presentation was different from that of the first three influenza A(H7N9) cases reported in China, all of whom presented with fever and cough [2]. However, adult and paediatric influenza A(H7N9) cases that presented without cough have been reported [10,11]. This illustrates possible limitations of current case definitions using fever and cough as one of the clinical criteria. Although inclusion of respiratory symptoms other than cough might improve sensitivity of the case definitions, broader clinical criteria might not necessarily lead to strengthened case confirmation, if testing on pharyngeal specimens at an early stage is not sensitive for influenza A(H7N9) virus detection. Alternatively, as exemplified by this case, physicians should be allowed to report suspected cases that do not fully meet the case definitions.

Further studies that characterise influenza A(H7N9) virus infection in humans will provide evidence for public health practices of case detection. For example, because a recent study showed maximal intervals of 10 days between poultry exposure and illness onset in influenza A(H7N9) cases [5], T CDC revised case definitions on 26 April to extend the maximal incubation period to 10 days. Studies that examine viral positivity at different anatomic sites and shedding over the disease course in comparison with seasonal influenza, such as previous studies on pandemic influenza A(H1N1)pdm09, could provide guidance for laboratory testing and monitoring of influenza A(H7N9) cases [12-14].

Conclusions

This first imported human influenza A(H7N9) case in Taiwan was reported through both the National Notifiable Disease Surveillance and severe CAP surveillance systems. Laboratory confirmation was achieved through astute pursuit of laboratory diagnoses by physicians, testing a deep endotracheal sample despite two earlier negative throat swabs and absence of cough as the initial presentation. A flexible surveillance system allows for timely revision of case definitions and sampling guidance. Sensitivity in case detection is likely to improve with collection of sputum, endotracheal aspirates, or other lower airway specimens in addition to pharyngeal swabs. Retrospective testing of severe CAP cases since January 2013 did not demonstrate any earlier influenza A(H7N9) cases. Preliminary results of contact investigations indicated no evidence of person-to-person transmission. We recommend rapid communication and dissemination of results of epidemiological and virological studies to ensure evidence-based surveillance and detection of influenza A(H7N9) virus infection.

Authors' contributions

Yi-Chun Lo, Wan-Chin Chen, Wan-Ting Huang, Yung-Ching Lin, and Ming-Chih Liu prepared the first draft of this manuscript. Hung-Wei Kuo, and Jen-Hsiang Chuang provided the surveillance data. Ji-Rong Yang, Ming-Tsan Liu, and Ho-Sheng Wu provided the virological data. Chin-Hui Yang, Jih-Haw Chou, Feng-Yee Chang interpreted the surveillance and virological data. All authors reviewed and revised the first and final drafts of this manuscript.

Conflict of interest

None declared.

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