ORIGINAL ARTICLE

Preliminary Report: Epidemiology of the Avian Influenza A (H7N9) Outbreak in China

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ABSTRACT

BACKGROUND

The first identified cases of avian influenza A (H7N9) virus infection in humans occurred in China during February and March 2013. We analyzed data obtained from field investigations to characterize the epidemiologic characteristics of H7N9 cases in China as of April 17, 2013.

METHODS

Field investigations were conducted for each confirmed case of H7N9 virus infection. A patient was considered to have a confirmed case if the presence of the H7N9 virus was verified by means of real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR), viral isolation, or serologic testing. Information on demographic characteristics, exposure history, and illness timelines was obtained from patients with confirmed cases. Close contacts were monitored for 7 days for symptoms of illness. Throat swabs were obtained from contacts in whom symptoms developed and were tested for the presence of the H7N9 virus testing by means of real-time RT-PCR.

RESULTS

Among 82 persons with confirmed H7N9 virus infection, the median age was 63 years (range, 2 to 89), 73% were male, and 84% were urban residents. Confirmed cases occurred in six areas of China. Of 77 persons with available data, 4 were poultry workers, and 77% had a history of exposure to live animals, including chickens (76%). A total of 17 persons (21%) died after a median duration of illness of 11 days, 60 remain critically ill, and 4 with clinically mild cases were discharged from the hospital; 1 pediatric patient was not admitted to the hospital. In two family clusters, human-to-human transmission of H7N9 virus could not be ruled out. A total of 1251 of the 1689 close contacts of case patients completed the monitoring period; respiratory symptoms developed in 19 of them (1.5%), all of whom tested negative for the H7N9 virus.

CONCLUSIONS

Most persons with confirmed H7N9 virus infection were critically ill and epidemiologically unrelated. Laboratory-confirmed human-to-human H7N9 virus transmission was not documented among close contacts, but such transmission could not be ruled out in two families.

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The first identified cases of human infection with a novel influenza A (H7N9) virus occurred in eastern China during February and March 2013 and were characterized by rapidly progressive pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), and fatal outcomes.[1] We analyzed available data from field investigations to characterize the descriptive epidemiology of laboratory-confirmed cases of avian influenza A (H7N9) virus infection in humans reported to the Chinese Center for Disease Control and Prevention (China CDC) as of April 17, 2013. In this report, we summarize the preliminary findings of case investigations and follow-up monitoring of close contacts of persons with confirmed cases of H7N9 virus infection who have been identified to date. This is an ongoing investigation.

Methods

Case Definitions

The case definitions of suspected and confirmed human infection with H7N9 virus were based on the H5N1 case definitions, as recommended by the World Health Organization (WHO) in 2006 (Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[2] The laboratory test assays for H7N9 virus that we performed have been described previously (Section S2 in the Supplementary Appendix).[3]

Identification of Cases

Suspected cases of H7N9 virus infection were identified through the Chinese surveillance system for pneumonia of unexplained origin, which was established in 2004.[4] Beginning on April 3, 2013, enhanced surveillance was implemented for suspected cases of H7N9 virus infection among persons with mild or moderate illness.[5] Persons with suspected cases of H7N9 virus infection with mild or moderate illness were identified from the Chinese sentinel surveillance system for influenza-like illness, which has been described previously.[6] Once each suspected case of H7N9 virus infection was identified, the local CDCs, including prefecture and provincial CDCs, conducted the initial field investigations and obtained respiratory specimens, which were shipped to the National Influenza Center of the China CDC in Beijing for H7N9 laboratory testing. A field investigation team comprising staff members of the China CDC and or local CDC conducted field investigations of the confirmed cases of H7N9 virus infection.

Data Collection

It was determined by the National Health and Family Planning Commission that the collection of data from H7N9 case patients and their close contacts was part of a continuing public health investigation of an outbreak and was exempt from institutional review board assessment. Data were collected through a review of medical records and interviews with relatives, contacts, and health care workers who provided medical care for the case patients. We collected information on the dates of illness onset, visits to clinical facilities, hospitalization, and clinical outcomes. Epidemiologic data were collected through interviews and field observations and were reported to the China CDC. Investigators interviewed the relatives of each patient with a confirmed case of H7N9 virus infection to determine exposure histories during the 2 weeks before the onset of the illness, including the dates, times, frequency, and patterns of exposures to poultry or other animals such as swine and wild birds. All epidemiologic information that was collected during the field investigations, including exposure history, timelines of events, and identification of close contacts, was cross-validated, since we were unable to interview any critically ill H7N9 case patients. Households and places that were known to have been visited by the case patients in the 2 weeks before the onset of illness were investigated to assess exposures to poultry and swine, as well as environmental exposures.

Identification and Follow-up of Close Contacts

We defined close contacts of patients with confirmed H7N9 virus infection as described previously for H5N1 field investigations[7] (Section S3 in the Supplementary Appendix); once we identified the close contacts, we monitored them daily for 7 days for symptoms of illness and collected throat swabs from contacts in whom symptoms developed to test for the presence of the H7N9 virus. Antiviral chemoprophylaxis was not provided to close contacts. Paired serum samples were obtained from patients with suspected H7N9 virus infection who did not have respiratory specimens available for H7N9 serologic test-

ing. Oseltamivir treatment was recommended for close contacts in whom symptoms developed (Section 3 in the Supplementary Appendix). Data on demographic characteristics and exposure were collected for close contacts.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize the epidemiologic characteristics and H7N9 testing results for persons with suspected cases of H7N9 virus infection, for those with confirmed cases, and for close contacts of those with confirmed cases. The methods we used for estimating the incubation period have been described previously.[8]

RESULTS

EPIDEMIOLOGIC CHARACTERISTICS OF CONFIRMED CASES

From March 25 through April 17, 2013, respiratory specimens from 664 hospitalized patients with pneumonia of unexplained origin were tested, and 81 patients (12.2%) were confirmed to be infected with the H7N9 virus. Of 5551 respiratory specimens obtained from outpatients with an influenza-like illness through the sentinel surveillance system for influenza-like illness, 1 (0.02%) tested positive for the H7N9 virus. As of April 17, 2013, a total of 82 laboratory-confirmed cases of H7N9 virus infection and 2 suspected cases had been identified (Fig. 1 and 2); cases were identified in the following provinces: Shanghai (31 confirmed cases and 1 suspected case), Zhejiang (25 confirmed cases), Jiangsu (20 confirmed cases and 1 suspected case), Anhui (3 confirmed cases), Henan (2 confirmed cases) and Beijing (1 confirmed case). The median age of patients with confirmed H7N9 virus infection was 63 years (range, 2 to 89); 38 cases (46%) occurred in persons 65 years of age or older, and 2 (2%) were in children younger than 5 years of age, both of whom had clinically mild upper respiratory illness (see Fig. S1 in the Supplementary Appendix for the age distribution). Most confirmed cases occurred in males (73%), 84% of the case patients were urban residents, and 54 of 71 patients with available data (76%) had underlying medical conditions (Table 1). Among 46 of 54 case patients with sufficient data for a more specific classification of underlying conditions, 40 (87%) were considered to be at increased risk for influenza complications owing to age (<5 years or ≥65 years) or prevalence of certain underlying medical conditions.[9] Four of the patients with confirmed cases

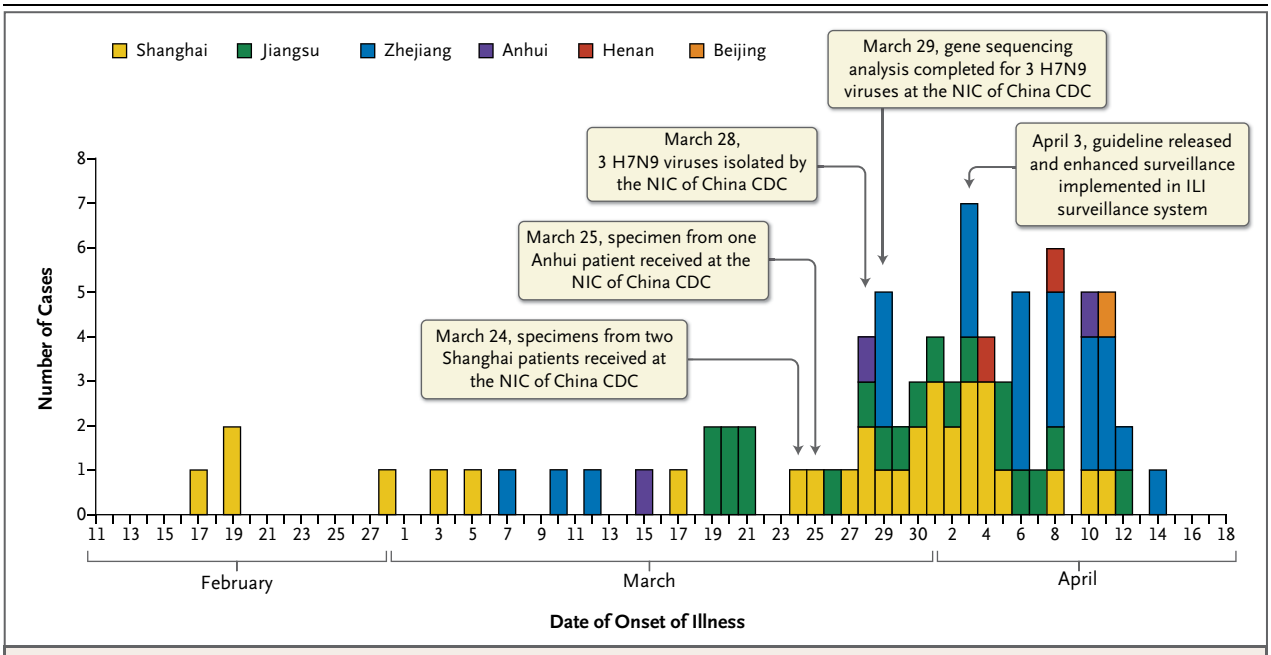

Figure 1. Date of Onset of Illness in First 82 Patients with Confirmed H7N9 Virus Infection, According to Province in China.
CDC denotes Chinese Center for Disease Control and Prevention, ILI influenza-like illness, and NIC National Influenza Center.

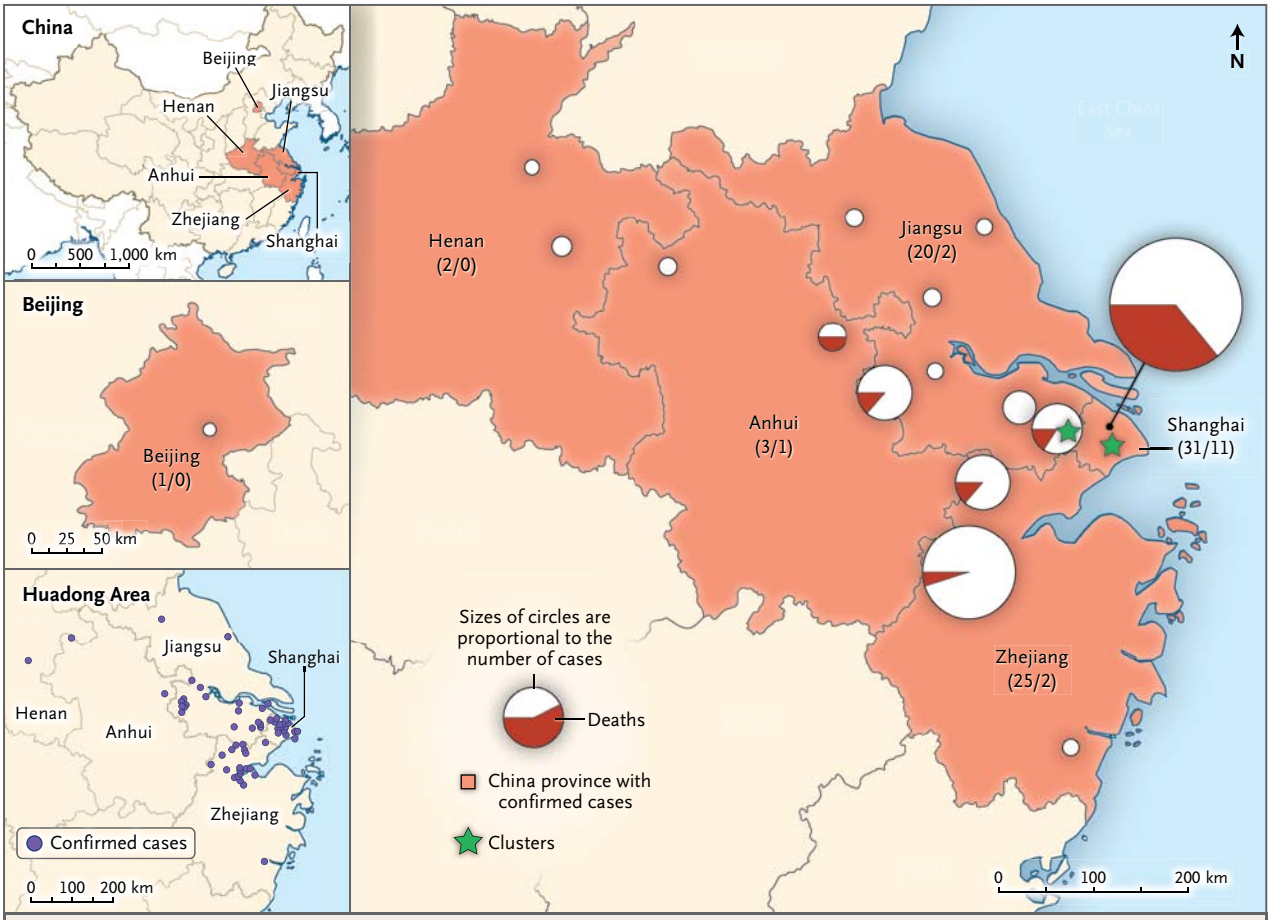

Figure 2. Geographic Distribution of 82 Confirmed and 2 Suspected Cases of H7N9 Virus Infection in China, as of April 17, 2013.
The numbers in parentheses below the names of the provinces are the number of cases/number of deaths.

(5%) worked as poultry workers: 3 slaughtered poultry at a live poultry market, and 1 transported live poultry.

A total of 81 of 82 patients with confirmed H7N9 virus infection (99%) were hospitalized. Among the 51 patients with confirmed cases for whom data were available, isolation precautions were instituted for 33 (65%) in an intensive care unit (ICU) because of severe lower respiratory tract disease. As of April 17, a total of 17 patients with confirmed H7N9 virus infection (21%) and 1 patient with suspected infection had died of acute respiratory distress syndrome (ARDS) or multiorgan failure, and 60 patients with confirmed cases and 1 with a suspected case remained critically ill; 4 with clinically mild cases had been discharged from the hospital, and 1 pediatric patient had not been admitted to the hospital. Among 82 confirmed cases of H7N9 virus infection, 7 (9%) were confirmed by means of virus isolation, 2 (2%) by means of serologic testing, and 73 (89%) by means of nucleic acid detection. Viral culture of 73 respiratory specimens that were confirmed as positive by means of real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays and diagnostic testing of specimens from suspected cases are ongoing.

Data on recent exposure to animals were available for 77 of the 82 patients with confirmed H7N9 virus infection. Of these, 59 (77%) reported a history of recent exposure to animals, (Table 1): 45 (76%) to chickens, 12 (20%) to ducks, and 4 (7%) to swine; the exposures occurred either while they were working at or visiting a live animal market. Other animals that these 59 patients reported having been exposed to included pigeons, geese, quail, wild birds, pet

Table 1. Epidemiologic Characteristics of 82 Patients with Confirmed H7N9 Virus Infection in China.

Characteristic	Patients with Confirmed Cases (N=82)
Age — yr	
Median	63.0
Interquartile range	50–73
Age <5 yr — no. (%)	2 (2)
Age ≥65 yr — no. (%)	38 (46)
Male sex — no. (%)	60 (73)
Type of residence — no. (%)	
Urban	69 (84)
Rural	13 (16)
Poultry worker — no. (%)*	4 (5)
Presence of underlying medical conditions — no./total no. (%)†	54/71 (76)
Exposure to symptomatic case patient within 2 wk before illness onset — no./total no. (%)‡	5/79 (6)
History of exposure to animals — no./total no. (%)§	59/77 (77)
Chickens	45/59 (76)
Ducks	12/59 (20)
Pigeons	8/59 (14)
Quail	1/59 (2)
Geese	1/59 (2)
Pet birds	1/59 (2)
Wild birds	6/59 (10)
Swine	4/59 (7)
Cats	2/59 (3)
Dogs	1/59 (2)
Type of exposure to animals — no./total no. (%)	
Direct contact with poultry	34/59 (58)
Direct contact with swine	2/59 (3)
Visit to live poultry market	38/59 (64)
Method used for diagnosis of H7N9 — no. (%)	
Virus isolation	7 (9)
Nucleic acid detection	73 (89)
Serologic testing¶	2 (2)

* Three poultry workers slaughtered poultry at a live poultry market, one each in Nanjing, Jiangsu province; Bozhou, Anhui province; and Zhoukou, Henan province. The other poultry worker transported live poultry in Shanghai.

† A total of 54 patients with confirmed H7N9 virus infection reported at least one underlying medical condition, including hypertension (31 patients), diabetes (14), heart disease (12), chronic bronchitis (7), hepatitis (4), smoking (4), rheumatic arthritis (4), rhinitis (2), and obstructive pulmonary emphysema, pulmonary emphysema, asthma, silicosis, cerebral infarction, lymphoma, thyroid cancer, rectal carcinoma, breast cancer, chronic nephropathy, gout, prostatitis, pregnancy, and alcoholism (1 patient each). For 11 of 82 patients with confirmed H7N9 virus infection (13%), collection of information on underlying medical condition is ongoing.

‡ Two family clusters were reported (see Section S4 in the Supplementary Appendix). One cluster included a father (with a confirmed case) and his two sons (one with a confirmed case and one with a suspected case) in Shanghai. Another cluster included a father (with a suspected case) and his daughter (with a confirmed case) in Jiangsu.

§ Among 59 case patients who reported recent exposure to animals, 52 (88%) reported a single exposure to bird or poultry, including chickens, ducks, geese, quail, pigeons, wild birds, and pet birds. The remaining 4 patients (6.8%) had multiple exposures to poultry and swine. Investigation of the history of exposure to animals is ongoing for 5 of 82 case patients (6%).

¶ The brother of the index case patient in the Shanghai family cluster and another patient in Shanghai were confirmed, with the use of a turkey red-cell hemagglutinin inhibition assay, to be seropositive for H7N9 virus antibodies, with an increase by a factor of 4 or more in antibodies in paired serum samples obtained during the acute and convalescent stages of illness.

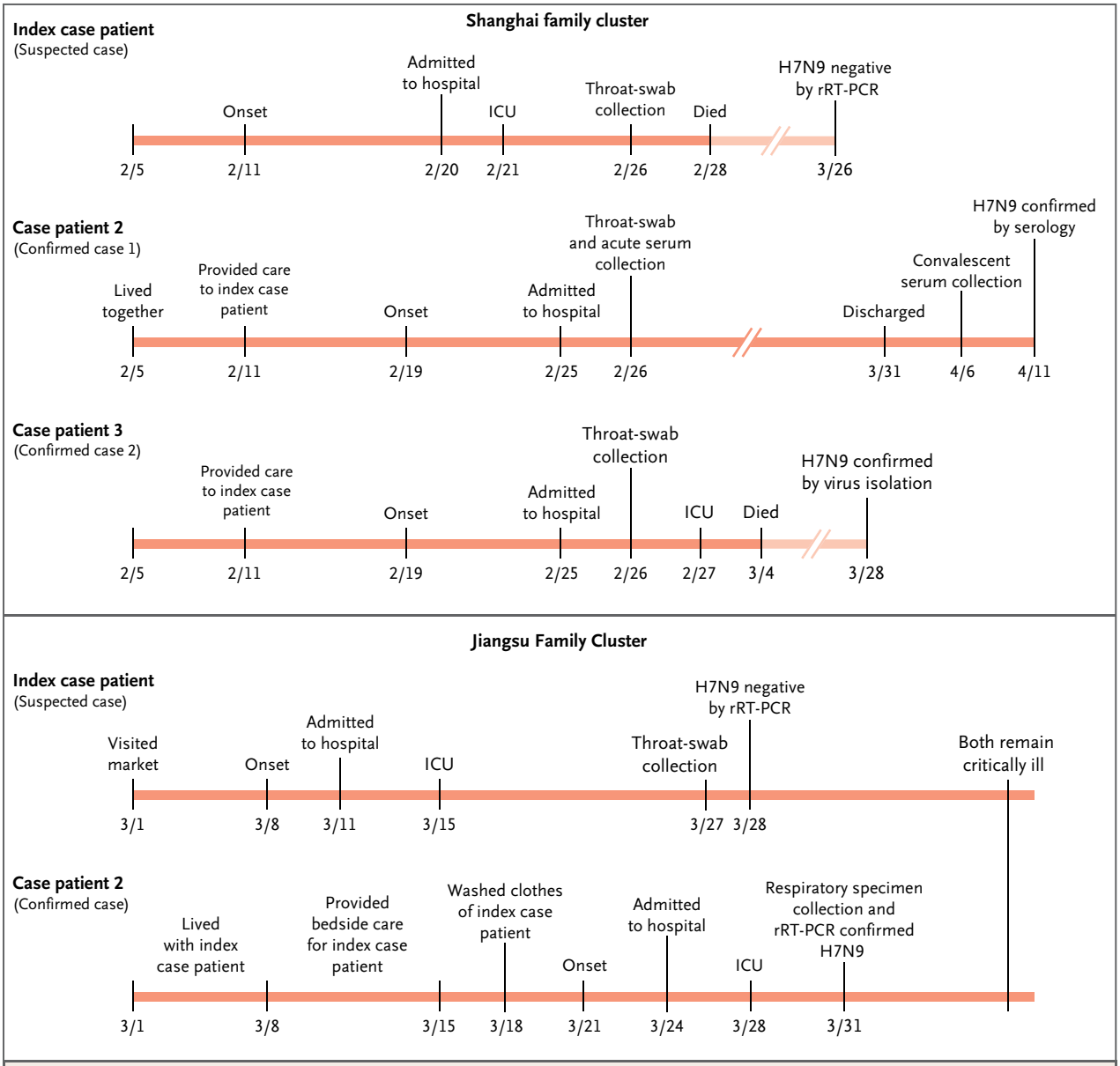

Figure 3. Timeline of Pertinent Exposures and Dates of Illness Onset in Two Family Clusters of Cases of H7N9 Virus Infection in China.
ICU denotes intensive care unit, and rRT-PCR real-time reverse-transcriptase–polymerase-chain-reaction assay.

birds, cats, and dogs. Information on a history of exposure to live animals is unclear for 5 patients with confirmed H7N9 virus infection, since the investigations are still ongoing. The estimated median incubation period in 23 patients with confirmed cases for whom detailed data on animal and environmental exposures was available was 6 days (range, 1 to 10) (Table S1 in the Supplementary Appendix).

FAMILY CLUSTERS

As of April 17, three family clusters had been identified in two provinces. Detailed exposure and timeline information are available for two family clusters that were identified early (Fig. 3, and Section S4 in the Supplementary Appendix); the investigation of one cluster in Shanghai is still ongoing. The first family cluster comprised two persons with confirmed H7N9 virus infec-

tion and one with a suspected infection. The index case patient and his father (confirmed case 2) lived in the same house, and the index patient's brother (confirmed case 1) lived with his wife nearby. After the index case patient (suspected case 1) became ill, his brother (confirmed case 1) and his father (confirmed case 2) had prolonged, close, unprotected contact with him, including eating together, providing care, and accompanying him to seek medical care before his hospitalization (Section S4 in the Supplementary Appendix). None of the three members of the cluster raised poultry or other animals, none brought live poultry into their home, and none had direct contact with sick or dead poultry. The index case patient had visited a live poultry market, purchased a chicken, observed the slaughtering process, brought the freshly killed chicken home, and prepared, cooked, and ate the chicken within 2 weeks before the onset of his illness.

Another family cluster was identified that included one person with confirmed H7N9 virus infection and one person with a suspected case (Fig. 2, and Section S4 in the Supplementary Appendix). After the father (suspected case) became ill, his daughter (confirmed case) had prolonged, close, unprotected contact with him, including eating together, providing care, and accompanying him to seek medical care before his hospital admission. She also provided unprotected bedside hospital care for her father during the period from March 11 through March 15. Diarrhea developed in the father, and the daughter washed her father's diarrhea-soiled underwear on March 18 while wearing gloves. The father had visited a live poultry market 7 days before the onset of his illness. The daughter did not raise poultry or animals at home and had not had any exposures to animals (i.e., had not brought live poultry into the home or visited a live poultry market or had any direct or indirect contact with poultry or pigs).

Table 2. Clinical Characteristics and Medical Care Timelines for 82 Patients with Confirmed H7N9 Virus Infection in China.*

Variable	Patients with Confirmed Cases (N=82)
Clinical outcome — no./total no. (%)	
Hospitalization†	81/82 (99)
ICU admission	33/51 (65)
ARDS	19/40 (48)
Death	17/82 (21)
Oseltamivir treatment — no./total no. (%)	41/64 (64)
Time from illness onset to oseltamivir treatment — days	
Median	6.0
Interquartile range	4.0–8.0
Time from illness onset to first medical care — days	
Median	1.0
Interquartile range	0–2.0
Time from illness onset to hospitalization — days	
Median	4.5
Interquartile range	3.0–6.0
Time from illness onset to ICU admission — days	
Median	7.0
Interquartile range	5.0–9.0
Time from illness onset to development of ARDS — days	
Median	8.0
Interquartile range	5.0–10.0
Time from illness onset to death — days	
Median	11.0
Interquartile range	7.0–20.0

* In the case of some characteristics, complete data were not available for all 82 patients with confirmed H7N9 virus infection. Case investigations are ongoing. ARDS denotes acute respiratory distress syndrome, and ICU intensive care unit.

† Four patients with confirmed cases had been discharged as of April 17, 2013. One 2-year-old male child with a confirmed case in Shanghai was not hospitalized, because his illness was mild; he recovered 5 days after the onset of illness.

MEDICAL CARE TIMELINES

Among the 81 patients with confirmed H7N9 virus infection for whom data were available (99% of the 82 patients with confirmed cases), the median time from the onset of illness to the first medical visit was 1 day, and patients were hospitalized a median of 4.5 days after the onset of illness (Table 2). Among 64 of the patients with available data on oseltamivir administration, 41 (64%) received oseltamivir treatment beginning a median of 6 days after the onset of illness. ARDS developed during the course of hospitalization in 19 of 40 patients with confirmed H7N9 virus infection for whom data were available (48%) after a median of 8 days, and 17 patients died a median of 11 days after the onset of illness.

CLOSE CONTACTS

As of April 17, data were available for 1689 close contacts of the 82 patients with confirmed cases in Shanghai (435 contacts), Jiangsu (448), Zhejiang (676), Anhui (100), Henan (28), and Beijing (2). Among the 678 close contacts of 33 patients

with confirmed cases for whom demographic information was available, 422 (62%) were health care workers, 134 (20%) were family member or relatives, and 122 (18%) were social contacts. As of April 17, a total of 1251 of the 1689 contacts had been followed for up for 7 days; among these close contacts (not including those in the family clusters), respiratory symptoms developed during the 7-day surveillance period in 19 (1.5%): 2 household members, 1 medical intern, 1 patient who shared a room with a confirmed case patient, and 15 health care workers (Section S5 in the Supplementary Appendix). All the throat swabs collected from these 19 ill contacts a median of 1 day (range, 0 to 7) after the onset of illness were negative for the H7N9 virus, as assessed by means of real-time RT-PCR.

DISCUSSION

An epidemiologic study of 82 confirmed cases of H7N9 virus infection in China among persons with illness onset during the period from February through April 17, 2013, indicates that the infection affected persons in a wide age spectrum and caused severe lower respiratory tract illness. To date, the mortality is 21%, but since many of patients with confirmed H7N9 virus infection remain critically ill, we suspect that the mortality may increase. Except for one family cluster with 2 confirmed cases, patients with confirmed H7N9 virus infection were epidemiologically unrelated and were identified in six areas of China. Most of the patients with confirmed H7N9 virus infection were considered to be at increased risk for complications from influenza owing to age (<5 years or ≥65 years; median age of patients with confirmed cases, 63 years) or the prevalence of certain underlying medical conditions.

Human infections with influenza A (H7) viruses have been reported sporadically and are usually associated with exposures to poultry.[10-12] Previous human cases of H7 virus infection have been characterized by mild illness (conjunctivitis or uncomplicated influenza) or moderate illness (lower respiratory tract disease) that results in hospitalization.[10,11,13,14] Only one fatal case of H7 virus infection has been reported previously; that case occurred in an adult with a highly pathogenic avian influenza A (H7N7) virus infection.[15] Many of the confirmed H7N9 case patients had critical and fatal illness, suggesting that the H7N9 virus is more virulent in humans than are other H7 viruses. The H7N9 case fatality proportion to date is lower than that for reported cases of H5N1 virus infection.[16] However, early surveillance for H7N9 cases was focused on case finding for severe lower respiratory tract illness, and since April 3, expanded testing of outpatients with influenza-like illness has identified some mild cases of illness with H7N9 virus infection. Enhanced surveillance for less severe illness with H7N9 virus infection will help to determine the clinical spectrum of the illness and the total number of cases of H7N9 symptomatic illness and to inform an understanding of the true case fatality proportion. Since this H7N9 virus appears to have emerged recently to infect humans, population immunity is expected to be low, and persons of any age may be susceptible to infection.

Although the source of the H7N9 virus infection in patients with confirmed cases who had exposure to animals cannot be verified without extensive H7N9 testing of animals, we suspect that it is likely to be infected poultry; additional studies are needed. No animal outbreaks were identified in the areas with confirmed H7N9 cases, but 77% of cases with available data occurred in patients who had exposure to live animals such as poultry or swine, including during visits to live animal markets. This raises the possibility of zoonotic H7N9 virus transmission from healthy-appearing swine or poultry to humans through direct or close contact or through exposure to environments that are contaminated with infected swine or poultry. For example, visiting a live poultry market, where avian influenza A viruses can be maintained and amplified, has been identified as a risk factor for H5N1 virus infection in Hong Kong[17] and urban China.[18,19] However, case–control studies are needed to identify risk factors for H7N9 virus infection. Until the source of H7N9 virus infection is known, implementation of control measures at live poultry markets, such as a ban on the selling of live poultry in market stalls or even market closure, poultry culling, and market disinfection — measures that have been taken to control the spread of H5N1 virus — may be considered in order to help control potential zoonotic transmission of H7N9 virus.

Follow-up prospective investigations of close contacts of patients with confirmed H7N9 virus

infection have not conclusively established human-to-human H7N9 transmission of the virus from one confirmed case to another to date. However, in two family clusters, limited human-to-human transmission of H7N9 virus after close, prolonged, unprotected contact with a symptomatic patient with suspected H7N9 virus infection remains a possibility, because specimens were not available for H7N9 testing from patients with suspected cases; one patient with a suspected case died before a specimen could be obtained, and H7N9 testing of the other patient with a suspected case is still ongoing. Similar family clusters of H5N1 cases that occurred after common poultry exposures or limited human-to-human transmission have been identified.[7,20,21] Paired serum samples are being obtained during the acute and convalescent stages of illness from contacts of case patients for further assessment of the potential for secondary human-to-human H7N9 virus transmission, including the identification of asymptomatic infections. Although the risk of human-to-human transmission of H7N9 virus appears to be low, the actual risk is currently unknown, and the Chinese national guidelines recommend implementing control measures, such as prompt isolation of the patient, active monitoring of close contacts, and implementation of standard, contact, and droplet precautions by health care personnel in hospitals. In addition, national guidelines recommend that antiviral treatment with oseltamivir should be administered as soon as possible in patients with suspected or confirmed cases of H7N9 virus infection.

The median time from the onset of illness to hospitalization among the 81 of 82 patients with confirmed H7N9 virus infection for whom data on hospitalization were available was 4.5 days, and the median time from the onset of illness to the development of ARDS among the 19 case patients with ARDS (out of 40 patients for whom data on ARDS were available) was 8 days; the corresponding median times among patients with H5N1 virus infection were 7 days and 7.5 days.[22] The median duration from the onset of illness to death among the 17 persons with confirmed cases who died was 11 days. The initial findings suggest that H7N9 virus infection can cause critical illness and fatal disease and may affect persons in a wider age range than the H5N1 virus has in China to date (Fig. S1 in the Supplementary Appendix). Patients with confirmed cases received oseltamivir antiviral treatment a median of 6 days after the onset of illness (median before April 3, 9 days), probably owing to delayed suspicion of influenza. Retrospective observational studies of influenza A (H1N1)pdm09 and H5N1 virus infections suggest that early oseltamivir treatment probably has the greatest clinical benefit but that starting treatment up to 5 days after the onset of illness may still reduce the risk of critical illness and death.[23-27] Preliminary data suggest that the H7N9 viruses isolated from humans and analyzed to date are resistant to adamantane antiviral agents and are susceptible to neuraminidase inhibitors. Early clinical suspicion of H7N9 virus infection and early administration of oseltamivir may help to reduce the severity of the disease.

Our study had several limitations. First, we did not collect detailed information from all patients on exposures, such as the times, frequency, intensity, and duration of exposures. Information on exposures is useful for estimating the incubation period after possible exposure to animals or live-animal markets and for evaluating the risk factors for H7N9 virus infection. Second, we may not have identified all the close contacts of case patients and were not able to conduct active follow-up of all contacts. As of April 17, 2013, complete follow-up data were not available for some of the close contacts. Third, we did not have a standard protocol and questionnaire to collect information from all contacts of the first 82 patients with confirmed cases. However, the China CDC has issued a guideline and protocol for field investigations of case patients and close contacts and since April 1 has provided training for personnel at all 31 provincial CDCs. This will help ensure standard data collection. Fourth, specimens were not available for H7N9 testing from some patients with suspected cases. Clinical outcomes in the 82 patients with confirmed H7N9 virus infection are reported as of April 17, 2013, and 60 case patients remain hospitalized. Paired serum samples have not been obtained from some of the contacts; no serologic testing results are available at this time, and given the fact that it is early in the investigation, more time is needed to allow for a humoral immune response in serum obtained during the convalescent period and to allow time for serologic testing to be performed.

In summary, a novel influenza A (H7N9) virus has caused severe and fatal illness in persons in six different areas of China to date. Some clinically mild cases have been identified since the surveillance was widened, suggesting that there is a wide clinical spectrum of H7N9 virus infection. The initial epidemiologic findings suggest that most confirmed H7N9 cases were epidemiologically unrelated. Follow-up investigations of contacts of patients with confirmed H7N9 virus infection suggest that the risk of secondary H7N9 virus transmission, including to health care personnel, is low at this time. However, in two family clusters that include persons with confirmed H7N9 virus infection and persons with epidemiologically linked suspected cases, limited nonsustained human-to-human H7N9 virus transmission could not be ruled out and may have occurred among blood-related family members. Enhanced surveillance for severe and mild human illness with H7N9 virus infection is needed to determine the clinical spectrum of the infection and the total number of symptomatic H7N9 infections. Case–control studies to identify risk factors and continued investigations of case patients and their contacts are indicated. Data from investigations of potential animal and environmental sources are urgently needed to inform public health control measures.

The views expressed in this article are those of the authors and do not represent the official policy of the Chinese Center for Disease Control and Prevention or the U.S. Centers for Disease Control and Prevention.

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REFERENCES

1. World Health Organization. Background and summary of human infection with influenza A(H7N9) virus — as of 5 April 2013 (http://www.who.int/influenza/human_animal_interface/update_20130405/en/).
2. *Idem*. WHO case definitions for human infections with influenza A (H5N1) virus (http://www.who.int/influenza/resources/documents/case_definition2006_08_29/en/).
3. Gao RB, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. N Engl J Med 2013. DOI: 10.1056/NEJMoa1304459.
4. Yu H, Shu Y, Hu S, et al. The first confirmed human case of avian influenza A (H5N1) in Mainland China. Lancet 2006; 367:84.
5. National Health and Family Planning Commission, People's Republic of China. Guidelines of case clinical intervention and disease control and prevention of human infection with avian influenza H7N9 virus (in Chinese) (http://www.moh.gov.cn/mohwsyjbgs/fkzs/list.shtml).
6. Yu H, Cauchemez S, Donnelly CA, et al. Transmission dynamics, border entry screening, and school holidays during the 2009 influenza A (H1N1) pandemic, China. Emerg Infect Dis 2012;18:758-66.
7. Wang H, Feng ZJ, Shu YL, et al. Probable limited human-to-human transmission of highly pathogenic avian influenza A (H5N1) virus in China. Lancet 2008; 371:1427-34.
8. Huai Y, Xiang N, Zhou L, et al. Incubation period for human cases of avian influenza A (H5N1) infection, China. Emerg Infect Dis 2008;14:1819-21.
9. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59(RR-8):1-62. [Errata, MMWR Recomm Rep 2010;59:993, 1147.]
10. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet 2004; 363:587-93.
11. Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004;10:2196-9.
12. Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. Emerg Infect Dis 2009;15:859-65.
13. Ostrowsky B, Huang A, Terry W, et al. Low pathogenic avian influenza A (H7N2) virus infection in immunocompromised adult, New York, USA, 2003. Emerg Infect Dis 2012;18:1128-31.
14. Avian influenza A/(H7N2) outbreak in the United Kingdom. Euro Surveill 2007; 12(5):E070531.2.
15. Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A 2004;101:1356-61.
16. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013 (http://www.who.int/influenza/human_animal_interface/EN_GIP_20130312CumulativeNumberH5N1cases.pdf).
17. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999;180:505-8.
18. Yu H, Feng Z, Zhang X, et al. Human influenza A(H5N1) cases, urban areas of People's Republic of China, 2005–2006. Emerg Infect Dis 2007;13:1061-4.
19. Zhou L, Liao QH, Dong LB, et al. Risk factors for human illness with avian influenza A (H5N1) virus infection in China. J Infect Dis 2009;199:1726-34.
20. Kandun IN, Wibisono H, Sedyaningsih ER, et al. Three Indonesian clusters of

H5N1 virus infection in 2005. N Engl J Med 2006;355:2186-94.
21. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005;352:333-40.
22. Yu H, Gao Z, Feng Z, et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. PLoS One 2008; 3(8):e2985.
23. Yu H, Feng Z, Uyeki TM, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis 2011;52:457-65.
24. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 2013;207:553-63.
25. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. Clin Infect Dis 2012;55: 1198-204.
26. Adisasmito W, Chan PK, Lee N, et al. Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. J Infect Dis 2010;202:1154-60.
27. Chan PK, Lee N, Zaman M, et al. Determinants of antiviral effectiveness in influenza virus A subtype H5N1. J Infect Dis 2012;206:1359-66.