A novel strain of influenza \( A(H7N9) \) virus has emerged in China and is causing mild to severe clinical symptoms in infected humans. Some case-patients have died. To further knowledge of this virus, we report the characteristics and clinical histories of 4 early case-patients.

Clinical Findings for Early Human Cases of Influenza \( A(H7N9) \) Virus Infection, Shanghai, China

Shuihua Lu,1 Yufang Zheng,1 Tao Li,1 Yunwen Hu,1 Xinian Liu, Xiaohong Xi, Qingguo Chen, Qingle Wang, Ye Cao, Yanbing Wang, Lijun Zhou, Douglas Lowrie, and Jing Bao

A viian influenza \( A(H7N9) \) virus normally circulates among birds; however, human infections with this virus were confirmed in China on March 31, 2013 (1,2). To help identify the best treatment strategies for influenza \( A(H7N9) \) virus infection, we summarized the clinical characteristics and outcomes for the first 4 patients who were transferred to Shanghai Public Health Clinical Center (SHPHCC) for treatment of influenza \( A(H7N9) \) virus infection. For each case, infection was confirmed by the Shanghai Municipal Centers for Disease Control and Prevention.

Case Reports

Clinical features of the 4 case-patients are listed in Table 1. All case-patients were 58- to 73-year-old married men, farmers or retirees, and long-term residents of Shanghai (Fengxian, Baoshan, Songjiang, and Pudong districts, respectively). Case-patient 1 had a history of coronary heart disease and hepatic schistosomiasis; case-patient 2 had no history of chronic disease; case-patient 3 had a history of hypertension and gout; and case-patient 4 had a history of hypertension and repetitive cough for >10 years during spring and autumn.

Case-patient 1 raised chickens at home. Case-patients 2–4 had no clear history of close contact with poultry; however, each had visited various farmers’ markets that sold live poultry. None of the patients raised pigeons or live in or near a heavily pigeon-infested area.

Before being transferred to SHPHCC on April 6, 2013 (patients 1 and 2) and April 7, 2013 (patients 3 and 4), the 4 patients had been treated in local hospitals; infection with influenza \( A(H7N9) \) virus had been confirmed by real-time reverse transcription PCR of nasopharyngeal swab samples before transfer. The case-patients had cough and fever and had been expectorating sputum for ≈6–7 days before admittance to SHPHCC. In addition, all had experienced cold-like symptoms and fatigue before influenza-like symptoms developed. Case-patient 4 had cough and fever for 18 and 10 days, respectively, before being transferred to SHPHCC; his case was the most serious of the 4, and the disease progressed rapidly after he was transferred to SHPHCC.

Total leukocyte counts for case-patients 1–4 were within or slightly below reference values: 5.50, 5.95, 3.50, and 4.60 × 10^9/L, respectively (reference value 4.00–10.00 × 10^9/L). The proportions of neutrophils were normal or slightly high: 79.6%, 62.6%, 72.4%, and 68.0%, respectively (reference value 50.0%–70.0%). Laboratory test results at admission are shown in Table 2. Radiograph findings mainly included ground-glass opacity and consolidation (Figures 1, 2; online Technical Appendix Figures 1, 2, wwwnc.cdc.gov/EID/article/19/7/13-0612-Techapp1.pdf). Computed tomography (CT) scans and radiograph findings, along with clinical manifestations and laboratory test results, helped establish early diagnoses.

To ensure proper treatment/management of the patients, an emergency team was established; the team followed the procedures shown in online Technical Appendix Figure 3. All 4 case-patients were administered antimicrobial drugs and the antiviral drug oseltamivir. Case-patient 1 began treatment 6 days after the onset of hypoxia, when large areas of lung inflammation were seen on radiographs. Case-patient 2 was treated 4 days after the onset of fever, when CT scan results revealed inflammation in the left upper lung lobe. Case-patient 3 began treatment 4 days after the onset of cough, sputum, and shortness of breath and after CT scan results revealed inflammation in the left lower lung lobe. Case-patient 4 began treatment 16 days after the onset of high fever, dyspnea on exertion, and hypoxemia. Additional details for each patient are included below, and results of viral testing done at admission and 5 days later are shown in online Technical Appendix Table 1. Disease characteristics for infections caused by influenza virus

1These authors contributed equally to this article.
renal function insufficiency at admission. On April 11, 11

Case-patient 1 was receiving noninvasive ventilator-assisted breathing when he arrived at SHPHCC. His oxygen saturation remained at ≈95%, and he was given continuous intravenous dopamine infusion. He had acute respiratory failure, coronary heart disease (stage 2 heart failure), and renal function insufficiency at admission. On April 11, 11 days after the onset of the symptoms and 2 hours after endotracheal intubation and mechanical ventilation began, he died from respiratory failure.

Case-patient 2 arrived at SHPHCC with a nasal cannula inserted to maintain oxygen saturation at 95%. His general condition improved steadily after commencing antiviral drug treatment, and he was discharged 18 days after illness onset.

Table 1. Clinical characteristics and treatment outcomes for 4 patients with early cases of influenza A(H7N9) virus infection, Shanghai, China

| Characteristic/treatment | 1 | 2 | 3 | 4 |
|--------------------------|---|---|---|---|
| Age, y/sex               | 73/M | 65/M | 67/M | 58/M |
| Occupation               | Farmer | Retiree | Retiree | Retiree |
| Location (district) in Shanghai | Fengxian | Baoshan | Songjiang | Pudong |
| Disease history          | Coronary heart disease; chronic hepatic schistosomiasis | Hypertension; articular gout; benign prostatic hyperplasia | None | Hypertension |
| History of poultry exposure | At home | At live poultry markets | At live poultry markets | At live poultry markets |
| Date of last visit to live poultry market | 2013 Mar 31 | 2013 Apr 1 | 2013 March 30 | 2013 March 28 |
| Date of symptom onset    | 2013 Apr 6 | 2013 Apr 6 | 2013 Apr 7 | 2013 Apr 7 |
| Date of infection confirmation | 2013 Apr 6 | 2013 Apr 6 | 2013 Apr 7 | 2013 Apr 7 |
| Date admitted to SHPHCC  | 2013 Mar 31 | 2013 Apr 1 | 2013 March 30 | 2013 March 28 |
| Clinical symptoms present when admitted SHPHCC | 6 d of fever (maximum temperature 39.3°C) and shortness of breath | 6 d of fever (maximum temperature 39.3°C) and 2 d of cough | 8 d of fever (maximum temperature 39.7°C) and cough | 18 d of cough, 10 d of fever (maximum temperature 39.7°C), and 5 d with shortness of breath |
| Chest radiograph or CT findings | Bilateral GGO | Bilateral GGO | GGO in left lingular lobe and left inferior lobe | Extensive infiltrates, with pleural effusion, in lung (bilateral) |
| Antiviral drug treatment | Oseltamivir (150 mg/bid) on days 7–12 of illness | Oseltamivir (75 mg/bid) on days 4–17 of illness | Oseltamivir (75 mg/bid) on days 6–21 of illness | Oseltamivir (75 mg/bid) on days 16–23 of illness; oseltamivir (150 mg/bid) on days 17–32 of illness |
| Antibacterial drug treatment | Moxifloxacin on days 7–12 of illness | Ceftriaxone on days 4–5 of illness; moxifloxacin on days 6–17 of illness | Azithromycin on days 5–9 of illness; ceftriaxone on days 1–5 of illness; moxifloxacin on days 14–21 of illness | Moxifloxacin on days 18–21 of illness; piperacillin and tazobactam on days 18–21 of illness; meropenem on days 21–34 of illness; linezolid on days 25–32 of illness |
| Glucocorticoid treatment | Methylprednisolone (40 mg/d) on days 7–12 of illness | No | Methylprednisolone (40 mg/d) on days 5–12 of illness | Methylprednisolone (40 mg/d) on days 16–37 of illness |
| Immunoglobulin treatment | Yes, on days 7–12 of illness | Yes, on days 6–12 of illness | Yes, on days 5–8 of illness | Yes, on days 16–37 of illness |
| ECMO treatment           | Yes | No | No | No |
| Oxygen use               | Noninvasive ventilation on days 6–12 of illness | Oxygen inhalation through nasal tube on days 4–17 of illness | Oxygen inhalation through nasal tube on days 7–20 of illness | On day 25 of illness Noninvasive ventilation on days 17–19 of illness |
| Endotracheal intubation and mechanical ventilation | Yes, on day 12 of illness | Yes, on day 12 of illness | Yes, on day 12 of illness | Yes, on days 19–32 of illness |
| Status as of 2013 Apr 21 | Died on day 12 of illness | Recovered, discharged on day 18 after illness onset | Recovered, discharged on day 21 after illness onset | Condition worsened, receiving invasive breath machine and ECMO treatment |

*NA, not applicable; SHPHCC, Shanghai Public Health Clinical Center; CT, computed tomography scan; GGO, ground-glass opacity; bid, 2 times a day; ECMO, extracorporeal membrane oxygenation.*
Case-patient 3 arrived at SHPHCC with a nasal cannula inserted to maintain oxygen saturation at 95%. He had a history of hypertension and gout. He was treated with oseltamivir, antimicrobial drugs, and steroids to suppress lung inflammation. His condition improved substantially, and he was discharged 21 days after illness onset.

Case-patient 4 arrived at SHPHCC in critical condition: oxygen saturation was 88%, and he had shortness of breath (30–35 breaths/min). He was immediately given noninvasive mechanical ventilation. One day after admission, his condition deteriorated; multiple organ dysfunctions in lung and kidney developed. His condition continued to deteriorate despite active treatment with oseltamivir and antimicrobial drugs. Severe hypoxemia developed. Two days after admission, invasive mechanical ventilation and then extracorporeal membrane oxygenation were implemented. The patient was still in critical condition on April 21, 2013.

Discussion

Clinical manifestations of disease in the 4 case-patients were consistent with those reported for other persons infected with influenza A(H7N9) virus (3). Case-patients 1 and 4 had a more severe disease course than case-patients 2 and 3. All patients sought medical care for unresolved fever, cough, expectoration of sputum, and shortness of breath. The severe cases progressed rapidly: body temperature was mostly sustained ≥39°C, and breathing was difficult and sometimes accompanied by hemoptysis. A rapid progression of acute respiratory distress syndrome

| Laboratory variable                | 1         | 2         | 3         | 4         | Reference value |
|-----------------------------------|-----------|-----------|-----------|-----------|-----------------|
| Leukocyte count, × 10⁹/L          | 2.95      | 3.74      | 2.89      | 5.38      | 4.00–10.00      |
| % Neutrophils                     | 80.4      | 76.7      | 78.6      | 94.6      | 50.0%–70.0%     |
| % Lymphocytes                     | 13.5      | 18.2      | 15.4      | 2.4       | 20.0%–40.0%     |
| Platelet count, × 10⁹/L           | 71        | 82        | 172       | 75        | 85–303          |
| Aspartate aminotransferase, U/L   | 86        | 77        | 45        | 172       | 8–40            |
| Lactate dehydrogenase, U/L        | 886       | 492       | 209       | 906       | 109–245         |
| Creatine phosphokinase, U/L       | 170       | 1,854     | 170       | 772       | 38.00–174       |
| Creatine kinase isoenzyme MB, U/L | 18        | 31        | 7         | 22        | 0–24            |

Table 2. Laboratory findings at admission for 4 patients with early cases of influenza A(H7N9) virus infection, Shanghai, China

Figure 1. Chest computed tomography (CT) scan and radiograph images of patient (case-patient 1) in a study of 4 persons with early cases of influenza A(H7N9) virus infection, Shanghai, China. Images were taken 1, 5, 7, and 11 days after illness onset. A, B) CT scan images on day 1, showing bilateral pleural effusion but no obvious lesions. C) CT scan image on day 5, showing extensive ground-glass opacity and consolidation. D, E) x-ray images on days 7 and 11, respectively, showing reduced light transmittance on both sides of the lung.
Human Influenza A(H7N9) Virus Infection, China

occurred in case-patients 1 and 4, along with mediastinal emphysema, shock, disturbed consciousness, and acute kidney injury. No close contacts of the 4 patients have had signs or symptoms of infection.

The currently available drug treatment for influenza A(H7N9) virus infection is neuraminidase inhibitors (e.g., oseltamivir). Their early use may be recommended (10) but is not always achieved. Case-patient 4 only began neuraminidase inhibitors 16 days after the onset of symptoms, by which time he was in a severe condition. Case-patient 1 was treated with oseltamivir 6 days after the onset of symptoms and, despite treatment, died 6 days after admission to SHPHCC. Earlier, higher doses combined with continuous treatment might improve patient outcomes (5). On the basis of clinical judgment, we now use 150 mg of oseltamivir twice daily for severe cases, monitoring for toxicity.

The benefits of oseltamivir treatment of influenza A(H7N9) virus infections are debatable; for example, case-patients 2 and 3 remained positive for the virus after 9–11 days of oseltamivir treatment (online Technical Appendix Table 1). Thus, it is essential to determine whether the virus has developed resistance to oseltamivir. Ineffectiveness of the oral oseltamivir formulations may also have contributed to treatment failure, especially for case-patients 1 and 4: the drug may not have been well absorbed, especially by patients in severe condition. If available in the future, systemic delivery of oseltamivir may be superior.

Of the 4 patients reported here, only case-patient 1 died shortly after admission to SHPHCC. He is also the only patient who had close contact with chickens. However, it is not clear that this contact contributed to the rapid progression of disease in case-patient 1, especially given the fact that case-patient 4, who is still in critical condition, also had rapid progression of disease. The other patients did not raise birds at home, but they visited live poultry markets.

Prompt and early communication of the clinical features of persons infected with avian influenza A(H7N9) virus is crucial to the development of effective treatment strategies (6). Research to understand the transmission pattern and effective control of this virus is urgently needed (7–9).

Acknowledgment

We thank Thomas Marcinko for his invaluable help editing the manuscript.

This study was funded in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services (contract no. HH-SN272200800014C).

Dr Lu is director of the Respiratory Department, SHPHCC, and is in charge of treatment and management of influenza A(H7N9) virus–infected patients. His primary interest is infectious diseases, especially tuberculosis in children.

References

1. Parry J. H7N9 avian flu kills seven and infects 23 in China. BMJ. 2013;346:f2222. http://dx.doi.org/10.1136/bmj.f2222
2. Parry J. H7N9 avian flu infects humans for the first time. BMJ. 2013;346:f2151. http://dx.doi.org/10.1136/bmj.f2151
3. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. N Engl J Med. 2013 [Epub ahead of print]. http://dx.doi.org/10.1056/NEJMoa1304459
4. Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA. 2009;302:1880–7. http://dx.doi.org/10.1001/jama.2009.1536
5. White NJ, Webster RG, Govorkova EA, Uyeki TM. What is the optimal therapy for patients with H5N1 influenza? PLoS Med. 2009;6:e1000091. http://dx.doi.org/10.1371/journal.pmed.1000091
6. Uyeki TM, Cox NJ. Global concerns regarding novel influenza A (H7N9) virus infections. N Engl J Med. 2013 [Epub ahead of print]. http://dx.doi.org/10.1056/NEJMmp1304661
7. Fauci AS, Collins FS. Benefits and risks of influenza research: lessons learned. Science. 2012;336:1522–3. http://dx.doi.org/10.1126/science.1224305

Figure 2. Chest computed tomography scan images of patient (case-patient 2) in a study of 4 persons with early cases of influenza A(H7N9) virus infection, Shanghai, China. A) Image taken 6 days after illness onset shows ground-glass opacity in the left lower and right upper lobes. B) Image taken 16 days after illness onset shows absorption of ground-glass opacity.
8. Patterson AP, Tabak LA, Fauci AS, Collins FS, Howard S. Research funding. A framework for decisions about research with HPAI H5N1 viruses. Science. 2013;339:1036–7. http://dx.doi.org/10.1126/science.1236194

9. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. N Engl J Med. 2013;368:1251–5. http://dx.doi.org/10.1056/NEJMsb1209510

Address for correspondence: Shuihua Lu, Shanghai Public Health Clinical Center, 2901 Caolong Rd, Jinshan, Shanghai 201508, Peoples’ Republic of China; email: tubercle@shaphc.org

Search past issues of EID at wwwnc.cdc.gov/eid
Clinical Findings for Early Human Cases of Influenza A(H7N9) Virus Infection, Shanghai, China

Technical Appendix

Technical Appendix Table 1. Virus detection in 4 patients with influenza A(H7N9) virus infection, Shanghai, China*

| Case-patient | No. days using oseltamivir | Virus detected | Day of illness | No. days using oseltamivir | Virus detected |
|--------------|---------------------------|----------------|----------------|---------------------------|----------------|
| 1            | 1                         | Yes            | 6              | 12                        | Yes            |
| 2            | 2                         | Yes            | 5              | 12                        | No             |
| 3            | 4                         | Yes            | 8              | 15                        | No             |
| 4            | 2                         | Yes            | 18             | 25                        | Yes            |

*Patients were admitted to Shanghai Public Health Clinical Center for treatment after confirmation of infection.

Technical Appendix Table 2. Comparison of H1N1, N5N1, and H7N9 in terms of epidemiology, symptoms, chest x-ray images, and disease prognosis

| Variable                | H1N1                                                                 | H5N1                                                                 | H7N9                                                                 |
|-------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| Epidemiology            | Patients as the main source of infection                              | History of environmental exposure to avian influenza                  | With or without history of environmental exposure to avian influenza |
| Symptoms                | Cough, expectoration, polypnea, and poor appetite; main signs were moist rales and rough breathing sounds in lungs | Fever, the whole body muscle aches, fatigue, cough, purulent sputum, sometimes with blood or pus, chest pain, diarrhea | Fever, whole body muscle aches, fatigue, cough, purulent sputum, sometimes with blood or pus, chest pain, diarrhea |
| Chest x-ray images      | Pneumonia, with or without pleural effusion                           | Pulmonary effusion, with or without pleural effusion                 | Pulmonary effusion, with or without pleural effusion                 |
| Disease prognosis       | Generally good prognosis                                               | Poor prognosis                                                       | Unknown                                                              |

Technical Appendix Figure 1. Chest computed tomography scan images of patient 3, taken on days 6, 8, and 16 after the onset of illness. A) Only a little ground-glass opacity is present in the left upper lobe on
day 6. B) On day 8, the area of ground-glass opacity was enlarged, as seen in the left lingular and inferior lobes. C) Some absorption of the lesions was seen on day 16.

Technical Appendix Figure 2. Chest computed tomography scan and radiograph images of patient 4, taken on days 21, 24, and 28 after the onset of illness. A) The computed tomography scan image shows extensive bilateral lung infiltrates on day 21. B) The radiograph image shows areas of low light transmittance on both sides of the lung on day 24. C) The radiograph image shows larger areas of low light transmittance on day 28.

Technical Appendix Figure 3. Procedures followed by an emergency team that was established at Shanghai Public Health Clinical Center (SHPHCC) for managing patients admitted for treatment of
confirmed influenza A (H7N9) virus infection, Shanghai, China. In brief, infection was confirmed and SHPHCC was notified before patients were transferred to the Center. Upon admission to SHPHCC, patients were evaluated thoroughly, and the disease condition was assessed. On the basis of the clinical diagnoses and results of routine laboratory tests, a consensus for managing, monitoring, and treating individual patients was established by a medical team composed of the chief physician in the SHPHCC intensive care unit, a chief physician in respiratory diseases, a chief anesthetist, and a chief physician in infectious diseases.