Asymptomatic, Mild, and Severe Influenza A(H7N9) Virus Infection in Humans, Guangzhou, China

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Targeted surveillance for influenza A(H7N9) identified 24 cases of infection with this virus in Guangzhou, China, during April 1, 2013–March 7, 2014. The spectrum of illness ranged from severe pneumonia to asymptomatic infection. Epidemiologic findings for 2 family clusters of infection highlight the importance of rigorous close contact monitoring.

During February–May 2013, the initial outbreak of human infection with avian influenza A(H7N9) virus in China resulted in 133 cases (1). Influenza A(H7N9) virus reemerged in southern China in October 2013 and had caused 85 laboratory-confirmed cases of infection in Guangdong Province as of March 7, 2014. In response to the outbreak, targeted surveillance programs were established in April 2013 in Guangzhou, the provincial capital of Guangdong Province. Here, we report results of this surveillance program through early 2014.

The Study

Since 2004, all clinical facilities in Guangzhou (population 13 million in 2013) have been required by the China National Health and Family Planning Commission to report any patient who meets the criteria of having pneumonia of unknown etiology (PUE): fever ($\geq 38^\circ C$), radiologic characteristics consistent with pneumonia, low-normal leucocyte count or low lymphocyte count in early-stage disease, and no alternative etiology (2). Upper or lower respiratory samples from these patients are collected for identification of possible causative pathogens. In response to the influenza A(H7N9) outbreak, PUE surveillance was enhanced in April 2013 by implementing laboratory testing specific for influenza A(H7N9) virus (3). Specimens are initially screened for influenza A and B viruses by real-time reverse transcription PCR (rRT-PCR); samples positive for influenza A are then subtyped as H1N1, H3N2, H5N1, or H7N9.

Surveillance for influenza-like illness (ILI) was initially conducted in 4 sentinel hospitals in Guangzhou and expanded to 19 hospitals in November 2013. Each hospital collects 10–20 convenience throat swab specimens weekly from ILI patients visiting the hospitals within 3 days of illness onset. The same laboratory screening protocols were adopted as for PUE surveillance.

Surveillance for influenza A(H7N9) virus was established in 24 live poultry markets (LPMs) in April 2013 and expanded to 42 LPMs in November 2013, covering all 12 districts in Guangzhou. From each LPM, 10–30 environmental samples are collected biweekly and tested by rRT-PCR. When human influenza A(H7N9) infection is confirmed, additional environmental sampling from epidemiologically linked LPMs is immediately launched to trace the possible source of infection. All poultry workers linked to influenza A(H7N9) virus–contaminated LPMs (i.e., LPMs with $\geq 1$ virus-positive environmental samples identified) are placed under medical observation for 7 days. Throat swab specimens are collected within 24 hours for detection of influenza A(H7N9) infection and second swab specimens are collected if symptoms appear.

Close contacts of influenza A(H7N9) case-patients are defined as any family member who shares residence, social contacts who visit, and health care workers who provide medical services without effective personal protection (4) during the period from 1 day before illness onset to isolation (5). All close contacts are monitored for 7 days for any symptoms. Pared serum samples, tested by hemagglutinin inhibition assay (6), and throat swab specimens are collected to detect possible secondary cases.

From April 1, 2013, through March 7, 2014, a total of 47,937 patients with pneumonia were reported in Guangzhou (Table 1). Of these, 1,923 (4.0%) met PUE criteria, and respiratory specimens were collected and tested. An influenza A(H7N9) case in Guangzhou was confirmed on January 10, 2014 (Figure 1); since then, an additional 15 cases with PUE were confirmed as influenza A(H7N9) case-patients. All were adults; 11 (69%) were $\geq 60$ years of age. Recent poultry exposure history was available for 14 (88%) patients (Table 2).

During the same period (April 1, 2013–March 7, 2014), a total of 4,149 throat swab specimens were collected from 349,712 ILI patients (Table 1); 3 (0.1%) specimens were positive for influenza A(H7N9) virus. All 3 patients were young urban residents who had mild upper respiratory symptoms.
symptoms (Table 2). As a safety measure, these patients were isolated and treated with oseltamivir. All 3 patients recovered quickly (within 5–7 days) and were discharged after test results for throat swab samples were negative for 2 successive days.

During April–October 2013, 3 of 3,355 environmental samples collected from 24 LPMs were positive for influenza A(H7N9) virus, all on May 16. In contrast, of the 5,220 samples collected from 48 LPMs during November 2013 through March 7, 2014, a total of 141 (2.7%) samples were positive (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/20/9/14-0424-Techapp1.pdf). A total of 375 poultry workers from 24 influenza A(H7N9) virus–contaminated LPMs were recruited and monitored, and

| Year, wk | No. patients with pneumonia | No. (%) patients with PUE | No. confirmed influenza A(H7N9) infections | No. patients with ILI | No. (%) samples tested | No. confirmed influenza A(H7N9) infections |
|----------|----------------------------|---------------------------|-------------------------------------------|----------------------|-----------------------|------------------------------------------|
| 2013     |                            |                           |                                           |                      |                       |                                          |
| 14       | 951                        | 22 (2.3)                  | 0                                         | 8,089                | 47 (0.6)              | 0                                        |
| 15       | 996                        | 28 (2.9)                  | 0                                         | 8,555                | 65 (0.8)              | 0                                        |
| 16       | 1,021                      | 36 (3.5)                  | 0                                         | 8,698                | 55 (0.6)              | 0                                        |
| 17       | 1,087                      | 44 (4.1)                  | 0                                         | 8,759                | 63 (0.7)              | 0                                        |
| 18       | 1,118                      | 48 (4.3)                  | 0                                         | 9,852                | 43 (0.4)              | 0                                        |
| 19       | 1,146                      | 62 (5.4)                  | 0                                         | 8,682                | 68 (0.8)              | 0                                        |
| 20       | 1,238                      | 65 (5.4)                  | 0                                         | 9,621                | 55 (0.6)              | 0                                        |
| 21       | 1,197                      | 55 (4.6)                  | 0                                         | 10,248               | 64 (0.6)              | 0                                        |
| 22       | 1,121                      | 48 (4.3)                  | 0                                         | 11,264               | 83 (0.7)              | 0                                        |
| 23       | 1,166                      | 41 (3.5)                  | 0                                         | 9,546                | 82 (0.9)              | 0                                        |
| 24       | 1,041                      | 37 (3.6)                  | 0                                         | 9,962                | 81 (0.8)              | 0                                        |
| 25       | 1,075                      | 42 (3.9)                  | 0                                         | 8,910                | 96 (1.1)              | 0                                        |
| 26       | 1,032                      | 35 (3.4)                  | 0                                         | 7,735                | 68 (0.9)              | 0                                        |
| 27       | 976                        | 31 (3.2)                  | 0                                         | 7,431                | 80 (1.1)              | 0                                        |
| 28       | 922                        | 28 (3.0)                  | 0                                         | 7,567                | 83 (1.1)              | 0                                        |
| 29       | 945                        | 26 (2.8)                  | 0                                         | 7,306                | 80 (1.1)              | 0                                        |
| 30       | 908                        | 28 (3.1)                  | 0                                         | 6,998                | 82 (1.2)              | 0                                        |
| 31       | 887                        | 20 (2.3)                  | 0                                         | 7,824                | 76 (1.0)              | 0                                        |
| 32       | 911                        | 17 (1.9)                  | 0                                         | 7,484                | 74 (1.0)              | 0                                        |
| 33       | 848                        | 19 (2.2)                  | 0                                         | 7,176                | 82 (1.1)              | 0                                        |
| 34       | 925                        | 11 (1.2)                  | 0                                         | 8,018                | 85 (1.1)              | 0                                        |
| 35       | 883                        | 16 (1.8)                  | 0                                         | 8,186                | 84 (1.0)              | 0                                        |
| 36       | 856                        | 11 (1.3)                  | 0                                         | 8,768                | 85 (1.0)              | 0                                        |
| 37       | 833                        | 13 (1.6)                  | 0                                         | 9,549                | 86 (0.9)              | 0                                        |
| 38       | 821                        | 12 (1.5)                  | 0                                         | 8,788                | 82 (0.9)              | 0                                        |
| 39       | 773                        | 14 (1.8)                  | 0                                         | 7,217                | 73 (1.0)              | 0                                        |
| 40       | 844                        | 17 (2.0)                  | 0                                         | 6,448                | 68 (1.1)              | 0                                        |
| 41       | 755                        | 12 (1.6)                  | 0                                         | 5,513                | 63 (1.1)              | 0                                        |
| 42       | 721                        | 10 (1.4)                  | 0                                         | 5,284                | 79 (1.5)              | 0                                        |
| 43       | 733                        | 16 (2.2)                  | 0                                         | 5,746                | 73 (1.3)              | 0                                        |
| 44       | 768                        | 18 (2.4)                  | 0                                         | 6,599                | 70 (1.1)              | 0                                        |
| 45       | 803                        | 26 (3.2)                  | 0                                         | 5,655                | 75 (1.3)              | 0                                        |
| 46       | 846                        | 28 (3.3)                  | 0                                         | 4,234                | 83 (2.0)              | 0                                        |
| 47       | 815                        | 42 (5.2)                  | 0                                         | 5,054                | 82 (1.6)              | 0                                        |
| 48       | 859                        | 40 (4.7)                  | 0                                         | 4,683                | 95 (2.0)              | 0                                        |
| 49       | 935                        | 46 (4.9)                  | 0                                         | 5,493                | 101 (1.8)             | 0                                        |
| 50       | 947                        | 51 (5.4)                  | 0                                         | 5,488                | 112 (2.0)             | 0                                        |
| 51       | 1,004                      | 43 (4.3)                  | 0                                         | 4,151                | 117 (2.8)             | 0                                        |
| 52       | 1,066                      | 52 (4.9)                  | 0                                         | 4,840                | 119 (2.5)             | 0                                        |

| 2014     |                            |                           |                                           |                      |                       |                                          |
| 01       | 1,124                      | 62 (5.5)                  | 0                                         | 6,497                | 113 (1.7)             | 0                                        |
| 02       | 1,091                      | 70 (6.4)                  | 1                                         | 7,313                | 121 (1.7)             | 0                                        |
| 03       | 1,198                      | 79 (6.6)                  | 3                                         | 6,401                | 126 (2.0)             | 0                                        |
| 04       | 1,257                      | 91 (7.2)                  | 0                                         | 6,089                | 118 (1.9)             | 0                                        |
| 05       | 1,286                      | 86 (6.7)                  | 1                                         | 6,048                | 105 (1.7)             | 1                                        |
| 06       | 845                        | 32 (3.8)                  | 1                                         | 4,656                | 68 (1.5)              | 1                                        |
| 07       | 1,036                      | 86 (8.3)                  | 5                                         | 4,172                | 98 (2.4)              | 1                                        |
| 08       | 1,122                      | 70 (6.2)                  | 4                                         | 4,340                | 113 (2.6)             | 0                                        |
| 09       | 1,123                      | 77 (6.9)                  | 1                                         | 6,850                | 111 (1.6)             | 0                                        |
| 10       | 1,084                      | 63 (5.8)                  | 1                                         | 5,925                | 117 (2.0)             | 0                                        |
| Total    | 47,934                     | 1923 (4.0)                | 16                                        | 349,712              | 4,149 (1.2)           | 3                                        |

*Real-time reverse transcript PCR testing for influenza A(H7N9) virus was implemented in April 1, 2013 (2013 week 14). Samples were collected from all patients with PUE and were laboratory tested. PUE, pneumonia of unknown etiology; ILI, influenza-like illness.
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381 throat swab specimens were collected; repeat specimens were collected from 6 workers who showed symptoms. Asymptomatic influenza A(H7N9) virus infection was detected in 1 worker who managed a live poultry stall and had daily direct contact with live poultry. Two environmental samples collected from his stall on January 27, 2014, and a throat swab sample collected from the worker on January 28 were positive for influenza A(H7N9) virus. The worker was isolated, but test results for 3 consecutive throat swab specimens collected on January 30 and 31 and February 6 were negative, and in the absence of any symptoms or abnormal chest radiograph findings, he was discharged.

A total of 361 pairs of serum samples and 411 throat swab specimens were collected from 384 close contacts of influenza A(H7N9) case-patients; 2 family clusters were detected. In family cluster 1 (Figure 2), influenza A(H7N9) infection was laboratory confirmed in the index case-patient on January 10 and in 1 close contact (his daughter) on January 14 by positive test results on 2 throat swab specimens. The daughter showed mild respiratory symptoms and recovered quickly. She had no known history of poultry exposure before illness onset but had close, prolonged, and unprotected contact with her sick father. In family cluster 2, the index case-patient slaughtered a live chicken on February 1, became ill on February 3, and had influenza A(H7N9) infection laboratory confirmed on February 10. Three asymptomatic close family contacts of this patient had influenza A(H7N9) infection confirmed by a 4-fold rise in HI titer, although test results on throat swab specimens were negative. All 3 of these contacts had been involved in buying, slaughtering, or handling chickens and had close and unprotected contact with the index case-patient before he was isolated (Figure 2).

Conclusions

Human infection with influenza A(H7N9) virus has been characterized by severe illness, in particular, rapidly progressive pneumonia and acute respiratory distress syndrome (7). However, the 21 case-patients with laboratory-confirmed influenza A(H7N9) that we identified in Guangzhou showed a wider spectrum of illness, ranging from severe pneumonia to mild ILI to asymptomatic infection. Clinical signs and symptoms differed notably across age groups; all mild cases occurred in those <20 years of age, whereas most severe cases occurred in older
patients, similar to findings from previous studies (8,9). The age variances may be attributed to more frequent poultry exposure, more co-existing chronic diseases, or delayed medical admission and antiviral treatment among older patients.

Evidence shows the potential for influenza A(H7N9) virus transmission from person to person (10,11). In particular, epidemiologic findings of the father-daughter cluster indicate that person-to-person transmission may occur among family members after prolonged and intimate contact, consistent with findings in several other family clusters (8,12,13). However, no widespread mild influenza A(H7N9) infection was detected through ILI surveillance, which indicates that the likelihood of community-level transmission is low.

Subclinical influenza A(H7N9) virus infections of poultry workers have been identified by serologic testing (14). However, the possibility of cross-reactivity with other antigenically similar viruses cannot be ruled out. Using rRT-PCR, our surveillance identified a poultry worker with asymptomatic influenza A(H7N9) virus infection, providing further evidence for an occupational risk for asymptomatic infection.

Our study is limited by potential underreporting and by the increased use of PUE and ILI surveillance during the study period compared with previous periods. However,
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Cluster 1

Index case-patient (father)

Managed tofu stall in retail wet market for 4 years
Illness onset
Visited hospital
Hospitalized and treated with oseltamivir
Throat swab specimen rRT-PCR(+)
Endotracheal aspirate sample rRT-PCR(+)
Transferred to regular ward
Recovered and discharged

Secondary case-patient (daughter)

Illness onset, hospitalized, treated with oseltamivir
Throat swab specimen rRT-PCR(+)
Two throat swab specimens rRT-PCR(−)
Discharged

Cluster 2

Index case-patient

Slaughtered live chicken
Onset
Visited hospital
Hospitalized
Endotracheal aspirate sample rRT-PCR(+)
Died

Secondary case-patient (daughter)

Brought a chicken home and raised it
Close contact with index case-patient
Acute serum sample collected
Convalescent serum sample collected
Infection confirmed by serologic testing

Lived together

2/1
2/2
2/3
2/4
2/5
2/6
2/7
2/8
2/9
2/10
2/11
2/12
3/1
3/2
3/3
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3/31

Secondary case-patient (wife)

Handled slaughtered chicken and cooked it
Close contact with index case-patient
Acute serum sample collected
Convalescent serum sample collected
Infection confirmed by serologic testing

Lived together

1/31
2/1
2/2
2/3
2/4
2/5
2/6
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2/10
2/11
2/12
3/1
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Secondary case-patient (son-in-law)

Helped to slaughter chicken
Close contact with index case-patient
Acute serum sample collected
Convalescent serum sample collected
Infection confirmed by serologic testing

Lived together

1/31
2/1
2/2
2/3
2/4
2/5
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2/10
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Figure 2. Timeline of illness for 2 family clusters of persons with confirmed influenza A(H7N9) virus infection, Guangzhou, China, 2014. ICU, intensive care unit; rRT-PCR, real-time reverse transcription PCR.

our results show that targeted surveillance during a period of elevated disease activity improved identification of mild or asymptomatic infections.

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Technical Appendix

Technical Appendix Figure.

Geographic distribution of confirmed influenza A(H7N9) cases and live poultry markets (LPMs) sampled in Guangzhou, China.