

## ORIGINAL ARTICLE

## Three Indonesian Clusters of H5N1 Virus Infection in 2005

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## ABSTRACT

**BACKGROUND**

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Since 2003, the widespread ongoing epizootic of avian influenza A (H5N1) among poultry and birds has resulted in human H5N1 cases in 10 countries. The first case of H5N1 virus infection in Indonesia was identified in July 2005.

**METHODS**

We investigated three clusters of Indonesian cases with at least two ill persons hospitalized with laboratory evidence of H5N1 virus infection from June through October 2005. Epidemiologic, clinical, and virologic data on these patients were collected and analyzed.

**RESULTS**

Severe disease occurred among all three clusters, including deaths in two clusters. Mild illness in children was documented in two clusters. The median age of the eight patients was 8.5 years (range, 1 to 38). Four patients required mechanical ventilation, and four of the eight patients (50%) died. In each cluster, patients with H5N1 virus infection were members of the same family, and most lived in the same home. In two clusters, the source of H5N1 virus infection in the index patient was not determined. Virus isolates were available for one patient in each of two clusters, and molecular sequence analyses determined that the isolates were clade 2 H5N1 viruses of avian origin.

**CONCLUSIONS**

In 2005 in Indonesia, clusters of human infection with clade 2 H5N1 viruses included mild, severe, and fatal cases among family members.

**T**HE AVIAN INFLUENZA A (H5N1) EPIZOOTIC has resulted in sporadic human cases and case clusters. Previously, H5N1 case clustering was observed in cousins in 1997<sup>1</sup> and in a father and son in 2003.<sup>2</sup> H5N1 clustering was described in 2004–2005 but without sufficient information to assess whether human-to-human transmission had occurred.<sup>3</sup> Although only one likely instance of limited human-to-human transmission of H5N1 virus was detailed in Thailand in 2004,<sup>4</sup> the investigation of case clusters is critically important, since an increase in clusters could suggest greater transmissibility of H5N1 viruses.

Since 2003, H5N1 outbreaks in poultry have occurred throughout Indonesia.<sup>5–7</sup> Indonesia's first human H5N1 case was confirmed in July 2005, and three clusters were noted among H5N1 cases through October 2005. In this report, we describe the epidemiologic, clinical, and virologic findings of the three H5N1 case clusters.

## METHODS

### EPIDEMIOLOGIC AND CLINICAL INVESTIGATION

After notification of a suspected case of H5N1, the Ministry of Health in Indonesia initiated an investigation with the assistance of public health authorities and the World Health Organization (WHO). Investigators collected nasal and throat swabs, tracheal aspirates (if available), and serum specimens from patients who were suspected of having the disease; all specimens were tested for the presence of H5N1 virus. Laboratory evidence of H5N1 was defined as virus isolation or detection of H5N1 viral RNA by testing of respiratory specimens or serologically by detection of H5N1 neutralizing antibodies. Cases were classified as suspected, probable, or confirmed H5N1 virus infection, according to WHO definitions.<sup>8</sup>

We collected epidemiologic and clinical data for patients with confirmed H5N1 virus infection and their contacts through interviews and a review of medical records. Contacts of patients with H5N1 infection were followed for illness. Environmental, poultry, and other avian specimens, if available, were tested for H5N1 virus. Clinical, epidemiologic, and laboratory data were analyzed with the use of descriptive statistics. We defined a cluster of H5N1 cases as consisting of at least two persons who had disease with laboratory evidence of H5N1 virus among household members, rela-

tives, or other contacts. This study was part of an ongoing public health investigation of outbreaks of H5N1 virus infection and was determined by the Ministry of Health to be exempt from approval from institutional review boards in Indonesia.

### LABORATORY INVESTIGATION

Indonesian laboratories screened clinical specimens from patients with suspected H5N1 infection for the virus. Respiratory and serum specimens were shipped frozen to WHO H5 Reference Laboratories for H5N1 testing by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), viral culture, molecular sequencing, antiviral resistance testing, microneutralization, and Western blot analyses (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

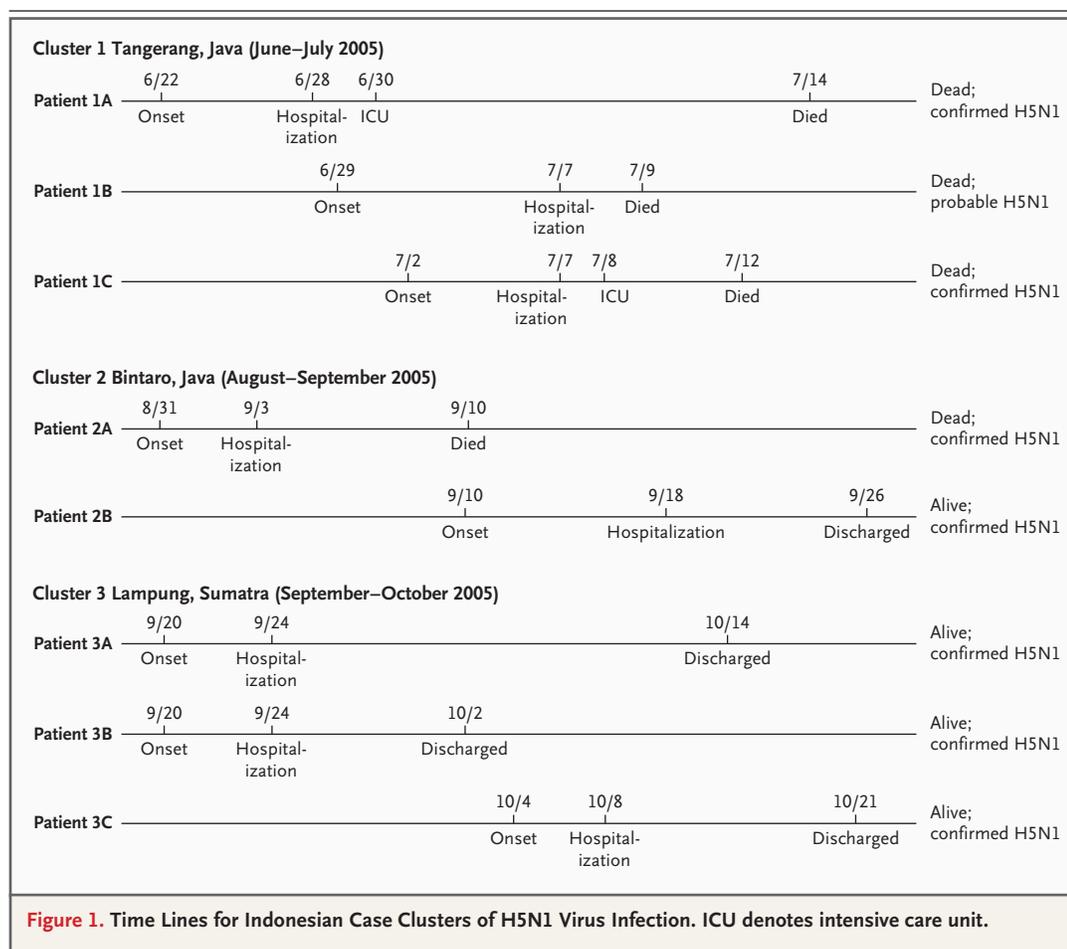
## RESULTS

Among eight previously healthy patients in three unrelated clusters, there were seven confirmed cases of H5N1 virus infection and one probable case (Fig. 1). The median age of the patients was 8.5 years (range, 1 to 38), and four of the eight patients (50%) died, including two adults and two children.

### CLUSTER 1

This cluster included three of five family members living together in a suburb west of Jakarta. Patient 1A, an 8-year-old girl in whom fever, headache, nausea, vomiting, and rhinorrhea developed, was hospitalized with pneumonia 6 days after the onset of symptoms. She was treated with albuterol, fluticasone, ceftriaxone, meropenem, ciprofloxacin, vancomycin, gentamicin, amikacin, linezolid, and mechanical ventilation for respiratory failure, but she died on the 26th day of illness. Serum specimens collected late in her illness showed evidence of acute H5N1 virus infection on microneutralization assay.

Patient 1B was a 1-year-old girl in whom fever developed 1 week after the onset of illness in her sister (Patient 1A). On the ninth day of illness, Patient 1B was hospitalized with fever, rhinorrhea, cough, diarrhea, and vomiting, and she received the diagnosis of pneumonia. She was placed on mechanical ventilation but died on the 12th day of illness. No specimens were available for H5N1 testing.



Patient 1C, who worked as a government auditor, was the 38-year-old father of Patients 1A and 1B. He had close contact with his sick daughters at home and during their hospitalizations. He had onset of fever 3 and 9 days, respectively, after the onset of his daughters' illnesses. On the seventh day of illness, he was hospitalized with pneumonia and was treated with albuterol, budesonide, aminophylline, dexamethasone, meropenem, ceftriaxone, and linezolid. Despite mechanical ventilation, he died on the 11th day of illness. H5N1 virus was isolated from a throat swab collected on day 7.

The three patients in cluster 1 reported having had no contact with poultry, wild birds, other animals, or any sick persons besides family members before the onset of illness. Family members shared a bed after the onset of illness and before hospitalization. Patient 1C's wife, son, and two housekeepers living in the home remained well. Of the 173 contacts who were followed for 2 weeks

(8 household members and neighbors, 143 health care workers, and 22 coworkers), no other ill persons were identified.

#### CLUSTER 2

This cluster included two relatives living near south Jakarta. On August 31, fever, rhinorrhea, and cough developed in a 37-year-old woman (Patient 2A). On the seventh day of illness, she was hospitalized with fever, shock, and respiratory failure requiring mechanical ventilation. Methylprednisolone, levofloxacin, and meropenem were administered, and oseltamivir was given on the 10th day of illness. She died 11 days after the onset of illness; H5N1 virus was isolated from tracheal aspirate.

Patient 2B was a 9-year-old boy who lived temporarily with Patient 2A (his aunt) during her illness. Three days after his aunt was hospitalized, he had onset of fever. He was hospitalized on the ninth day of illness, with persistent fever, sore throat, and tachypnea. No supplemental oxygen,

antibiotics, or antiviral treatment was administered, and his fever resolved on the 10th day of illness. The presence of H5N1 virus was confirmed by RT-PCR in respiratory specimens obtained on the fourth day of illness.

Patients 2A and 2B did not report having had contact with poultry, wild birds, other animals, or other ill persons, but chickens died nearby, and poultry were slaughtered daily approximately 50 m from the home. In her home garden, Patient 2A used fertilizer containing poultry feces that tested positive for H5N1 by RT-PCR. Of the 132 contacts of Patients 2A and 2B (76 household members and neighbors and 56 health care workers), no other ill persons were identified.

### CLUSTER 3

Three relatives living in the same rural village in southern Sumatra made up the third cluster. In mid-September 2005, backyard chickens started dying in the village. Three days after holding two dead chickens, Patient 3A, a 21-year-old man with a history of smoking cigarettes, had an onset of fever, chills, rhinorrhea, cough, and headache. On the fifth day of illness, he was hospitalized with pneumonia and treated with ceftriaxone. Oseltamivir was started on the seventh day of illness. One week later, his respiratory status worsened, requiring supplemental oxygen, and a pleural effusion was noted on chest radiography. His condition improved, and he was discharged on day 25 of illness. A throat swab that was collected on admission tested positive for H5N1 by RT-PCR. H5N1 virus was isolated from a lung specimen obtained from a chicken close to the home.

Patient 3B, the 5-year-old brother of Patient 3A, had an onset of illness (fever, rhinorrhea, and cough) on the same day as Patient 3A, was hospitalized on the fifth day of illness, recovered without treatment, and was discharged 9 days later. Serologic confirmation of H5N1 virus infection was made more than 3 months later for Patient 3B. Patient 3C was the 4-year-old son of a sister of Patient 3A and Patient 3B. He lived in a separate home and did not have contact with his uncles during their illnesses but moved to their home after they were hospitalized. Patient 3C did not have any known contact with ill persons or with sick or dead poultry, but his mother had handled dead chickens and buried them. On October 4, fever, rhinorrhea, and dry cough developed in Patient 3C, but the fever lasted only 2 days. After

a throat specimen tested positive for H5N1 by RT-PCR, he was hospitalized on day 5 and treatment with oseltamivir was started. A chest radiograph on day 7 revealed mild bilateral perihilar and interstitial infiltrates. He remained afebrile, received oseltamivir for 7 days, and was discharged 17 days after the onset of illness. Of the 33 household and neighborhood contacts that were followed for 2 weeks, all others remained well.

### CLINICAL FINDINGS

The median time from the onset of illness to hospitalization was 7 days (range, 5 to 9) (Table 1). All patients with fatal disease presented with fever, bilateral pneumonia, and respiratory distress, and three patients presented with leukopenia, lymphopenia, and moderate thrombocytopenia. In all five patients with severe disease, including four who required mechanical ventilation, hypoxemia or hypoxia either was present on admission or developed later, requiring supplemental oxygen. None of the three mild cases required supplemental oxygen. Patients 2B and 3C had normal leukocyte, lymphocyte, and platelet counts on admission and had fever for 2 and 10 days, respectively. Only Patients 2A, 3A, and 3C received treatment with oseltamivir, beginning on illness days 10, 7, and 5, respectively. Six patients received antibiotics to treat possible bacterial coinfection, but no invasive bacterial infections were identified.

Of six patients whose serum albumin levels were measured either at or close to their hospital admission, four patients with fatal disease had hypoalbuminemia (albumin range, 2.2 to 3.1 g per deciliter). One patient with severe but nonfatal disease had an albumin level of 2.4 g per deciliter, and one patient with very mild disease had a level of 4.3 g per deciliter. Four patients with severe disease had moderately elevated levels of aspartate aminotransferase and alanine aminotransferase, with levels of aspartate aminotransferase higher than those of alanine aminotransferase, at or shortly after admission, as compared with one patient with mild disease who had normal levels.

### H5N1 TESTING

H5N1 virus was isolated from a throat swab from Patient 1C on illness day 7 and from a tracheal aspirate from Patient 2A on day 10 (Table 2). Molecular sequencing of H5N1 viruses isolated from Patient 1C (A/Indonesia/5/2005) and Patient 2A

**Table 1.** Clinical Data for Patients from Three Indonesian Clusters of H5N1 Virus Infection in 2005.\*

| Patient No. | Age  | Sex | Chronic Conditions           | Day of Illness at Hospital Admission | Symptoms and Signs  | Findings on Admission |                                 |  |                           |                |   |
|-------------|------|-----|------------------------------|--------------------------------------|---|-----------------------|---------------------------------|--|---------------------------|----------------|---|
|             |      |     |                              |                                      |   | Temperature<br>°C     | Respiratory Rate<br>breaths/min | Total White-Cell Count<br>per cubic millimeter | Absolute Lymphocyte Count | Platelet Count | Chest Radiography                                     |
| 1A          | 8 yr | F   | None                         | 7                                    | Fever, 7 days; cough, headache, nausea, vomiting                                | 38                    | 40                              | 1780   | 445                       | 185,000        | Bilateral infiltrates                                 |
| 1B          | 1    | F   | None                         | 7                                    | Fever, 7 days; cough, 2 days; rhinorrhea and diarrhea, 3 days; dyspnea, 1 day   | 38.8                  | 25                              | 4200   | NA                        | 221,000        | Bilateral infiltrates                                 |
| 1C          | 38   | M   | History of cigarette smoking | 7                                    | Fever, cough, shortness of breath, difficulty breathing, abdominal pain         | 39.3                  | 34                              | 2310   | NA                        | 146,000        | Bilateral infiltrates                                 |
| 2A          | 37   | F   | None                         | 7                                    | Fever, 7 days; rhinorrhea, cough, shortness of breath, hypotension              | 39                    | 42                              | 2980   | NA                        | 208,000        | Bilateral infiltrates                                 |
| 2B          | 9    | M   | None                         | 9                                    | Fever, 9 days; sore throat  | 38.8                  | 34                              | 7600   | 2356                      | 313,000        | Not done  |
| 3A          | 21   | M   | History of cigarette smoking | 5                                    | Fever, cough, 5 days  | 38.3                  | 48                              | 5000   | 850                       | 145,000        | Bilateral infiltrates                                 |
| 3B          | 5    | M   | None                         | 5                                    | Fever, rhinorrhea, cough, headache, 5 days                                      | NA                    | NA                              | 2900   | 1421                      | 138,000        | Not done  |
| 3C          | 4    | M   | None                         | 5                                    | Fever, rhinorrhea, cough, 2 days; all symptoms resolved 3 days before admission | 37                    | 30                              | 7600   | 4256                      | 373,000        | Mild bilateral interstitial and perihilar infiltrates |

\* NA denotes not available.

(A/Indonesia/6/2005) indicated that both H5N1 viruses were of the Z genotype. In addition, all eight genes of both H5N1 viruses were of avian origin and were clade 2 viruses, as defined previously.<sup>9</sup> Both A/Indonesia/5/2005 and A/Indonesia/6/2005 had M2 gene sequences, indicating susceptibility to adamantanes. Sequencing of the neuraminidase genes and assaying for susceptibility to neuramin-

idase inhibitors found that both H5N1 viruses were sensitive to such agents. Of the five patients whose disease was confirmed by RT-PCR, the same specimens tested negative by rapid antigen testing. Throat swabs had a higher yield for detection of H5N1 virus by RT-PCR assay and viral isolation than did nasal swabs. A throat swab from Patient 3B was positive on RT-PCR assay on illness day 8,

Table 1. (Continued.)

| Maximum Temperature | Mechanical Ventilation                  | Oseltamivir Treatment  | Corticosteroid Therapy | Time from Onset to Death or Discharge | Outcome  |
|---------------------|---|--|------------------------|---------------------------------------|----------|
| °C                  |   |  |                        | days                                  |          |
| 39.2                | Yes (on hospital day 2, illness day 8)  | No   | Yes                    | 22                                    | Death    |
| 38.8                | Yes (on hospital day 2, illness day 11) | No   | Yes                    | 8                                     | Death    |
| 40.0                | Yes (on admission, illness day 7)       | No   | Yes                    | 11                                    | Death    |
| 41.0                | Yes (on admission, illness day 7)       | Yes (on illness day 10, started on 75 mg twice daily orally for 1 day) | Yes                    | 11                                    | Death    |
| 38.8                | No                                      | No   | No                     | 17                                    | Recovery |
| 38.3                | No                                      | Yes (on illness day 7, started on 75 mg twice daily orally for 5 days) | Yes                    | 25                                    | Recovery |
| NA                  | No                                      | No   | No                     | 14                                    | Recovery |
| 37.0                | No                                      | Yes (on illness day 5, started on 35 mg twice daily orally for 7 days) | No                     | 17                                    | Recovery |

even though the patient had fever for only 2 days and began receiving oseltamivir on day 5.

#### DISCUSSION

Our study documents clusters of clade 2 H5N1 virus infection among Indonesian families. These findings and other reports of clusters among family members and relatives in Hong Kong, Vietnam, Thailand, China, Azerbaijan, and Turkey<sup>1-4,10-14</sup>

raise questions as to whether genetic or other factors may predispose some persons to H5N1 virus infection or to severe disease. Since the completion of this investigation, additional H5N1 case clusters have been identified in Indonesia, including a large cluster in northern Sumatra in May 2006. WHO recommends close follow-up and oseltamivir chemoprophylaxis for household members and relatives of patients with H5N1 virus infection who had close contact either with the pa-

**Table 2.** Results of Laboratory Testing for H5N1 Virus Infection from Patients in Three Indonesian Clusters in 2005.\*

| Patient No. | Age yr | Sex | Days after Onset Specimen Collected | Specimen                      | Rapid Test† | RT-PCR (HA/H5)‡ | MN Titer     | H5N1 Virus Isolated                   | H5N1 Case Classification |
|-------------|--------|-----|-------------------------------------|-------------------------------|-------------|-----------------|--------------|---------------------------------------|--------------------------|
| 1A          | 8      | F   | 17                                  | Nasal and throat swabs, serum | N           | INDO<br>N, N    | WHO<br>1:320 | No                                    | Confirmed                |
| 1B          | 1      | F   | 11                                  | Serum                         | —           | —               | 1:640        | —                                     | Probable                 |
| 1C          | 38     | M   | 7                                   | Nasal and throat swabs, serum | N, N        | P, P            | N            | Yes: A/Indo/5/2005 (from throat swab) | Confirmed                |
| 2A          | 37     | F   | 7                                   | Nasal and throat swabs, serum | N, N        | N, P            | N            | No                                    | Confirmed                |
| 2B          | 9      | M   | 4                                   | Nasal and throat swabs, serum | N, N        | N, P            | N            | No                                    | Confirmed                |
| 3A          | 21     | M   | 5                                   | Throat swab, serum            | N, N        | P               | 1:80         | —                                     | Confirmed                |
| 3B          | 5      | M   | 5                                   | Nasal and throat swabs, serum | N, N        | N, N            | 1:640        | No                                    | Confirmed                |
| 3C          | 4      | M   | 8                                   | Nasal and throat swabs, serum | N, N        | N, P            | 1:20         | No                                    | Confirmed                |
|             |        |     | 101                                 | —                             | —           | —               | 1:1280       | —                                     | Confirmed                |
|             |        |     | 1                                   | Nasal and throat swabs        | N, N        | N, P            | —            | No                                    | Confirmed                |
|             |        |     | 8                                   | Nasal and throat swabs, serum | N, N        | N, P            | N            | No                                    | Confirmed                |

\* HA denotes hemagglutinin, MN microneutralization, INDO Indonesian laboratory, WHO World Health Organization H5 Reference Laboratory, N negative, and P positive. A dash indicates that the indicated test was not performed.

† Only nasal- and throat-swab specimens were analyzed by the rapid antigen test.

‡ HA/H5 refers to H5 hemagglutinin-specific primers and probes.

§ Tracheal aspirate from this patient was not analyzed by the rapid antigen test.

tient with the disease or with sick or dead poultry.<sup>15</sup> Prompt antiviral treatment of any associated identified ill persons is also recommended.

We identified three pediatric patients with clinically mild disease in two clusters. This finding is consistent with data from 1997, when most pediatric patients with H5N1 virus infection in Hong Kong had relatively mild disease.<sup>16,17</sup> Another study identified mild and asymptomatic H5N1 virus infection in two adult health care workers in 1997.<sup>18</sup> Identification of three mild H5N1 cases in this study and one case in Turkey (as reported by Oner et al.<sup>12</sup> elsewhere in this issue of the *Journal*) has implications for surveillance, since most H5N1 case findings have focused on patients who were hospitalized with severe pneumonia.

We were not able to determine the source of H5N1 virus infection for the index patients in two clusters, and transmission through contact with environmentally contaminated material remains a possibility. In the first cluster, a caged bird with H5N1 virus infection near the home suggested the possibility of environmental contamination with H5N1 virus, although no virus was detected around the residence. The index patient in the second cluster could have acquired infection through contact with fertilizer containing H5N1-contaminated poultry feces. The presence of a poultry-slaughtering operation approximately 50 m from the home and dead chickens in the neighborhood also suggests that H5N1 environmental contamination could have been a source.

Limited person-to-person H5N1 transmission could not be excluded in two clusters among patients who had no known contact with poultry or other animals. Although Patient 1B was not tested, her clinical characteristics and evidence that her sister (Patient 1A) and her father had acute H5N1 virus infection all strongly suggest she also had H5N1 virus infection. Both Patient 1B and her father had close contact with Patient 1A before their illnesses. Similarly, the only identified exposure for Patient 2B was close contact with his aunt (Patient 2A) during her illness. Limited, non-sustained H5N1 virus transmission from Patient 1A to her sister and father, from Patient 1B to her father, and from Patient 2A to her nephew remain possible explanations given the epidemiologic investigation.

As compared with nasal swabs, throat specimens provided the highest yield for the detection

of H5N1 virus. Rapid antigen testing did not detect any H5N1 cases, which is consistent with data reported for clade 1 infections<sup>19</sup> and supports guidance against using such tests for the detection of H5N1 virus.<sup>20</sup>

Few Indonesian patients with clade 2 H5N1 virus infection in these clusters had diarrhea, unlike patients with clade 1 H5N1 virus infection.<sup>19,21,22</sup> Most patients with H5N1 virus infection had hypoalbuminemia at or close to the time of hospital admission, which has not been reported previously. Whether this finding is related to viral, renal, hepatic, gastrointestinal, iatrogenic, or other factors is unknown. The effects of corticosteroid therapy or late oseltamivir treatment could not be determined. Both H5N1 clade 2 viral isolates were sensitive to adamantanes and neuraminidase inhibitors, although adamantanes are not recommended by the WHO owing to a high frequency of H5N1 viruses that are resistant to amantadine and rimantadine.<sup>15</sup> Resistance to oseltamivir has been reported in patients with clade 1 H5N1 virus infection.<sup>13,14</sup> A recent study showed a correlation between a high H5N1 viral load and hypercytokinemia, and the investigators concluded that early antiviral treatment is needed to suppress viral replication and to prevent the overwhelming inflammatory response implicated in H5N1 pathogenesis.<sup>23</sup> Therefore, much more research is needed to define optimal treatment for patients with H5N1 virus infection.

Our findings of a wide range of clinical features and outcomes associated with clade 2 H5N1 virus infection in Indonesia highlight the importance of careful clinical examination, laboratory diagnosis, and sequential monitoring of all patients with suspected H5N1 virus infection and their close contacts. Further research is needed to understand the role of mild cases in the epidemiology of this disease and whether genetic, behavioral, immunologic, and environmental factors may contribute to case clustering of H5N1 virus infection.

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