

An Investigation of a Human H5N1 Influenza Case by a Joint Thai and Lao Team, February 2007

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Introduction

Sporadic cases of human infection with avian influenza H5N1 have been reported since 1997. Beginning in late 2003, sporadic human zoonotic infections with high fatality have been associated with large and recurring outbreaks of avian influenza H5N1 in poultry in several Asian countries. Following outbreaks among migratory birds in China during 2005, H5N1 spread rapidly through Mongolia and Russia to many European, Middle Eastern and African countries¹. As of January 2007, 270 human cases had been reported to the World Health Organization from Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey and Vietnam². Although there have been a few cases of limited human-to-human transmission³, the species barrier between poultry and humans remains significant¹. However, the virus has pandemic potential and therefore, surveillance for human cases is implemented particularly in areas with confirmed poultry outbreaks.

On 23 Jan 2007, the Thai Ministry of Public Health reported an H5N1 outbreak among poultry in Srichaingmai District, Nong Khai Province which borders Sisattanak District in Lao PDR. Following this report, in early February, a Lao PDR investigation team conducted a rapid assessment in 198 villages near the Thailand-Lao PDR border aimed at active surveillance for human and avian H5N1 infections.

As a result, poultry outbreaks of H5N1 were found

in Sisattanak District and 20 villages were identified as belonging to the red zone (1km radius) around the infected poultry farm. Results of cloacal swabs from healthy poultry in Sisattanak District, Vientiane Province, Laos were reported as positive for H5N1 infection. Active surveillance for possible human infections was conducted during February to first week of March 2007.

Although forty one (0.5%) of the 7,800 residents have had Influenza-Like Illness (ILI), none of them were positive for influenza by rapid tests. In addition, the Lao PDR investigation team identified three suspected cases, one reportedly admitted to Sethathirath Hospital, Vientiane. The Lao PDR investigation team learned that the suspected case had been transferred to a hospital in Nong Khai, and informed the Nong Khai Provincial Health Office by telephone on 19 Feb 2007. An investigation of the hospitalized case was started on 20 Feb 2007 by the local teams. At that time, specimens for H5N1 were taken, and the patient was transferred from a private hospital to the public hospital where isolation facilities were available.

On 21 Feb 2007, the Nong Khai Surveillance and Rapid Response Team (SRRT) informed the Bureau of Epidemiology that a Laotian was admitted to the Nong Khai General Hospital with severe pneumonia and Acute Respiratory Distress Syndrome (ARDS). The patient was found positive for avian influenza H5N1 by RT-PCR at the National Institute of Health (NIH). This test result was confirmed by the Siriraj Hospital on 23 Feb 2007. The exposure history of the patient was uncertain. Hence, a team composed of field epidemiologists from the Thai and Lao PDR Ministries of Health participated in the joint cross-border investigation on 24-25 Feb 2007 to describe the epidemiological and clinical characteristics of the

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case, identify the mode of transmission and recommend measures to prevent additional cases and control spread of the disease.

Methods

This investigation was conducted in Nong Khai, Thailand and Vientiane, Lao PDR by a team composed of staff from the Thai SRRT team (Nong Khai Provincial Health Office, FETP Thailand and staffs from Bamrasnaradura Infectious Disease Institute) and the Lao PDR investigation team (Health Department in Vientiane Capital, Sisattanak Distinct Health Office, National Center Laboratory and WHO epidemiology staff in Lao PDR).

We reviewed medical records and interviewed clinicians at the hospital in Lao PDR and the private hospital in Nong Khai and the Nong Khai General Hospital where the case was treated in order to obtain the clinical history of the patient. The specimens obtained from the patient included blood; nasopharyngeal, nasal and throat swabs; endotracheal secretions; sputum; fluid washed from chest drain; stool; urine and instruments used for the patient (terminal end of endotracheal tube, nasogastric tube, intercostal drainage catheter, foley catheter). Specimens were submitted to the Thai NIH and laboratories of the Siriraj Hospital, Mahidol University in Bangkok for H5N1 virus detection. Lao PDR Ministry of Health also sent the samples to the WHO reference laboratory in Tokyo.

All specimens were tested by conventional Reverse Transcription Polymerase Chain Reaction (RT-PCR) analysis, real-time RT-PCR, cell culture and embryonated egg inoculation for viral isolation, including two or three blind passages, as previously described⁴⁻⁶. Paired serum samples were tested for H5-specific antibody by microneutralization assay using autologous isolate, A/Laos/Nong Khai 1/2007 (H5N1), as the test virus. The serum samples were serially diluted from 1:5 to 1:640 and assayed in duplicate⁷.

We interviewed the patient's relatives and neighbors who visited her at the Nong Khai Hospital. The interviews focused on getting an accurate timeline of events and possible *poultry exposure*. *Poultry exposure* was defined as any of the following: contact with sick or dead poultry by any means including buying, selling, carrying live or dead poultry or poultry meat; having freshly butchered or live poultry in the home within two weeks prior to onset of illness; a history of butchering poultry or living in

a poultry farm within two weeks prior to onset of illness.

The joint investigation team also conducted environmental surveys to assess the risk of exposure in the areas surrounding the patient's residence and poultry farms around the house where she had visited two weeks prior to onset of illness. We also reviewed the process of screening and patient referral at the Lao PDR and Thai border checkpoints.

Preliminary findings of the investigation were presented and discussed at a conference held on 25 Feb 2007 at the Nong Khai General Hospital. Clinicians and epidemiology staff from Thailand and Lao PDR, infectious disease specialists from Bamrasnaradura Infectious Disease Institute, Thailand and WHO Lao PDR country office staff attended the meeting.

Results

Clinical History

The patient was a 15-year-old female residing within the red zone in a suburb of Vientiane, Lao PDR, where an H5N1 outbreak among poultry had been confirmed on 7 Feb 2007⁸. She became sick on 10 Feb 2007. Initial symptoms were fever, headache, coryza and myalgia. From onset of illness to admission to a hospital in Vientiane, she did not have any respiratory symptoms. Figure 1 shows the sequence of events from onset of illness to death of the patient.

Table 1. Medications given to the patient in the Nong Khai-based hospitals by number of days after the onset date (17 Feb-7 Mar)

| Drugs | Number of days after the onset date (10 Feb 2007) | | | | | | | | | | | | | | | | | | |
|--------------|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 |
| Oseltamivir | | | | | | | | | | | | | | | | | | | |
| Cefoperazone | | | | | | | | | | | | | | | | | | | |
| Sulperazole | | | | | | | | | | | | | | | | | | | |
| Vancomycin | | | | | | | | | | | | | | | | | | | |
| Amikacin | | | | | | | | | | | | | | | | | | | |

*shaded days are the days those medicines were given

At the private hospital in Nong Khai Province, as the patient presented fever and rapid progressive dyspnea with patchy infiltration at both lungs, severe pneumonia caused by bacterial and/or viral infection was suspected. The other differential diagnosis was *Pneumocystis carinii* Pneumonia (PCP), however, it was ruled out due to her negative result on anti-HIV testing. Volume overload as a result from treatment of dengue infection which was first diagnosed in Sethathirath Hospital was also

mentioned. In response to two possible viral infections of severe pneumonia, the antiviral drug (oseltamivir) as well as antibiotics (a combination of cefoperazone and sulperazole) were prescribed on day 8 of admission (17 Feb 2007) in the private hospital. At Nong Khai Provincial Hospital, sputum culture yielded *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

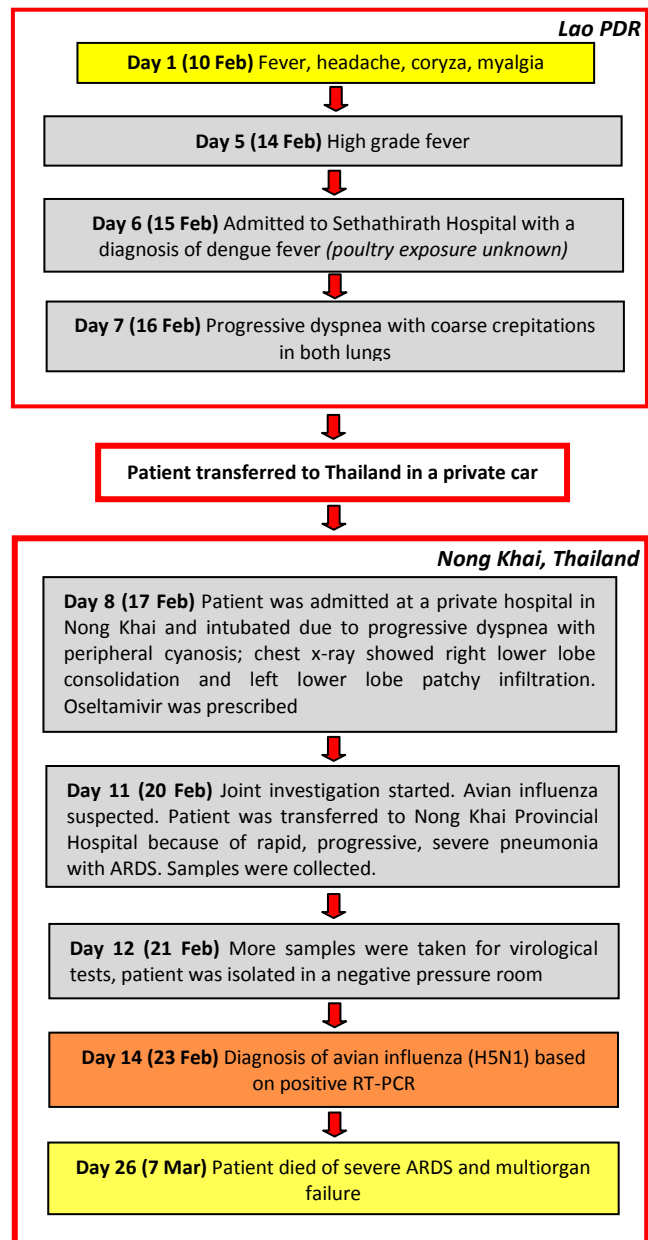


Figure 1. Clinical progression of illness of avian influenza (H5N1) case from 10 Feb to 7 Mar 2007 in Vientiane, Lao PDR

Laboratory Results

Laboratory investigation at private hospital and Nong Khai Hospital found rapid test negative for Flu A and B. Nasopharyngeal swab, nasal swab and throat swab on 20 Feb 2007 were negative for H5 by RT-PCR at Thai NIH.

The endotracheal suction specimen collected on 21 Feb 2007 (day 12 of illness) was positive for H5N1

based on RT-PCR tests performed at the Thai NIH and Siriraj Hospital. Subsequent samples collected on 25 Feb 2007 were also RT-PCR positive as tested by the Siriraj Hospital laboratory and WHO Collaborating Laboratory, NIID in Japan.

Highly pathogenic H5N1 virus was isolated from endotracheal secretion collected on 21 Feb 2007. A four-fold increase in neutralizing antibody titers from 80 to 320 was detected in paired blood specimens collected on 25 Feb and 1 Mar 2007, as assayed against the autologous virus. The virus isolation result was negative for endotracheal samples collected on 25 Feb and 1 Mar 2007. Puthavathana, et al give a more detailed description of the virus isolated from the patient and virological test results in their letter to the editor of the *Emerging Infectious Diseases Journal*⁷.

Environmental Survey

The patient's house was located in a red zone in Sisattanak District, Vientiane, Lao PDR. Aside from the patient, six other relatives lived in the house (two parents, two brothers, an uncle and an aunt). At the time of our visit on 24 Feb 2007, no poultry was found in the house or nearby. About 100 meters from the house was a farm which previously had some poultry. During our visit, we did not see any live poultry in the farm and in neighbors' houses. Residents claimed that in early February 2007, three to ten chickens began to die gradually followed by about 200 chickens died in the farm.

At that time, all the remaining live chickens were sold. A patient's friend said that "we cooked and sold the grilled internal organs of dead chickens from the farm in a market". However, this was not confirmed by the patient's family members.

The patient was transferred from the hospital in Vientiane to the hospital in Nong Khai in a private vehicle without any referral documents, no screening was done at the border checkpoints.

Discussion

The patient was the first confirmed human case of avian influenza H5N1 in Lao PDR. This cross-border investigation by a joint team of Thai and Lao health staff was helpful for both sides. It enabled us to get a better understanding of the circumstances regarding the case, and showed us the areas in surveillance and response that needed to be strengthened.

On initial presentation at the hospital in Lao PDR, a positive tourniquet test, leucocytopenia and

borderline thrombocytopenia (platelet count of 100,000/cu.mm.), an unclear history of poultry exposure and low index of suspicion led to a misdiagnosis of dengue fever. The health sector did not know there was suspected H5N1 activity in poultry while the patient was initially admitted to the hospital, so avian influenza was not considered as a differential diagnosis. Oseltamivir was started on day 8 of illness. Avian influenza was just suspected on day 11, and confirmed on day 14 of illness. The isolation of *Klebsiella pneumoniae* and *Acinetobacter baumannii* from sputum suggested the possibility of nosocomial infection.

Another opportunity was missed when the patient was transported to Nong Khai. Screening procedures at the border checkpoint failed to detect and refer a suspected case of avian influenza.

In Nong Khai, the patient was first brought to a private hospital where the routine surveillance for severe acute respiratory infections was not conducted. In addition, public health policy on confining the avian influenza cases to a designated public hospital was not done as the disease was not suspected. Private hospitals did not have negative pressure rooms and might not have adequate personal protection equipments (PPEs) for health workers who attended the patient. Health staff in Thailand were also unaware of the areas in Lao PDR with confirmed H5N1 poultry outbreaks.

Despite extensive collection of clinical specimens, only endotracheal secretions were found positive for H5N1 virus. The reasons were likely that the virus was staying deep in the lower respiratory tract, and the patient was already receiving oseltamivir when the specimens were taken.

The patient was likely to be infected with the H5N1 virus in her neighborhood since she lived in a red zone. Handling internal organs of an infected chicken without gloves may have been the mode of exposure.

Public Health Action and Recommendations

Close contacts to the patient (family members and health care workers) were identified and were monitored daily. The adults were provided with oseltamivir prophylaxis. None of the contacts developed influenza-like illness during the monitoring period. The Ministry of Health in Lao PDR has announced the first human case of infection with the avian influenza H5N1 virus to the public on 27 Feb 2007⁹, and her death was reported on 8 Mar 2007¹⁰.

Surveillance activities were strengthened in Lao PDR, and a second case (42-year-old female) was identified in Vientiane. She became febrile on 26 Feb 2007, and was hospitalized on 1 Mar 2007. She died on 4 Mar 2007. A duck positive for H5N1 virus was found in her household. None of her close contacts showed signs of infection¹¹.

This investigation highlighted the importance of health staff awareness on the occurrence of poultry outbreaks in their areas and the possibility of encountering human cases. Surveillance in areas with poultry outbreaks should include private health facilities. Referral mechanisms between private and public hospitals should be strengthened. In the future, it would be useful to collect endotracheal specimens at the time of initial intubation from cases with severe pneumonia.

Cross-border cooperation among veterinary and health staff should be strengthened, and adequate border screening procedures should be in place to detect and refer suspected avian influenza cases. A key outcome of this case investigation was that the Mekong Basin Disease Surveillance (MBDS) group implemented a Nong Khai–Vientiane cross-border project in 2009.

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Suggested Citation

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