

Outbreaks of Avian Influenza A (H5N1) in Asia

Interim Recommendations for Evaluation and Reporting of Suspected Cases ---

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During December 2003--February 2004, outbreaks of highly pathogenic avian influenza A (H5N1) among poultry were reported in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam. As of February 9, 2004, a total of 23 cases of laboratory-confirmed influenza A (H5N1) virus infections in humans, resulting in 18 deaths, had been reported in Thailand and Vietnam. In addition, approximately 100 suspected cases in humans are under investigation by national health authorities in Thailand and Vietnam. CDC, the World Health Organization (WHO), and national health authorities in Asian countries are working to assess and monitor the situation, provide epidemiologic and laboratory support, and assist with control efforts. This report summarizes information about the human infections and avian outbreaks in Asia and provides recommendations to guide influenza A (H5N1) surveillance, diagnosis, and testing in the United States.

Poultry Outbreaks

On December 12, 2003, an outbreak of avian influenza A (H5N1) among poultry in South Korea was reported. Subsequent influenza A (H5N1) outbreaks among poultry were confirmed in Vietnam (January 8, 2004), on a single farm in Japan (January 12), in Thailand (January 23), in Cambodia (January 24), in China (January 27), in Laos (January 27), and in Indonesia (February 2). On January 19, a single peregrine falcon found dead in Hong Kong also tested positive for influenza A (H5N1) virus, but no poultry outbreak has been identified.

In Vietnam, as of February 9, a total of 18 human influenza A (H5N1) infections had been reported, resulting in 13 deaths. Patients ranged in age from 4 to 30 years; 10 patients were aged <18 years. The cases included fatal infections in two sisters who were part of a cluster of four cases of severe respiratory illness in a single family.

In Thailand, influenza A (H5N1) infection was confirmed in four males, aged 6--7 years, and one female, aged 58 years. All five patients died ([1](#)). Other cases are under investigation.

Analysis of Viruses

Antigenic analysis and genetic sequencing distinguish between influenza viruses that usually circulate among birds and those that usually circulate among humans. Sequencing of the H5N1 viruses obtained from five persons in Vietnam and Thailand, including one sister from the cluster in Vietnam, has indicated that all of the genes of these viruses are of avian origin. No evidence of genetic reassortment between avian and human influenza viruses has been identified. If reassortment occurs, the likelihood that the H5N1 virus can be transmitted more readily from person to person will increase. Although all the genes are of avian origin, the current H5N1 viruses are antigenically distinguishable from those isolated from humans in Hong Kong in 1997 and 2003.

Genetic sequencing of the five human H5N1 isolates from Thailand and Vietnam also indicates that the viruses have genetic characteristics associated with resistance to the influenza antiviral drugs amantadine and rimantadine. Antiviral susceptibility testing confirms this finding. Testing for susceptibility of the H5N1 isolates to the neuraminidase inhibitor oseltamivir has demonstrated the sensitivity of these viruses to the drug; testing to determine susceptibility to the neuraminidase inhibitor zanamavir is under way.

Interim Recommendations for U.S. Surveillance and Diagnostic Evaluation

CDC recommends that state and local health departments, hospitals, and clinicians enhance their efforts to identify patients who could be infected by influenza A (H5N1) virus and take infection-control precautions when influenza A (H5N1) is suspected ([Box](#)). Testing of hospitalized patients for influenza A (H5N1) infection is indicated when both of the following exist: 1) radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternative diagnosis has not been established and 2) a history of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza infections in poultry or humans. Ongoing listings of countries affected by avian influenza are available from the World Organization for Animal Health*.

Testing for influenza A (H5N1) also should be considered on a case-by-case basis in consultation with state and local health departments for hospitalized or ambulatory patients with all of the following: 1) documented temperature of $>100.4^{\circ}\text{F}$ ($>38^{\circ}\text{C}$); 2) cough, sore throat, or shortness of breath; and 3) history of contact with poultry or domestic birds (e.g., visited a poultry farm, a household raising poultry, or a bird market) or a known or suspected patient with influenza A (H5N1) in an H5N1-affected country within 10 days of symptom onset.

Recommended Laboratory Testing Procedures

The highly pathogenic avian influenza A (H5N1) virus requires Biosafety Level (BSL)-3+ laboratory conditions for certain procedures. CDC recommends that virus isolation studies on respiratory specimens from patients who meet the testing criteria should not be performed unless all BSL-3+ conditions are met. However, clinical specimens can be tested by polymerase chain reaction (PCR) assays by using standard BSL-2 work

practices in a Class II biological safety cabinet. CDC has developed real-time PCR protocols[†] for various respiratory pathogens, including SARS and influenza A and B viruses. In addition, commercially available antigen-detection tests can be used under BSL-2 levels to test for influenza. Although these rapid tests for human influenza also can detect avian influenza A (H5N1) viruses, the sensitivity of these tests is substantially lower than that of virus culture or PCR (2).

Specimens from persons meeting clinical and epidemiologic indications for testing should be sent to CDC if they test positive for influenza A either by PCR or antigen detection testing, or if PCR assays for influenza are not available locally. CDC also will accept, for follow-up testing, specimens from persons meeting the clinical and epidemiologic indications but testing negative on the rapid tests when PCR assay was not available. Requests for testing by CDC should come through local and state health departments, which should contact CDC's Emergency Operations Center, telephone 770-488-7100.

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Editorial Note:

Since 1997, human infection with avian influenza viruses has been confirmed on five occasions[§]. The ability of avian viruses to transmit from person to person appears limited. Rare person-to-person infection was noted in the A (H5N1) outbreak in Hong Kong in 1997 (3,4) and in the A (H7N7) outbreak in the Netherlands in 2003 (5), but these secondary cases did not result in sustained chains of transmission or communitywide outbreaks. These previous experiences with avian influenza viruses suggest that limited person-to-person transmission of the current H5N1 viruses could occur.

The majority of the human H5N1 cases are apparently associated with direct exposure to infected birds or to surfaces contaminated with excretions from infected birds. The family respiratory illness cluster in Vietnam suggests the possibility of limited person-to-person transmission. However, other possibilities (e.g., transmission through exposure to surfaces contaminated by H5N1-infected poultry feces) cannot be ruled out. Although no evidence for sustained person-to-person transmission of influenza A (H5N1) has been identified, influenza viruses have the capacity to change quickly. Continued monitoring for new transmission patterns is an important aspect of the current investigation.

In 1997, the influenza A (H5N1) outbreak among persons in Hong Kong ended abruptly after the culling of poultry. However, the current outbreaks present challenges because of the large geographic areas and numbers of affected poultry. Asian poultry populations are maintained both on large commercial farms and in backyard flocks. In addition, infections among wild bird populations might be extensive, and the resources to address this problem are limited in certain affected countries. Because of increasing evidence that avian influenza viruses infect humans, persons involved in the slaughter of poultry potentially infected with avian influenza viruses or their contaminated environments should follow WHO recommendations for worker protection[¶].

Because the influenza A (H5N1) virus could develop the ability to maintain sustained person-to-person transmission, WHO collaborating centers are working to coordinate vaccine development. Efforts are under way in the United Kingdom and the United States to develop influenza A (H5N1) reference viruses for use in vaccine preparation. The minimum estimated time necessary to complete reference virus development and safety testing is 3 months. Production by vaccine manufacturers of pilot lots of vaccine for clinical testing can begin only after reference virus development and safety testing have been completed. Decisions on whether to proceed with vaccine manufacture will depend, in part, on the evolution of the current outbreaks.

On February 4, CDC issued an order for an immediate ban** on the import of all birds from Cambodia, China (including Hong Kong), Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam. Birds from these affected countries potentially can infect humans with influenza A (H5N1). This order complements a similar action taken by the U.S. Department of Agriculture (USDA).

CDC advises that travelers to countries in Asia with documented H5N1 outbreaks should avoid poultry farms, contact with animals in live food markets, and any surfaces that appear to be contaminated with feces from poultry or other animals. More information on travel is available from CDC at <http://www.cdc.gov/travel>. Additional information on influenza viruses and avian influenza is available from CDC at <http://www.cdc.gov/flu>. Updated information on human infections is available from WHO at <http://www.who.int/en>.

References

1. [CDC. Cases of influenza A \(H5N1\) --- Thailand, 2004. MMWR 2004; 53:100--3.](#)
2. [CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices \(ACIP\). MMWR 2003; 52\(No. RR-8\).](#)
3. Bridges CB, Lim W, Hu-Primmer J, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997--1998. *J Infect Dis* 2002;185:1005--10.
4. Bridges CB, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis* 2000;181:344--8.
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* Available at http://www.oie.int/eng/en_index.htm.

† These protocols are available to public health laboratories and have been posted, under SARS (password required), by the Association of Public Health Laboratories at http://www.aphl.org/members_only/index.cfm.

[§] Influenza A (H5N1) in Hong Kong in 1997 and 2003, influenza A (H9N2) in Hong Kong in 1999 and 2003, and influenza A (H7N7) in the Netherlands in 2003.

[¶] Available at <http://www.wpro.who.int/avian/docs/recommendations.asp>.

** Additional information on the embargo is available at <http://www.cdc.gov/flu/avian/embargo.htm>.

Box

BOX. Interim recommended infection-control precautions* for influenza A (H5N1)

- All patients with a febrile respiratory illness should be asked about their recent travel history and managed using *Respiratory Hygiene/Cough Etiquette in HealthCare Settings* guidelines[†].
- Isolation precautions for all hospitalized patients who have or are under evaluation for influenza A (H5N1) are the same as those that should be used for severe acute respiratory syndrome (SARS), as follows:
 - Pay careful attention to hand hygiene before and after all patient contact.
 - Use gloves and gown for all patient contact.
 - Wear eye protection when within 3 feet of the patient.
 - Place the patient in an airborne isolation room (i.e., monitored negative air pressure in relation to surrounding areas with six to 12 air changes per hour).
 - When entering the patient's room, use a fit-tested respirator at least as protective as an N95 filtering-facepiece respirator approved by the National Institute for Occupational Safety and Health.
- Outpatients or hospitalized patients discharged in <14 days should be isolated in the home setting on the basis of principles for home isolation of SARS patients[§].
- These precautions should be continued for 14 days after onset of symptoms until an alternative diagnosis is established or diagnostic test results indicate that the patient is not infected with influenza A virus.

* Additional information about health-care isolation precautions is available at <http://www.cdc.gov/ncidod/hip/isolat/isolat.htm>.

[†] Available at http://www.cdc.gov/flu/professionals/infectioncontrol/resp_hygiene.htm.

[§] Available at <http://www.cdc.gov/ncidod/sars/guidance>.

Scale of flu pandemic not predictable, WHO says

Robert Roos ■ News Editor

Dec 9, 2004 (CIDRAP News) – The World Health Organization weighed in yesterday on the debate about the potential magnitude of the next influenza pandemic by saying it's impossible to confidently predict how many lives a pandemic might claim.

"While it is impossible to accurately forecast the magnitude of the next pandemic, we do know that much of the world is unprepared for a pandemic of any size," the WHO said in a prepared statement. At the same time, the agency said a pandemic virus could "affect between 20-50% of the total population."

The WHO and flu experts around the world are worried that the widespread H5N1 avian influenza in Asia could spark a human flu pandemic, conceivably on the scale of the devastating Spanish flu pandemic of 1918-1920, which killed an estimated 20 million to 50 million people.

"Experts' answers to this fundamental question" of the likely scale of a pandemic "have ranged from 2 million to over 50 million," the WHO said. "All these answers are scientifically grounded. The reasons for the range are many fold."

Until recently the WHO had been estimating the possible global death toll in a potential pandemic at 2 million to 7 million. But in a Nov 29 speech, Dr. Shigeru Omi, the WHO's Western Pacific regional director, said that a pandemic could kill 20 million to 50 million people, or even up to 100 million.

Some other experts have gone higher. Disease expert Michael T. Osterholm, PhD, MPH, has estimated publicly that a pandemic could kill up to 1.7 million people in the United States and as many as 177 million worldwide. Osterholm is director of the University of Minnesota Center for Infectious Disease Research and Policy (CIDRAP), publisher of this Web site.

Henry L. Niman, a Pittsburgh medical researcher who is described as a critic of the WHO, said a pandemic could conceivably kill a billion people if the 72% mortality rate seen in recent confirmed human H5N1 cases prevailed, according to a Nov 29 *New York Times* report. In the same story, Klaus Stohr, chief of the WHO's influenza program, rejected Niman's estimate as unscientific and unjustified, saying the H5N1 death rate may be overstated because less severe cases might have gone undiagnosed.

US Health and Human Services (HHS) Secretary Tommy Thompson, in announcing his resignation plans last week, cited what he said was a WHO estimate that a pandemic could cause 30 million to 70 million deaths.

On the lower end of the scale is a 1999 estimate cited in HHS's pandemic preparedness plan, released in August. It said that a pandemic could cause up to 207,000 deaths in the United States. If the global death rate were the same as in the United States, that would mean a world toll of roughly 4.4 million.

The WHO today listed four reasons why it's hard to predict how bad a flu pandemic might be:

- Important details about past pandemics, including death tolls, are disputed. Even for the most recent pandemic, in 1968, estimates range from 1 million to 3 million deaths.
- Estimates based on previous pandemics "are problematic because the world in 2004 is a different place from 1918. The impact of greatly improved nutrition and health care needs to be weighed against the contribution the increase in international travel would have in terms of global spread."
- The characteristics of a future pandemic virus can't be predicted. It could affect anywhere from 20% to 50% of the population. No one knows how pathogenic the virus would be or which age-groups it would affect.
- The level of preparedness will influence the death toll.

"Because of these factors, confidently narrowing the range of estimates cannot be done until the pandemic emerges," the WHO said. "Therefore, response plans need to be both strong and flexible.

"Even in the best case scenarios of the next pandemic, 2 to 7 million people would die and tens of millions would require medical attention. If the next pandemic virus is a very virulent strain, deaths could be dramatically higher."

The agency went on to say it will convene a meeting on preparedness planning next week and will publish an assessment tool in the next few weeks "to evaluate and focus national preparedness efforts." Many WHO member countries have not even begun to plan for a pandemic, the statement added.

In response to the statement, Osterholm critiqued the WHO for not repudiating its previous estimate of 2 million to 7 million deaths and for not presenting at least a range of mortality numbers that could guide health policymakers.

He said current global deaths from ordinary flu total roughly 1.8 million every 2 years, which is about how long a pandemic would be expected to last. Therefore, "No one believes 2 million to 7 million is a remotely realistic situation" in a pandemic, he said.

Osterhom asserted that the WHO should explore "a wide range of numbers that reflect what would be considered a relatively mild world pandemic to what could realistically be considered a serious world pandemic . . . if for no other reason than that planners could get a sense of the morbidity and mortality they need to address in their plans. In short, the WHO needs to do more to provide better definition even in the context of a wide range of mortality estimates."