

Avian Influenza Update: New Cluster of Human Victims in Sumatra; WHO Releases Guidelines for Treatment and Prophylaxis of Avian Influenza

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Cluster of 8 Family Members in Sumatra Infected with H5N1

On May 23, the World Health Organization (WHO) acknowledged the likelihood that a large cluster of human cases of H5N1 infections in the northern portion of the Indonesian island of Sumatra is due to human to human transmission [1]. The cluster comprises 8 individuals of one extended family. On April 27, a 38 year old woman became ill, and then died on May 4. While she was never tested for H5N1 infection, 7 members of her extended family--3 adult siblings, 2 adolescent sons, a 10 year old nephew and an 18 month old niece--subsequently became ill with WHO-confirmed H5N1 infections, and 6 of the 7 have died. The source of the woman's infection is not known. Three of the infected family members shared a room with her on the night of April 29 while she was actively sick and coughing. The other family members lived nearby. While each of the 7 confirmed cases had prolonged and close contact with an actively sick individual, it appears that they may not have had close contact with the index case, raising the possibility of more than one generation of transmission. No one outside the family has become ill, and only blood relatives (i.e. not spouses or in-laws) have been involved.

Full sequence analysis of 2 viral specimens from this cluster shows no evidence of reassortment or of known mutations thought to increase the likelihood of human to human transmission. In addition, the sequences appear to be similar to those of birds from the region last year. Live virus has not been found in the area, and there have been no reported outbreaks in animals, although serological studies have found evidence of H5 antibodies in pigs, chickens and ducks nearby. It is reported, however, that farmers in the area have not been cooperating with efforts to test their animals [2].

While many other family clusters of H5N1 have been reported, this is the largest. In addition, while several previous clusters have been thought to indicate limited human to human transmission, this is the first instance in which more than one generation of transmission is considered likely. The fact that only blood relatives are involved has also been noted, and has been observed in all previous clusters of human H5N1 infection as well, leading some experts, including Dr. Robert Webster, to speculate that this may be evidence of a genetic susceptibility to the infection [3].

WHO Releases Guideline for Treatment and Prophylaxis of Avian Influenza

The WHO has just issued guidelines for the treatment and prophylaxis of avian influenza A (H5N1) virus infection [4], and stated that with the H5N1 virus now confirmed in birds in more than 50 countries, additional sporadic human cases should be anticipated. The guidelines were formulated by an international panel of experts that included clinicians with experience in treating H5N1 infected patients. The panel considered the benefits, harms, burdens and cost of interventions.

The WHO's evidence-based guidelines classify recommendations as strong or weak, characterize the quality of the evidence as high, moderate, low and very low, and are specific to the current pre-pandemic conditions. It is important to note that there are no available data from controlled clinical trials of treatment or prophylaxis for H5N1 infection, and most evidence was formulated from data gathered from small observational case series, animal studies, and extrapolation of treatment and chemoprophylaxis data derived from seasonal influenza cases. While these guidelines are an important contribution, clinical data to establish the optimal treatment regimen for infected patients are urgently needed.

Table 1: Key recommendations for the treatment of patients in which H5N1 infection has been confirmed or is strongly suspected

Availability of Therapy	Treatment	
Neuraminidase inhibitors available	1 st line	oseltamivir
	Alternative	zanamivir

	Other	M2 inhibitor (amantadine, rimantadine) might be added to neuraminidase inhibitor if local surveillance data shows virus susceptibility
Neuraminidase inhibitors not available	1 st line	M2 inhibitor if local surveillance data shows virus susceptibility

Although animal studies have indicated that a prolonged course of high-dose oseltamivir increases survival [5], the WHO guidelines recommend treating H5N1 infected patients with the same regimen used for the treatment of seasonal influenza.

With regard to geographic susceptibility of M2 inhibitors, clade 1 H5N1 virus isolated from humans in Thailand carries mutations associated with resistance to M2 inhibitors, whereas, to date, clade 2 virus isolated from China does not seem to carry these mutations.

Table 2: Key recommendations for chemoprophylaxis of patients potentially exposed to H5N1

Availability of Therapy	Risk Exposure Category (see table 3, below)	Prophylaxis	
Neuraminidase inhibitors available	High: prophylaxis should be administered	1 st line	Oseltamivir, continuing 7 to 10 days after last exposure
		Alternative	Zanamivir, continuing 7 to 10 days after last exposure
	Moderate: prophylaxis might be administered	1 st line	Oseltamivir, continuing 7 to 10 days after last exposure
		Alternative	Zanamivir, continuing 7 to 10 days after last exposure
	Low: prophylaxis should probably not be administered		
Neuraminidase inhibitors not available	High and moderate: prophylaxis might be administered		M2 inhibitor if local surveillance data shows virus susceptibility
	Low: prophylaxis should not be administered		

Notes: 1.) M2 inhibitors (amantadine or rimantadine) should not be administered as prophylaxis in pregnant women.
2.) Amantadine should not be administered as prophylaxis to the elderly, to individuals with renal insufficiency, or to persons who are taking neuropsychiatric medications or who have neuropsychiatric or seizure disorders.

Table 3: Risk Exposure Categories

Low	Moderate	High
> Health care workers who have kept a distance of greater than 1 meter from a patient strongly suspected or confirmed to be infected with H5N1 > Those who have donned proper PPE during exposure	> Individuals who handle sick animals or decontaminate affected environments in the absence of proper personal protective equipment (PPE) > Those with unprotected and close	> Household or family members in close contact with a strongly suspected or confirmed H5N1 infected patient.

<p>> Those involved with general culling of non-infected animal populations</p> <p>> Those who have handled sick animals or have decontaminated affected environments while donning proper PPE.</p>	<p>exposure to sick or dead infected animals</p> <p>> Health care or laboratory personnel in close contact with strongly suspected or confirmed H5N1 infected patients or virus-containing samples in the absence of proper PPE.</p>	
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Recommendations for other Treatments

The panel does not recommend the use of corticosteroids, interferon alpha, immunoglobulin therapy, or ribavirin unless evaluation of these treatments is undertaken under the auspices of a randomized, controlled clinical trial. Antibiotics should be administered only if clinically indicated for the treatment of bacterial pneumonia, but not for the general prevention of secondary bacterial pneumonia

Conclusions

This week's developments are worrisome. Press reports [6] indicate that in Sumatra, residents of the affected village have demonstrated fear of and hostility toward authorities. It has also been reported that one the infected persons who died refused to take oseltamivir. Such developments suggest that the effective implementation of public health guidelines may prove as challenging as the disease itself.

References

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