

**WHO Inter-country Consultation
Influenza A/H5N1 in Humans in Asia
Manila May 6th-7th 2005**

ASSESSMENT

Some important epidemiological features of human H5N1 infections occurred in northern Viet Nam during January through April 2005 and appeared to differ in some respects from those seen in 2004 in other parts of Asia, and in the concurrent period in southern Viet Nam. These included an increase in the number of case clusters in the north compared with the south, a prolonged interval between the first and last cases in clusters, detection of sub-clinical infections, an expanded age range of cases and fewer fatal cases. Investigators were not able to prove that human-to-human transmission had occurred. However they expressed concerns, which were shared by local clinicians, that the pattern of disease appeared to have changed in a manner consistent with this possibility.

These differences suggest that the epidemiology of H5N1 infections may be evolving in Asia. The changes in epidemiological patterns are consistent with the possibility that recently emerging H5N1 viruses may be more infectious for humans. Furthermore, sequencing analyses of H5N1 genes from avian and human H5N1 viruses from several countries suggest that they are becoming more antigenically diverse and may be forming distinguishable groupings based on phylogenetic analyses.

While the implications of these epidemiological and virological findings are not fully clear, they demonstrate that the viruses are continuing to evolve and pose a continuing and potentially growing pandemic threat. Based on these concerns and findings, it would be prudent to take increased steps to improve risk assessment procedures, to strengthen the ability of affected countries to respond promptly to local outbreaks, to accelerate control of avian influenza in poultry and to implement or complete pandemic preparatory actions as soon as is possible, even if current H5N1 outbreaks in Asia cease or diminish during the summer.¹

1. Background

Since late 2003, avian influenza A (H5N1) virus infections in Asia have resulted in the death or culling of more than 100 million poultry. In addition, H5N1 viruses have repeatedly “jumped the species barrier,” and infected (as of 5 May 2005) at least 92 adults and children in Viet Nam, Thailand and Cambodia resulting in 52 deaths (57%). Despite this already considerable impact, H5N1 viruses have the potential to cause far greater harm if they evolve and gain the ability to easily infect and transmit among people. An H5N1 virus with this ability could lead to a global pandemic and many millions of deaths worldwide. So far, most human infections have occurred sporadically, but clusters of infections predominantly affecting household members have occurred in Thailand and Viet Nam and, most likely, Cambodia. Most human H5N1 infections so far are thought to have occurred through some form of contact with live or dead infected poultry but isolated instances of probable person-to-person transmission were documented in Hong Kong in 1997, in Thailand in 2004, and cannot be excluded in some of the Cambodian or the recent and earlier clusters in Viet Nam. The affected countries have already responded to the emergence of H5N1. The Expert Consultation was impressed with a number

¹ It should be noted that at the time of writing (May 11th) this report the last case of human H5N1 reported in North Viet Nam occurred in early April.

of the actions taken including the establishment of national multisectoral control committees (Vietnam), thorough investigation of potential clusters (Cambodia) and close collaboration between the agricultural and human health sectors (Thailand).

Since the first H5N1 outbreak in Hong Kong in 1997, regional and international public health authorities have monitored H5N1 viruses to identify viral or epidemiological changes possibly signifying that the virus has become significantly more infectious for people and therefore closer to causing a pandemic. However, the task of identifying such changes is complicated. Evolution of a pandemic strain of virus may be preceded by numerous small steps, none of which is sufficient to signal clearly that a pandemic is about to start. This poses a difficult public health dilemma. If public health authorities move too soon, then unnecessary and costly actions may be taken. However, if action is delayed until there is unmistakable evidence that the virus has become sufficiently transmissible among people to allow a pandemic to develop, then it most likely will be too late to implement effective focal, national or regional responses, and opportunities will be missed to “Get Ahead of the Curve” and prevent large numbers of infections and deaths.

During 15 – 25 April, 2005, a WHO team of expert consultants was invited by the authorities in Viet Nam to assess the current H5N1 situation, especially in Northern Viet Nam. Based on the epidemiological information presented, this team concluded that the epidemiology of H5N1 could be changing in that part of the country and that the risk for pandemic influenza could have risen. Therefore a second urgent Expert Consultation was held involving a group of epidemiologists, virologists, public health and animal health experts with international experience, and country representatives from Cambodia, Thailand, and Viet Nam. Its objectives were *to review the current situation of the A/H5N1 in humans in Asia and provide an overview on the current risk for an influenza pandemic* and in the light of this *to identify priorities for continued international collaboration on situation assessment and pandemic preparedness*². This assessment was held at WHO regional offices in the Western Pacific (WPRO) in Manila during 6-7 May, 2005. Presentations were made by representatives of the three countries that provided information on the epidemiological, clinical and virological findings related to human and animal H5N1 infections. In addition, information was made available from other Asian countries along with new data and analyses from the WHO Global Influenza Network. The three countries also summarised their extensive plans and actions in preparation for outbreaks of H5N1 and their programmes for pandemic preparedness.

2. Supporting Information for the Assessment

2.1 Supporting epidemiological observations – Human H5N1 infections in northern Viet Nam 2005

- More clusters have occurred in the north (8) than in southern Viet Nam (2). Small clusters, observed prior to 2005, were reported by Thailand and Cambodian representatives.
- The most recent clusters span longer time periods (i.e., took place over more days) (cf 2004) raising the possibility that the more recent clusters may reflect a mixture of transmission modes, including exposure to ill birds, environmental transmission, prolonged exposure to asymptomatic birds that are shedding virus, or person-to-person transmission.
- Between 2004 and 2005, the average age of people infected rose from 17 years to ~31 years but remained almost unchanged (~15 years to ~18 years) in southern Viet Nam. In addition, the age range of people infected by H5N1 has broadened and now extends from those < 1 year to >80 years while in southern Viet Nam, the range is 2 years to under 40 years. The age range

² Terms of Reference for WHO Inter-country consultation on influenza A/H5N1 in Asia. WHO April 28th 2005.

was 2 – 58 years in wave 1 (median 12 years) in Thailand and in Cambodia, the range has been 8 – 28 years (median 20 years).

- The observed case fatality rate has declined to 34% (16/47) but is 83.3% (20/24) in southern Vietnam. The case fatality rate in Thailand was 71% (12/17) and 100% in Cambodia (4/4) in 2004.
- Three asymptomatic infections have been documented among close contacts of confirmed cases in Viet Nam suggesting that milder H5N1 infections are occurring. Four persons who culled H5N1 infected birds in Japan and two animal attendants caring for infected tigers in Thailand also have antibodies to H5 virus. Asymptomatic infections were also detected retrospectively in Hong Kong following the 1997 outbreak.

2.2 Supporting viral observations

- In general, H5N1 viruses isolated during 2004 from humans with severe respiratory infections were very similar to avian isolates from the same country, both genetically and antigenically. H5N1 human and avian viruses isolated in the Indochina peninsula (Cambodia, Laos, Malaysia, Thailand and Viet Nam) tightly clustered within clade 1, while H5N1 viruses isolated from birds in China, Indonesia, Japan and South Korea belonged in a second clade which showed greater genetic divergence.
- The HA gene of viruses isolated from humans in Viet Nam in the first 3 months of 2005 showed several amino acid changes relative to 2004 viruses. None of the changes in the HA were common to all of the 2005 viruses analysed so far. However, the most commonly observed changes are located close to the receptor binding site and could potentially modulate receptor binding specificity. Recent viruses circulating in Northern Viet Nam have lost an arginine residue in the multibasic amino cluster at the proteolytic cleavage site of the HA protein. It does not seem to be responsible for reduced pathogenicity since the structure of the cleavage site still remains typical of highly pathogenic viruses. However at this time these are possibilities that have yet to be further investigated by analysing more viruses.
- Phylogenetic analysis of all H5N1 human isolates along with a subset of avian viruses from clade 1 isolated during 2004 and 2005 in Cambodia, Thailand and Viet Nam indicates that the viruses from northern Viet Nam and Thailand have begun to form a somewhat separate cluster from viruses isolated from southern Viet Nam and Cambodia. As of yet, the ‘bootstrap’ values (which provides a measure of certainty with which clades can be accurately separated) are low due a lack of data. Sequences from additional viruses from the northern and southern regions of Viet Nam would add statistical power to the phylogenetic analysis.
- H5N1 human isolates from Viet Nam in 2005 are somewhat antigenically heterogeneous . In particular, A/Viet Nam/JPHN3021/2005 is antigenically distinct from the 2004 reference/ vaccine strains A/VN/1203/04 and A/VN/1904/04. Other 2005 H5N1 human isolates exhibit more antigenic heterogeneity than did those isolated in 2004.
- Sequence analysis of NA genes and neuraminidase inhibitor susceptibility testing of H5N1 human 2005 isolates from Viet Nam has also revealed that one virus (A/VN/HN30408/05) has a “mixed” virus population of amino acid residues 274-H (wild-type) and 274-Y (resistant) sequences. Although this virus does not exhibit a fully resistant phenotype, the IC₅₀ value for oseltamivir is shifted upward and consequently this virus is less susceptible to oseltamivir than other H5N1 isolates tested. The patient from whom this virus was isolated had been/was being treated with oseltamivir. The community emergence and spread of viruses resistant to oseltamivir, if it were to occur, would have significant implications for influenza A/H5N1 prevention and control.

In summary, analysis of the virologic data has identified trends in phenotypic and genotypic properties of 2005 human isolates that must be examined more closely using additional recent human and avian H5N1 isolates. It is essential that avian and human isolates are included and compared to determine if the 2005 viruses isolated from humans simply reflect the genetic and antigenic diversity found among H5N1 viruses obtained from poultry or if viruses isolated from humans are beginning to exhibit antigenic drift from avian viruses. The latter pattern would be of major concern since it would likely indicate that a higher level of human-to-human transmission is occurring. Finally, while the antigenic and genetic data indicate that the 2005 human isolates are drifting antigenically and genetically from their 2004 predecessors and the H5N1 viruses isolated from the northern and southern parts of Viet Nam tend to fall into different groups, there is no direct evidence to date that these changes can be correlated with apparent changes in disease patterns between the north and the south. Additional data from 2005 human and avian H5N1 isolates must be obtained and analyzed together with data from older H5N1 viruses.

3. Discussion of the Findings

There are several plausible interpretations of the apparent changes in epidemiological patterns of H5N1 virus infections and the Expert Consultation considered all of these.

3.1 The changes could be artefactual or inconsequential

1. It is possible that the apparently new epidemiological patterns could simply reflect random variation in the data since the number of cases is relatively small. This was considered unlikely since the changes were all consistent with the avian virus possibly adapting to a human host.
2. It is possible that changes in surveillance or laboratory testing methods have created changes that are more apparent than real. However, no significant changes in methods to identify, report or investigate suspected H5N1 cases are known to have been made in Viet Nam since last year that could account for the changes.

3.2 The changes could be significant

1. It is possible that the avian H5N1 viruses are becoming more infectious for people, facilitating infection in a greater number or range of people and resulting in more clusters. It might not be that this led to human to human transmission.
2. It is possible that avian H5N1 viruses are becoming more capable of human-to-human transmission.
3. It is possible that there is a change in exposures or behaviours placing people at risk for infection. For example direct touching of poultry or poultry faeces contaminated surfaces, eating uncooked poultry products (e.g., blood) or preparing poultry have been considered the probable routes of exposure leading to infection in most older children and adults. However, infections of children <1 year are more difficult to explain by these exposures and raise other possibilities such as contact with contaminated household surfaces, or eating or drinking contaminated water or food, or possibly through direct transmission from another person.
4. It is possible that changes among people reflect an increase in transmission from asymptomatic but infectious poultry. It was noted that some human clusters were detected before cases were found in poultry, which also suggests inadequate surveillance or under-reporting of avian infection or disease in poultry. Therefore, current comparisons of disease prevalence in poultry between countries and even parts of one country may not be valid. In addition, significant

percentages of ducks can shed virus while remaining asymptomatic. However, if this is true, then it suggests that epidemiology among birds in the north is diverging from patterns in the south and would not explain why relatively fewer people appear to be acquiring infections in the south where avian poultry infections (including ducks) have remained generally high or why more clusters have been reported from the north.

- 5 It is possible that the widening age range reflects increasing persistence of the virus in local environments providing more chances for more people of all ages to become exposed and infected. However, this would not address the apparent divergence in patterns in the north and south.

4. Recommendations

The recommendations followed directly from the Expert Consultation's assessment process. They reflect both the difficulties that were experienced in reaching a clearer assessment because of a relative lack of relevant information as well as recommendations for immediate actions that reflect the higher level of concern about the possibility of pandemic influenza, based on the assessment.

4.1 Related to the Assessment

Immediate steps should be taken to improve the ability to monitor and assess the risk for pandemic influenza more rapidly, continuously and completely in all countries where avian H5N1 viruses are present. Specifically:

- WHO should continue to mobilize technical assistance as needed and requested by affected countries.
- All relevant data should routinely be made available for review by the WHO Pandemic Task Force which should now be convened by WHO to meet regularly to assess the risk for pandemic influenza.
- Animal and human health sectors, at every level from FAO/OIE/WHO down to the local level, should coordinate their approaches to epidemiological, virological and clinical surveillance across specialties. The coordination should lead to regular, timely and meaningful exchange of information and plans
- WHO should coordinate with FAO, OIE and key agricultural, public health and private sector partners to develop a mechanism through which detailed information on the genetic and antigenic characterization of animal and human influenza H5N1 viruses, and the viruses themselves, can be exchanged more freely and rapidly between laboratories and among countries. Information should flow in both directions. The need is especially urgent for ongoing information on the genetic and antigenic makeup of recent isolates of H5N1 viruses from poultry, other birds and animals and people across Asia to facilitate comparisons of H5N1 viruses detected in humans and poultry.
- Surveillance for human H5N1 infections should include identification and characterization of clusters of suspected and confirmed H5N1 infections including in returning travelers from risk areas.
- WHO should, as a priority, complete the development of its handbook on the approach to investigating possible H5N1 clusters.
- Countries and individual researchers should urgently analyze and disseminate information that has already been collected on H5N1 viruses and related activities.

4.2 Related to pandemic preparedness

- All countries, both those affected and unaffected by avian H5N1, and with the assistance of WHO and other agencies as needed, should move ahead as quickly as possible and develop or finalise practical operational pandemic preparedness plans.
- WHO should continue to explore and develop international approaches that can be used to reduce the threat or impact of pandemic influenza including an international stockpile of antiviral drugs from which supplies can be very rapidly provided for use in control of an outbreak of human H5N1 infection that threatens to spread beyond its initial confines.
- Further exercises should be undertaken by individual countries, with the assistance of WHO as needed to rehearse the early and rapid responses to early outbreaks including deployment of the stockpile.
- WHO should explore all possible mechanisms for making human H5N1 vaccine available to affected countries in Asia before the start of a pandemic by bringing together technical experts, countries, manufacturers and potential donors to establish the feasibility of increasing global H5N1 vaccine production. This should include an assessment of the need for a new vaccine seed strain if recent isolates are genetically and antigenically distinct

4.3 Related to control of avian influenza

- It was observed that in places where infection in poultry has been controlled or eliminated, human cases no longer occur. In the current period, prevention of H5N1 avian influenza in humans is best achieved by controlling infection in poultry. As already recommended by FAO and OIE, control strategies for this disease should consider vaccination of poultry, which has been used successfully before. Evidence to date suggests that the index case in most of the human clusters in Viet Nam occurred after exposure to infected poultry, indicating that the disease is still a zoonotic infection.

4.4 Related to funding

- Countries requiring external funds to enhance their technical capacity to address H5N1 infections and other emerging disease threats should coordinate and prioritize the national needs of agricultural and public health sectors and provide this information to WHO and donors to facilitate the funding process.
- International funding agencies should coordinate their efforts to minimize any redundant and duplicate funding of activities and to eliminate gaps. Support should be given to capacity building as well as urgent or emergency solutions and should target broader emerging infections and general needs for controlling endemic diseases as well as influenza. Agencies supporting development should be specifically approached by countries and WHO because of the potentially profound implications for health security, social and economic development regionally and worldwide from a pandemic.