

**Background Paper**

**2.1 c Highly Pathogenic Avian Influenza A (H5N1) & Risks to Human Health**

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**1. Introduction**

Human infection with highly pathogenic avian influenza A(H5N1) virus was first described in Hong Kong (1997), with 18 laboratory confirmed cases (6 fatal) reported from the H5N1-affected area. Almost four years after the re-emergence of H5N1 infections in poultry populations in South East Asia<sup>1</sup>, the virus is still circulating and threatening human health in two separate, yet related ways : firstly, as a zoonotic human threat posed by the highly pathogenic avian influenza A(H5N1) virus itself, and secondly, in the possibility that an influenza virus with pandemic potential may emerge from either the H5N1 strain or from any other influenza virus.

WHO has developed a strategic plan for pandemic influenza in relation with the specific H5N1 threat <sup>2</sup>. The following five public health actions remain of high priority to WHO for continuous prevention and control of human H5N1 infection and for limiting opportunity for H5N1 virus mutation or reassortment into a pandemic strain, as well as for containing at source a potential pandemic virus and building national capacities to cope with a pandemic.

Strategic action	Goal
1. Reduce human exposure to the H5N1 virus	Reduce opportunities for human infection and, in so doing, reduce opportunities for a pandemic virus to emerge
2. Strengthen the early warning system	Ensure that affected countries, WHO, and the international community have all data and clinical specimens needed for an accurate risk assessment
3. Intensify rapid containment operations	Prevent the H5N1 virus from further increasing its transmissibility among humans or delay its international spread
4. Build capacity to cope with a pandemic	Ensure that all countries have formulated and tested pandemic response plans and that WHO is fully able to perform its leadership role during a pandemic
5. Coordinate global scientific research and development	Ensure that pandemic vaccines and antiviral drugs are rapidly and widely available shortly after the start of a pandemic and that scientific understanding of the virus evolves quickly

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## 2. The Zoonotic threat<sup>3</sup>

### Pathogenicity in humans

Highly pathogenic avian influenza A(H5N1) virus is able to cross the species barrier and cause infection and illness in humans. From November 2003 to 14 June 2007, a total of 312 laboratory confirmed cases of human H5N1 infection (190 fatal) were reported from 12 countries<sup>4</sup>. Most of the cases were reported from South East Asia<sup>5</sup>. Laboratory confirmed cases of human infection continue to be reported<sup>6</sup>, and documentation of the incidence of human disease and of the characteristics of laboratory confirmed cases is on-going<sup>7,8</sup>.

The pathogenesis of the disease is not completely understood. The main clinical feature of the disease is, still, severe pneumonia often complicated by Acute Respiratory Distress Syndrome (ARDS). Although mild cases and sub-clinical illness have been reported<sup>9,10</sup>, most patients experience severe illness, and overall the case fatality rate among laboratory confirmed cases remains as high as sixty percent. An optimal treatment regimen has not yet been established. Early recognition of patients and timely administration of an influenza-specific antiviral agent using standard protocols are essential for further evaluation of the effectiveness of antivirals<sup>11</sup>.

### Identifying the source of human H5N1 infection during outbreak investigation

Human infection with H5N1 virus seems to be associated with contact with infected birds. The incidence of cases seems to be higher in countries where established cultural practices (including live animal markets and keeping/slaughtering/preparing poultry in households) promotes frequent and intense interactions between humans and poultry<sup>12</sup>.

It remains unclear which specific activities (e.g. slaughtering, de-feathering, butchering, meat preparation, collecting eggs, playing with poultry, engaging in cock-fighting activities, having poultry within the household) place individuals at a higher risk of infection and whether people get infected through aerosolization of the virus during these activities, by self inoculation (e.g. through contaminated hands), and/or via other exposure routes.

Another question is, why those exposed in the same way, or at the same time, as confirmed cases do not get infected and ill. Is a blood relationship important?

Childhood infections following contact with birds while playing have been reported, but the importance of this particular exposure pathway is difficult to analyze in settings where humans and animals closely share the same living spaces.

For some confirmed cases no indication of direct contact with birds has been found, and only the presence of sick or dying poultry in the neighbourhood or visiting of a live animal market was reported. If sufficient supportive data were available, such findings on exposure might suggest indirect transmission of the virus. For example, considering the virus' ability to survive in the environment, exposure might occur through self inoculation with contaminated hands after contact with contaminated environments or fomites.

There are also cases for whom no putative source of infection has been identified. In these situations, fear of reprisals for owning, selling or consuming sick poultry, fear of income loss consequent to the culling of the flock, and the stigma associated with owning an infected flock, might have led to non-reporting poultry disease or death, even when official reporting systems are in place. Illegal actions such as organizing cock-fights, smuggling pet birds or poultry, or hunting protected wild birds could also have played a role in information bias during the investigation of cases<sup>13</sup>. Still other hypothetical sources of H5N1 virus infection need to be more closely studied, including consumption of undercooked poultry meat and eggs, handling of fertilizers made from bird feces, exposure to other contaminated environments including surface water<sup>14,15</sup>, general lack of hygiene, the role of exposure to infected species other than birds, and the role played by asymptotically infected but nevertheless infectious birds, need to be studied further<sup>16</sup>. However, it has been established that there is no risk of infection from properly cooked poultry meat or eggs if cross contamination is controlled<sup>17</sup>.

In a few clusters, limited human-to-human transmission of H5N1 virus has been the most likely mode of transmission, as was documented in Thailand<sup>18</sup>. This was suspected for a few cases when very close and unprotected contact with a case occurred at a critical phase of illness. In all these situations the transmission chain ended spontaneously. Disentangling human-to-human transmission from bird-to-human and from contaminated environment-to-human transmission data is challenging given the living conditions that often exist within the affected households, where all these different possible exposure pathways might have occurred concomitantly.

Improving documentation of exposure and infection source for every case is crucial for a better understanding of the transmission from animals to humans and for a more accurate estimation of the incubation period in humans.

### **Research on the risk factors for infection and illness**

As described above, no specific risk factors for human infection, beyond unprotected handling of sick and unexpectedly dead poultry or sharing living areas with them in the few days prior to disease<sup>19,20,21</sup>, have yet been identified with certainty nor validated through research.

Further research is needed to understand the distribution of illness and to better identify groups at risk of infection. In particular, it remains unclear why, despite their potentially high exposure to infection<sup>22</sup>, professional poultry industry workers in H5N1-infected areas have over the past 3 years only on very rare occasions developed the disease.

The observation of disease in blood-relatives in the same cluster<sup>23,24,25</sup> may well be due to common behaviors or shared contaminated environment, rather than linked to genetic predisposition, although both hypotheses need to be studied<sup>26</sup>.

The true incidence of human H5N1 infection remains unclear. Unfortunately, systematic testing of asymptomatic close contacts of laboratory confirmed cases during outbreak investigation is often hampered not only by testing constraints<sup>a</sup>, logistic problems of contact tracing, legal restrictions related to international shipment of biological specimens, and ethical considerations (e.g. the need for an agreed research protocol), but also by refusal of contacts to participate in studies<sup>b</sup>, limiting our understanding of the real spread of infection. Research activities could also play a key role in understanding how infection is spread and why H5N1 disease incidence is still low compared to the possible level of exposure to infected animals. Some sero-prevalence studies have been carried out amongst social contacts of cases<sup>27</sup>, cullers<sup>28</sup> and among the population in H5N1-affected areas<sup>29</sup> and recently in groups at occupational risk of exposure to avian viruses in non-H5N1-affected countries<sup>30,31</sup> to try to answer these questions, but research remains largely insufficient.

The current risk of nosocomial transmission of H5N1 virus exists but was assessed as very low<sup>32,33,34,35</sup> compared to human seasonal influenza viruses<sup>36</sup>. However, these findings are based on a small number of studies and continuous assessment is needed.

### **Early case detection and surveillance**

Human avian influenza symptoms are not specific and may lead to delayed diagnosis, especially in countries or areas where H5N1 infections have not been reported in poultry. The diagnosis might sometimes only be suspected when the patient severely deteriorates (i.e. 5-6 days after symptom onset) or after learning that a close contact of the patient has recently died from or developed a similar disease.

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<sup>a</sup> Testing of asymptomatic contacts is done on paired serum specimens collected 2 weeks and using microneutralisation, a technique available only in few reference laboratories and requiring a higher bio-safety level (BSL3+).

<sup>b</sup> E.g. for fear of being identified as H5N1 case or being tested without consent for HIV infection.

Surveillance and early warning systems for human disease have been introduced or strengthened in many countries affected with avian influenza outbreaks and in some other high risk and/or neighboring countries. The performance of these systems remains largely sub-optimal and unpredictable, especially in countries with competing health priorities and which are resource poor environments, and/or where no human cases of infection have yet been reported.

Sero-surveillance is needed in groups with occupational exposure (including health care workers, poultry and pig farm workers, veterinarians, cullers, live animal market vendors) for documentation of the incidence of infection and of the clinical spectrum of illness, and should be carried out in the frame of comprehensive study protocols

### **Virus evolution**

Virological surveillance to date has allowed the identification and categorization of H5N1 viruses affecting birds into 10 clades. Several of these viruses variants - so far all of pure avian origin - have been responsible for human infection and illness, as seen in Cambodia, Viet Nam and Thailand (clade 1), Indonesia (clade 2.1), Azerbaijan, Egypt, Iraq, Turkey, and Nigeria (clade 2.2) and China and Laos (clade 2.3).

The rapid evolution of the H5N1 viruses has important implications. Reagents used for laboratory confirmation of human cases need to be up-dated regularly, and selection of representative strains for research and development of human H5N1 vaccine prototype needs to be carried out regularly<sup>37</sup>. As well, evolution of viruses isolated from animals must be considered when reagents and vaccines are being developed.

However, the H5N1 virus isolates and sequences available publicly for research and evaluation are limited in geographic, temporal, and species coverage, complicating the ability of the scientific and public health communities to make timely assessments of viral evolution and its epidemiological significance. As well, for many of the available sequences, basic temporo-spatial data are unavailable, further limiting the capacity for assessment of geographical spread.

Development of vaccines and testing reagents is challenged by continuous virus evolution, a characteristic of influenza viruses, and the work of each of the laboratory of the Global Influenza Surveillance Network<sup>38</sup> will be key in carrying out this assessment at all stage of a pandemic<sup>39</sup>.

### **3. The pandemic threat**

Influenza pandemics are unpredictable, in timing and in their consequences. They can be responsible for a high death toll, and for major social disruption<sup>40</sup>. However, variability in morbidity and mortality have been seen over the last century not only from one pandemic to the other but also between waves of a same pandemic. The pattern of spread can also vary in a single place during the same pandemic.

With circulation of highly pathogenic avian influenza A(H5N1) virus in avian, mammalian<sup>41,42,43,44,45,46, 47</sup> and human populations, two of the three prerequisites for the start of a pandemic have been met i.e. (1) the general population has no immunity to the virus, and (2) the virus is able to replicate in humans and cause serious illness<sup>48</sup>. However, sustained human-to-human transmission, the third prerequisite, has not been observed to date, and, according to WHO Global Influenza Preparedness Plan<sup>49</sup>, the world is still in phase 3 of the pandemic alert period as of June 2007, a phase where no or very limited human-to-human transmission has been observed<sup>50</sup>.

The widespread distribution of H5N1 virus not only increases the chances of mutation of this virus into a readily human-to-human-transmissible strain, but also provides more opportunities for H5N1 virus to reassort with another influenza A virus subtype in a susceptible species (e.g. humans, pigs) during dual infection. Both mechanisms - avian virus mutation and virus reassortment - are known to have been at the origin of the latest influenza pandemics, respectively in 1918 and in 1957/1968<sup>51,52,53,54</sup>.

Some scientists also suggest that an increase in the range of mammals susceptible to H5N1 infection would represent an increase risk for further adaptation to humans.

Apart from H5N1 virus, other avian influenza A viruses such as H7 and H9 types are also potential zoonotic and pandemic threats to human health<sup>55, 56</sup> through the same virus modification mechanisms. Infection by these subtypes is currently even less frequently documented in humans than those by H5N1 virus<sup>57,58</sup>, and they show different pathogenicity and transmission patterns. Some of these virus subtypes, such as H7N7, have been more easily transmitted from person-to-person than H5N1 virus<sup>59,60,61</sup>, whereas for others, such as H9N2 virus, no to human-to-human transmission has been observed<sup>62</sup>. Swine influenza viruses may also be a threat to human health<sup>63,64</sup>.

Finally, re-circulation of human influenza A(H2N2) virus in partly naive populations after several decades also represents a potential influenza pandemic threat.

#### **4. Conclusion**

Both zoonotic and pandemic threats due to influenza viruses will remain as long as the viruses circulate in animal populations.

Although highly pathogenic avian influenza A(H5N1) virus is not the only influenza virus threat to human health, the pandemic threat is higher than ever since 1968 given its wide and continuous circulation.

The epidemiology, clinical spectrum of human infection with this pure avian virus, and transmission patterns to- and between-humans are still not fully understood.

Risk groups for infection, illness, and death also need to be better documented so as to improve prevention and control policies.

Close monitoring of characteristics of cases in time, place, person and of H5N1 virus distribution and genetic and antigenic characteristics are key to early detection of the emergence of a potential pandemic strain.

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