CHAPTER V

RESEARCH RESULTS

5.1 Discussions

The study includes the largest number of H5N1 cases described from one country to date, and comprises the complete exposure date and illness time lines of all 25 Chinese H5N1 cases that were reported through October 2006 during the two-year period since the detection of the first H5N1 case through surveillance in 2005 (Chotpitayasunondh et al., 2005). The report is the first to estimate incubation period and analyze the clinical time lines of H5N1 cases. (Detailed clinical and epidemiological findings, which were not included in this study, will be published elsewhere).

All H5N1 cases except one had exposure to poultry or had visited a wet poultry market prior to illness onset, which is consistent with risk factors reported in other studies (Chan et al., 1998; Chan, 2002; Tran et al., 2004; Areechokchai et al., 2006; Olsen et al., 2006). It is difficult to define the risk of such exposures, which may have included multiple poultry exposures prior to symptom onset. (A case control study, designed to analyze risk factors of human infection with H5N1 in China, is currently being analyzed.) Most human cases of H5N1 infection have been sporadic to date, but family clusters have occurred in China. 2 cases in a family cluster with limited person-to-person transmission reported elsewhere were excluded for analyses (Wang et al., 2008). Of these two cases, the most likely incubation period after the father's unprotected exposure to his severely ill son is 4-5 (range 3-6) days.

Direct physical contact with sick or dead poultry has been identified as the primary risk factor (Areechokchai et al., 2006; Dinh et al., 2006). In addition to exposure to H5N1 virus, susceptibility to human infection with H5N1 viruses could be mediated by age or immunologic, genetic, or other factors. All other 9 cases resided in urban areas of China, and likely had more exposures to wet poultry market than cases in rural areas. Recently, an article reviled that after exposure to infected poultry, the incubation period generally appears to be 7 days or less, and in many cases this period is 2 to 5 days. In clusters in which limited, human-to-human transmission has probably occurred, the incubation period appears to be approximately 3 to 5 days, although in one cluster it was estimated to be 8 to 9 days (Abdel-Ghafar et al., 2008). In China, the estimated incubation period of urban cases was longer than 7 days which is also recommended by WHO in their case definition to obtain exposure history and surveillance recommendation on close contact tracking and enhance surveillance. (Abdel-Ghafar et al., 2008). The most reliable estimates of H5N1 incubation periods up to now were based on studies of cases having direct exposure to sick or dead poultry. However, the case patients in China were located in both rural and urban areas. In addition, the H5N1 cases arising from a single exposure may not be representative of all H5N1 cases. The present study provides such an estimate to cover nearly all confirmed H5N1 cases in China since 2005. The incubation period of influenza is usually two days but can range from one to five days. WHO suggested a case with one or more listed exposures in the 7 days prior to symptom onset should consider as suspected H5N1 case. Recently, the 7 days was included in a diagram for case management. (Abdel-Ghafar et al., 2008). Compare with situations in South East Asia, two categories of cases had happened in china, they wer case patients in rural area and case patients in urban settings. The surveillance system may fail to capture the case, if infection acquired from infected but a symptomatic animals such as ducks, an incubation period > 7 days, or infection from a contaminated environment such as wet poultry market. The incubation periods may underestimate actual , as it was impossible to ascertain when H5N1 virus infection occurred after exposure to poultry, including multiple poultry exposures, as well as to environmental sources such as visiting a wet poultry market.

A rapidly progressive disease course was evident in all cases. Most case patients were not initially suspected as having H5N1 virus infection by health care providers. This might be due to the fowling factors:

1. Early nonspecific signs and symptoms of H5N1. Early clinical presentation included fever, upper-respiratory-tract and/or lower-respiratory-tract syndromes that were not distinguishable from the "influenza syndrome".
2. Failure to elicit a history of contact with sick or dead poultry or a history of wet poultry market visiting. Because contact with poultry is widespread in most countries where avian influenza has been reported, and because poultry in China are under high rate of vaccination, one would expect a lower possibility for physicians in health facilities to obtain case patient's exposure history accurate.
3. Unfamiliarity of medical providers with the clinical features of H5N1 and lack of diagnostic capabilities. Most of Chinese H5N1 case patients had their medical consultation in a village clinic or health center in community. Physicians in lower level health facilities relatively lack of experience to make a correct diagnosis. Thus, most of cases had been discharged as OPD patients or had been transfer

between health facilities. But the poor conditions in lower level heath facilities such as one which lacks of X ray machine should also need to be take in to consideration.

Similar to other countries in which case patients were hospitalized a median of 6 days after onset. Most Chinese case patients with H5N1 infection sought medical care early but admit to hospitals late during the course of their illness. Case patients had been diagnosed as URI and transfer between hospitals before they were suspected as PUO might contribute the high H5N1 mortality observed in China. If the case was not identified as PUO, the patient rarely received antivirus treatment and therefore may have increased the possibility of further transmission.

For human influenza virus, throat samples may have better yields than nasal samples. The detection of viral RNA in respiratory samples appears to offer the greatest sensitivity for early identification, but the sensitivity depends heavily on the primers and assay method used. Avian influenza A (H5N1) infection may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. Earlier studies in Hong Kong also found low viral loads in nasopharyngeal samples. In our study, LRT specimens had a higher yield for detecting H5N1 virus than did URT specimens.

5.2 Limitations

The study was limited to data available for H5N1 cases identified through surveillance during the study period. The analytical dataset did not include data on a recent confirmed case in 2008, or from retrospectively confirmed cases in 2003 and 2007. Even during the study period, surveillance and laboratory testing may not have identified all Chinese H5N1 cases, including mild clinical manifestations or case patients did not seek medical attention especially in rural areas where the health service is relatively limited. The cases not captured by surveillance system might present different characteristics which could different from the data include into this study. The assessment of incubation period was based on information obtained through interviews with case patients and their household and family members. However, 15 case patients who died could not be interviewed directly, and their exposure histories may therefore reflect some incompleteness or inaccuracy.

5.3 Conclusions and recommendations

Exposures to potential sources of A (H5N1) more than 7 days before illness onset should then be sought. The duration of enhanced surveillance activities will need to be assessed for each investigation but typically would be expected to be undertaken for a minimum of 2 weeks (i.e. two incubation periods) after the last human case is identified.

The possibility of avian influenza A (H5N1) should be considered in all patients with severe acute respiratory illness in countries or territories with animal avian influenza A (H5N1), particularly in patients who have been exposed to poultry. However, some outbreaks in poultry were recognized only after sentinel cases occurred in humans. Early recognition of cases is confounded by the non specificity of the initial clinical manifestations and high background rates of acute respiratory illnesses from other causes.

For detection of H5N1 viral RNA in patients with suspected H5N1 virus infection, specimens should e collected from different respiratory sites on multiple days, including nasal and throat swabs from patients who are not under going mechanical ventilation and endotracheal aspirates from intubated patients.

The findings suggest that further studies are necessary to investigate differences in the clinical course of H5N1 among pediatric and adult H5N1 cases. In the absence of any currently available definitive therapy for H5N1 patients with such high mortality, prevention activities and risk reduction must be more seriously emphasized. Public education to reduce risk behaviors for H5N1 virus infection such as direct contact with sick or dead poultry is needed, especially among children in rural areas. Analytical investigations such as case-control studies will help to better define risk factors for H5N1 in China, and to help identify specific H5N1 risk factors in urban wet poultry markets. Other investigations, in collaboration with animal health authorities will be important to measure the benefits and risks of poultry vaccination regarding risk factors for H5N1.

Funding

The financial support of this study was provided mainly by the China CDC.