

Rapid communications

(YET) ANOTHER HUMAN A/H5N1 INFLUENZA CASE AND CLUSTER – WHEN SHOULD EUROPE BE CONCERNED?

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A Chinese report of a case from Jiangsu province of an almost certain son-to-father transmission of avian influenza type A/H5N1 infection was published this week, along with an accompanying comment [1,2]. The source of the 24-year-old son's infection was not established, but the authors suggest this might have occurred during a visit to a market where there was live poultry [1]. Such a way of acquiring infection (rather than direct or close contact with sick domestic poultry) has been suggested in a number of the few human cases recently detected in China [3]. However, in the case described in *The Lancet*, contact with poultry was not certain and, despite some retrospective investigations in the market, no H5N1 viruses were detected in birds. The son eventually died and his 52-year-old father almost certainly acquired the infection while caring for him in the hospital, as was the case in another probable human-to-human transmission in Thailand in 2004 [1,4]. In the recent Chinese cluster, the cases, their contacts and the circumstances of transmission were well investigated epidemiologically and virologically, with over ninety contacts traced. Control measures were vigorous, with contacts being treated with chemoprophylaxis, as recommended by the World Health Organization (WHO) [1,5]. The rigour of the investigation contrasts with many earlier outbreaks and is praised in the accompanying comment [2,6]. Only two of the contacts developed illness that was compatible with bird flu by symptoms and timing, but both were negative for markers of A/H5N1 infection (i.e. their illness had to be due to another cause) [1].

Although the viruses in the father and son were almost identical, the authors still could not be entirely certain that this was human-to-human transmission [1], because it was impossible to entirely rule out shared or common exposure to infected birds or environmental contamination. This explanation is commonly considered in the investigations of human A/H5N1 cases and is the reason why attempts to determine the number of person-to-person transmissions have been unsuccessful. Their results are lists of clusters with varying levels of probabilities [6,7]. Attempts at modelling these clusters have been made [8], but these cannot substitute proper field and laboratory investigations, such as were carried out in the Chinese cluster [1]. However, it would be unreasonable for anyone to still argue that person-to-person transmission of A/H5N1 has never occurred [5]. Indeed, it probably occurs more often than it seems, simply because of the multiple possible routes of exposure in most clusters. Usually, where birds could be the source, they are assumed to be the source of all human infections [6].

A cause for concern for epidemiologists in these and other recent cases in China (and Vietnam) is the difficulty in identifying the primary source of infection for the human cases. How did the viruses get from birds into humans? This could not be determined in Jiangsu and sometimes cannot be done elsewhere [1,3]. It has been suggested that this may partially reflect the success of the impressive Chinese veterinary campaigns to immunise all domestic poultry. These have been highly effective in reducing outbreaks in birds and hence much of the need for mass culling of birds. This in turn has eliminated the economic and social misery that follows for the owners, who may not always be compensated in a timely manner. However, since poultry immunisation prevents disease but cannot eliminate infection in birds, it probably has left A/H5N1 silently transmitting among poultry, and existing in the environment near poultry albeit at low levels [9]. This is probably also making detection and surveillance for human A/H5N1 cases more difficult. The previous marker of contact with a die-off in poultry in sick humans with atypical pneumonias as a trigger for testing for A/H5N1 has been lost. Local officials and clinicians in endemic countries find it hard to test for H5N1 in all people with symptoms compatible with human A/H5N1 infection. This is being attempted in Thailand but not elsewhere, probably because of the costs and logistics [10,11].

Human-to-human transmission of A/H5N1 is not new. Indeed some of the most certain transmissions occurred from patients to health care workers in Hong Kong when A/H5N1 was first observed in humans in 1997 [12].

This latest Chinese report of human-to-human transmission does not change anything. It fits with the European Centre for Disease Prevention and Control (ECDC) risk assessment (published in 2005 and revised in 2006) and with the WHO Pandemic Alert Phase 3, which allows for occasional human-to-human transmissions to take place [13,14]. Looking broadly at the recent epidemiology and virology of the A/H5N1 influenza continuously reported by the WHO [15], there is nothing of late to suggest that A/H5N1 has changed its behaviour in a worrying manner. However, an important caveat to this statement is the case of Indonesia, which accounts for more human cases than any other country (15 of the 28 confirmed human A/H5N1 cases reported for 2008 by WHO to 8 April) and which has seen some of the largest clusters of cases in earlier years, with perhaps third-generation transmission [16,17]. Although the detection and investigation of cases has improved in Indonesia, since early 2007 the authorities have stopped sharing

human A/H5N1 viruses with the rest of the world through the WHO-managed Global Influenza Surveillance Network (GISN), despite the 2005 International Health Regulations, whose spirit if not wording dictates transparency and ready sharing of data and specimens [18,19,20]. Hence, it is impossible at present to know in any timely manner whether or not the A/H5N1 viruses are changing virologically in that country. Yet, if a pandemic is to start in any country, the time factor will be of the essence for early investigation and intervention [21,22].

So should European authorities be concerned about individual human A/H5N1 cases and probable transmissions like the one described in *The Lancet* and another two reported retrospectively from Pakistan [1,23]? The time has probably come to be less excited about media or confirmed reports of isolated human cases that occur on almost a daily basis in the media and in newsletters from bodies like the Flu Information Centre in China (FIC, <http://www.flu.org.cn/en/default.html>). The virus remains highly pathogenic to humans (the most recent review undertaken by WHO still reports a case fatality rate of over 60 percent [5]), so these cases are often personal and family tragedies. However, sporadic confirmed cases now seem to represent background incidence in countries where A/H5N1 is entrenched in domestic poultry and there is close contact between birds and humans. Sporadic cases and small clusters like that in Jiangsu are common and, unless A/H5N1 fades away (as some other avian influenza viruses have), the world may remain in the Pandemic Alert Phase 3 (as defined by WHO [14]) for some years.

What European authorities must be concerned about are any ominous changes in the behaviour and the virology of the A/H5N1 viruses in humans, but also in poultry. In particular, more clusters of human A/H5N1 cases, larger clusters and lengthening chains of transmission which could indicate that these viruses are acquiring pandemic qualities (Pandemic Alert Phase 4 and 5 in WHO parlance [14]). That has not happened as yet. If anything, clusters seem to be less common and smaller at present than they were in 2005 and 2006. However, it has been pointed out that it would be dangerous to assume that because H5N1 has not yet acquired pandemic characteristics it does not have that potential, which is a point also made in the ECDC's risk assessment [2,13]. Continuing work by international organisations, governments and veterinarians to root out highly pathogenic avian influenza infections from poultry is fundamental. Where this is not possible in the short and medium term, it means there will be pressure on clinicians and public health authorities in the countries where the virus is endemic, common or simply regularly occurring in domestic poultry. It is difficult to know precisely which countries are concerned, but notable are Cambodia, China, Egypt, Laos, Indonesia, Myanmar, South Korea, Thailand and Vietnam, and recently also Bangladesh and Pakistan [25]. However, there are also countries like Nigeria, where A/H5N1 was seen in birds but is currently not reported, and other parts of sub-Saharan Africa where veterinary surveillance for highly pathogenic avian influenza in poultry is patchy (although improving following international investment). Does no signal mean that the virus has gone or rather that there are problems in surveillance?

Wherever the virus is present in poultry and people come into close contact with them, there needs to be continued detection of potential human cases, viral isolation and rapid sharing of virus through GISN and vigorous investigation around the cases to ensure they are only sporadic, and not part of a large or expanding cluster. Considering the resources deployed in Jiangsu by the provincial and

national specialists [1], it can be seen that this will not be easy for poorer countries, certainly not without support from the rest of the world. Less sophisticated and resource-demanding investigations will probably need to be developed and made sure to be carried out and sustained at least for some years to come.

References

1. Wang H, Feng Z, Shu Y, Yu H, Zhou L, Zu R, et al. Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. *The Lancet*. Early Online Publication, 8 April 2008.
2. Hien NT, Farrar J, Horby P. Person-to-person transmission of influenza A (H5N1). Comment. *The Lancet*. Early Online Publication, 8 April 2008.
3. Yu H, Feng Z, Zhang X, Xiang N, Huai Y, Zhou L, Human influenza A (H5N1) cases, urban areas of People's Republic of China, 2005-2006. *Emerg Infect Dis*. 2007;13(7):1061-4.
4. Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W, Puthavathana P, Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med*. 2005;352(4):333-40.
5. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, Abdel-Ghaffar AN, Chotpitayasunondh T, Gao Z, Hayden FG, Nguyen DH, et al. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med*. 2008;358(3):261-73.
6. Nicoll A. Human H5N1 infections: so many cases – why so little knowledge? *Euro Surveill* 2006;11(5):74-5. Available from: <http://www.eurosurveillance.org/em/v11n05/1105-221.asp>
7. Olsen SJ, Ungchusak K, Sovann L, Uyeki TM, Dowell SF, Cox NJ, et al. Family clustering of avian influenza A (H5N1). *Emerg Infect Dis*. 2005;11(11):1799-1801.
8. Uyeki TM, Bresee JS. Detecting human-to-human transmission of avian influenza A (H5N1). *Emerg Infect Dis*. 2007;13(12):1969-71.
9. Savill NJ, St Rose SG, Keeling MJ, Woolhouse ME. Silent spread of H5N1 in vaccinated poultry. *Nature*. 2006;442(7104):757.
10. Olsen SJ, Ungchusak K, Birmingham M, Bresee J, Dowell SF, Chunsuttiwat S. Surveillance for avian influenza in human beings in Thailand. *Lancet Infect Dis*. 2006;6(12):757-8.
11. Ministry of Public Health, Thailand. Avian Influenza (Bird Flu) Control. Available from: http://thaigcd.ddc.moph.go.th/Bird_Flu_main_en.html
12. Buxton Bridges C, Katz JM, Seto WH, Chan PK, Tsang D, Ho W, 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(1):344-8.
13. ECDC. The Public Health Risk from Highly Pathogenic Avian Influenza Viruses Emerging in Europe with Specific Reference to type A/H5N1. June 2006. Available from: http://www.ecdc.europa.eu/Health_topics/Avian_Influenza/pdf/060601_public_health_risk_HPAI.pdf
14. World Health Organization. WHO global influenza preparedness plan. The role of WHO and recommendations for national measures before and during pandemics. Geneva, 2005. Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf
15. World Health Organization. Situation updates - Avian influenza. Available from: http://www.who.int/csr/disease/avian_influenza/updates/en/index.html
16. World Health Organization. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. Accessed on 8 April 2008. Available from: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_04_08/en/index.html
17. Kandun IN, Wibisono H, Sedyaningih ER, Yusharmen, Hadisoedarsuno W, Purba W, et al. Three Indonesian clusters of H5N1 virus infection in 2005. *N Engl J Med*. 2006;355(21):2186-94.
18. ECDC. Influenza Virus Sharing – Interim ECDC Briefing. November 2007. Summary. Available from: http://ecdc.europa.eu/pdf/ECDC_influenza_briefing.pdf
19. World Health Organization. Global Influenza Surveillance Network. Available from: <http://www.who.int/csr/disease/influenza/influenzanelwork/en/index.html>
20. World Health Organization. International Health Regulations (2005). Available from: <http://www.who.int/csr/ihr/en>
Revision of the International Health Regulations. Full text. Available from: http://www.who.int/gb/ebwha/pdf_files/WHA58/WHA58_3-en.pdf

21. Ferguson NM, Cummings DA, Cauchemez S, Fraser C, Riley S, Meeyai A, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature*. 2005;437(7056):209-14.
22. World Health Organization. Interim Protocol: Rapid operations to contain the initial emergence of pandemic influenza. Available from: http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/en/index.htm
23. World Health Organization. Avian influenza - situation in Pakistan - update 2. 3 April 2008. Available from: http://www.who.int/csr/don/2008_04_03/en/index.html
24. Food and Agriculture Organization (FAO), World organisation for animal health (OIE). The Global Strategy for Prevention and Control of H5N1 Highly Pathogenic Avian Influenza. Revised March 2007. Available from: http://www.fao.org/docs/eims/upload/210745/glob_strat_HPAI_apr07_en.pdf
25. World Organisation for Animal Health (OIE). Update on highly pathogenic avian influenza in animals (type H5 and H7). Available from: http://www.oie.int/download/AVIAN%20INFLUENZA/A_AI-Asia.htm

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