Assessing the potential pandemic risk of recent avian influenza viruses

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It is essential to carefully monitor avian H5Nx influenza viruses as they continue to evolve
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Highly pathogenic avian influenza viruses (HPAI) of the influenza A, H5N1 subtype (the H refers to the type of haemagglutinin and the N refers to the type of neuraminidase) have circulated in various parts of Asia since 1996, infecting millions of birds and, occasionally, humans [1, 2]. Since 2014, a subclade of these viruses has further reassorted into what have been referred to as H5Nx viruses, owing to the variety of N genes that have successfully reassorted with this H5 haemagglutinin. These reassortants have spread in an unprecedented fashion over 60 countries [3], with H5N8 and H5N2 outbreaks in Europe and North America [4, 5] having caused major economic losses in the poultry industry. The H5N6 has replaced H5N1 as the dominant HPAI in Southern China, especially in ducks and geese [6]. The H5N6 virus appears to have low mortality in ducks and geese even though it was still 100% lethal in chickens [7] and has also occasionally infected humans in China, where 16 cases have been detected in the last 2 years, with 11 deaths (ages, 11–65 years; median age, 40 years) [8].

Given the spread and pathogenicity of these H5Nx viruses, especially the H5N6 viruses, it is important to understand the current and future risks that these viruses pose to human health and determine the chances of these viruses becoming more transmissible in man and potentially causing the next influenza pandemic. A key factor in making this assessment is knowledge of the binding specificity of these viruses. In the World Health Organization Tool for Influenza Pandemic Risk Assessment [9] and the US Centers for Disease Control and Prevention Influenza Risk Assessment Tool [10], receptor binding properties are ranked number 1 and number 3, respectively, in the risk element weightings for measuring the likelihood of a virus becoming pandemic. A report in this issue of the *European Respiratory Journal* led by Dr Michael Chan from Hong Kong University entitled “Tropism and innate host responses of influenza A/H5N6 virus: an analysis of *ex vivo* and *in vitro* cultures of the human respiratory tract” attempts to address this issue by examining the tropism of these recent H5N6 viruses for their ability to bind and replicate in mammalian respiratory cells [11].

CHAN *et al.* [11] compared the binding and replication of one human derived H5N6, two avian derived H5N6, two human derived H5N1 and one human A(H1N1) virus from the 2009 pandemic (A(H1N1) pdm09), in a series of *in vitro* tests using human tissue explants and cultures of human primary respiratory cells. The H5N6 virus A/Guangzhou/39715/2014 (A/GZ) they used was originally isolated from a 59-year-old male patient on day 8 of his illness, from which he recovered, after being hospitalised in Guangzhou, China. The A/GZ virus replicated efficiently in explants of human lung and bronchus at

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similar levels to the human 2009 pandemic H1N1 virus and was significantly better than the two recent avian A(H5N6) viruses and two earlier A(H5N1) viruses isolated from humans in 1997 and 2011. Replication was also assessed by immunohistochemical staining of tissue explants 24 h after infection with the A/GZ virus, and this showed viral protein from H5N6 in both the bronchus and lung tissues predominately in the type II alveolar epithelial cells. The A/GZ virus also replicated best in cultures of primary human alveolar cells and induced higher levels of the pro-inflammatory cytokines IFN- β and CCL2 than the A(H1N1)pdm09 virus but lower levels than the A(H5N1) virus.

While these results should be viewed with caution as they only cover a single recent human derived A(H5N6) virus that had been isolated in embryonated chicken eggs (which may have subtly modified the virus in terms of its binding properties), they nevertheless raise concerns about the increasing adaption of these viruses for human respiratory tissues. Their work is supported by a recent publication by Sun *et al.* [12] who found that four avian-derived A(H5N6) viruses (all with high homologies to A/GZ H protein) had comparable binding affinity to avian (SA α 2,3Gal) and human (SA α 2,6Gal) sialic acid receptors in both solid-phase binding experiments and haemagglutination assays using re-sialylated chicken red blood cells. In contrast, a chicken derived A(H5N1) and a human derived A(H1N1)pdm09 virus did not show cross reactivity with each of the receptor types and retained their expected specificity for their host species as seen in another 2008 study. This study also performed virus-binding studies to paraffin sections of human trachea and lung sections and found that their A(H5N6) viruses bound in a similar pattern to the human derived A(H1)pdm virus. Another study by Guo *et al.* [13] examined the binding of various recombinant haemagglutinin proteins (rH) made from an A(H5N8) virus A/chicken/Netherlands/14015526/2014, an H5N1 virus (A/wild duck/Hunan/211/2005) and a seasonal A(H1N1) virus (A/Kentucky/UR06-0258/2007). The A(H5N1) rH showed good binding to fetuin (high in human 2–6-linked sialosides) and no binding to transferrin (high in avian 2–6-linked sialosides), while the A(H1N1) rH showed low-level binding to fetuin and good binding to transferrin. Notably, while the H5N8 rH had good binding to fetuin, it also had low-level binding to transferrin. This indicated to the authors that the A(H5) rH had a preference for binding to α 2–3-linked sialic acids but also showed an increased ability to bind to α 2–6-linked sialosides, similar to those found in human respiratory tissues, compared to the earlier H5N1 rH.

Apart from the receptor-binding characteristics, other factors are important in determining the potential for a virus to spread efficiently from person to person, and these can be assessed in animal models of virus transmission. Some work has already been performed with the H5N6 [12] and H5N8 [14] viruses in the ferret transmission models. Neither of these viruses were capable of aerosol transmission from the donor ferrets (artificially infected with virus) to naïve recipient ferrets that were separated by a wire mesh. However, both the avian H5N6 viruses tested were capable of infecting recipient ferrets that had been in close contact (co-housed) with the infected donors. In contrast, a 2008 H5N1 virus could not transmit from donor ferrets to either contact- or aerosol-exposed ferrets, while a human-derived H1N1 virus from the 2009 pandemic could infect ferrets by using both the contact and aerosol modes. Examination of mice experimentally inoculated with H5N6 [12] or ferrets given H5N6 [12] or H5N8 [14] showed that their pathogenicity is reduced compared to H5N1 viruses; however, the H5N6 viruses still appears to be quite lethal in humans with around a 70% hospitalised fatality rate to date. In summary, this present study, supported by other studies, make it essential to carefully monitor these H5Nx viruses as they continue to evolve, to ensure we have a complete picture of their virological and epidemiological characteristics, so that we can attempt to control their spread in avian species or limit their contact with humans, while continuing to produce suitable seed vaccines in case these viruses become more easily transmissible in humans.

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