Avian influenza and the implication for human infection

David J Speers

Department of Microbiology
PathWest Laboratory Medicine WA
Queen Elizabeth II Medical Centre
Hospital Avenue, Nedlands
WA 6009, Australia
Tel +61 8 9346 2197
Fax +61 8 9346 3960
Email
david.speers@health.wa.gov.au

Highly pathogenic avian influenza due to H5N1 virus has decimated poultry flocks throughout the eastern hemisphere and resulted in over 600 human infections. Despite the H5N1 virus being endemic in several Asian countries, with ongoing human exposure and infection, efficient human-to-human transmission has not been reported. There is much concern over the pandemic potential of this virus should this transmissibility develop due to its widespread circulation, continued evolution and recent research showing relatively few mutations are needed for airborne mammalian transmission. It is unknown whether the emergence of such a mutated H5N1 virus would cause a pandemic owing to uncertainties of how the virus would behave in humans.

Influenza pandemics require a susceptible human population, usually achieved by a new influenza A virus with a novel haemagglutinin (HA), and a virus that can infect then efficiently transmit between humans[1]. The concern that the highly pathogenic avian influenza (HPAI) H5N1 virus may lead to another pandemic is for three reasons. Firstly, the 1918, 1957 and 1968 influenza pandemics, due to HA subtype H1, H2 and H3 viruses respectively, have not provided humans with immunity to influenza viruses with other HA subtypes. Secondly, pandemic influenza viruses all have their origin in avian viruses[2]. The viruses responsible for the 1957 and 1968 pandemics were the result of human influenza viruses reassorting their gene segments with an avian virus to obtain the avian HA gene segment, whereas the 1918 pandemic was more likely due to an avian virus adapted to efficient transmission between humans. Thirdly, the 1957 and 1968 pandemics originated in southern Asia, with its dense populations of people, terrestrial poultry, wild birds and pigs, where the HPAI H5N1 virus is now endemic[3]. This increases the likelihood of reassortment occurring between human influenza virus and H5N1 virus during co-infection to produce a new H5 influenza virus capable of efficient human-to-human transmission. The development of a human-transmissible H5N1 virus would probably cause a pandemic[4].

Outbreaks of HPAI in bird flocks occurred regularly through the last century in Europe, North America and Australia and outbreaks of HPAI resulting in human infection are not new. Most human cases have followed direct handling of infected terrestrial poultry, but it is unclear if this reflects an increased probability of exposure or viral adaptation to poultry resulting in a greater propensity to transmit to humans. The current era of introduction of avian influenza into humans was heralded in 1997 by an H5N1 HPAI virus in Hong Kong, which resulted in 18 human cases, six of whom died. This was followed in 2003 by an H7N7 HPAI outbreak in Dutch poultry that caused 83 human cases of conjunctivitis and one death due to acute respiratory distress syndrome, and repeated introductions of H9N2 viruses in Hong Kong and China causing mild flu-like illness[2]. However, the social, economic and health impact of these outbreaks were to be overshadowed by the current H5N1 HPAI epidemic.

Since December 2003, 606 cases of H5N1 human infection have been reported from 15 countries[5]. Moreover, serological studies in exposed human populations have found incidences of 1–2%, suggesting human infection may be more common but that many cases are asymptomatic or mild[1]. The route of infection may be via the respiratory tract, the gastrointestinal tract or following conjunctival exposure. Similar to seasonal influenza, HPAI human disease has no age predilection (3 months to 75 years), with an incubation period of 2–4 days and initial symptoms of fever and cough[2]. Unlike H7 HPAI viruses, conjunctivitis appears to be rare with H5N1 infection, as are CNS manifestations. In most cases, rapid progression to primary viral pneumonia occurs with symptoms of diarrhoea and vomiting frequently found. It is likely that milder disease is missed, but the overall mortality of cases reported to the World Health Organization (WHO) is high (60%)[5] with a median duration from onset to death of nine days due to respiratory failure. The mortality rate is highest in those in the

10- to 19-year age group (76%) and lowest in those over 50 years (40%). Fatal H5N1 disease during pregnancy has been reported[2].

So, how likely is the emergence of an H5 influenza virus able to efficiently transmit between humans? Limited cases of HPAI H5N1 human-to-human transmission have been reported among family members following significant physical contact with an infected individual but not widespread transmission. Considering the massive exposure of the H5N1 virus to humans since its emergence over a decade ago, the conditions that allow the development of a human-transmissible H5 virus must be exceedingly difficult to achieve. This has led some to question the value of human H5N1 vaccine development[4]. It was initially thought that the lack of efficient human-to-human transmission was due to the differential binding of the avian and human influenza virus HA to the sialic acid (SA) receptors on the human (α-2,6-linked SA) and avian (α-2,3-linked SA) respiratory epithelium[2]. More recent research, however, suggests the mechanisms for host tropism and the reasons why HPAI H5N1 cannot transmit efficiently between humans are more complex[6,7].

In an attempt to understand what changes to the H5N1 virus would be required to allow efficient mammalian transmission, two groups of influenza researchers developed mutations of the H5N1 virus to increase mammalian transmissibility. The National Science Advisory Board for Biosecurity initially recommended against publishing the detailed scientific methods of these two studies due to concerns over dual-use research (where the research could also be used for nefarious purposes)[8] but later reversed this decision allowing revised versions of both studies to be published in full[9]. Imai *et al*.[4] showed that a reassortment virus containing a mutated HA from HPAI H5N1 and seven gene segments from the H1N1 2009 pandemic virus was capable of droplet transmission in their ferret model. Of more concern, Herfst *et al*.[10] achieved airborne transmissibility between ferrets without recombination and with only five amino acid substitutions in the H5N1 genome. They used a combination of site-directed mutagenesis to enhance transmissibility then serial passage through ferrets.

It is not known if an H5 influenza virus transmissible in ferrets will also be transmissible in humans or if a H5N1 virus that has adapted to efficient human-to-human transmission will remain virulent. Of note, the H5 reassortment virus created by Imai *et al.*[4] and the mutated H5N1 virus created by Herfst *et al.*[10] did not cause mortality in the ferrets following transmission. A sobering thought is that two of these mutations occur commonly in H5N1 viruses and a few H5N1 isolates found in nature are only two mutations away from those created by these researchers[11].

H5N1 influenza A virus has been evolving since its emergence and now comprises multiple sublineages of multiple genotypes with dominant clades in several countries[1]. Although an H5 influenza pandemic has not occurred, this rapid evolution and divergence means we must not become complacent. Ongoing surveillance in regions of HPAI H5N1 circulation is essential to look for the emergence of receptor-binding variants of H5N1 virus which may increase its pandemic potential, while we consider the options of pre-pandemic vaccination, new vaccine technologies to shorten production times or a universal influenza vaccine. Our experience concerning influenza pandemics is limited to four such events over the last 100 years and laboratory predictions of virus phenotype based on nucleotide sequence are imprecise[12]. This, together with the uncertainties of how the virus would behave in humans and evolve mandates a cautious approach when considering the pandemic potential of the H5N1 virus.

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Biography

Dr Speers is Head of Microbiology, Queen Elizabeth II Network, PathWest Laboratory Medicine WA, an Infectious Diseases Physician at Sir Charles Gairdner Hospital, and a Clinical Senior Lecturer at the School of Medicine and Pharmacology, The University of Western Australia. His interests include virology and the molecular and serological diagnosis of infections.