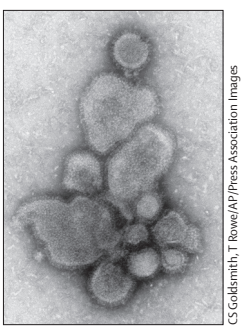
Genesis of avian-origin H7N9 influenza A viruses



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Since March, 2013, 126 laboratory-confirmed cases of avian influenza A H7N9 have been detected in ten provinces or municipalities in east and southeast China (as of April 30, 2013).[1] Most H7N9-infected patients are older (approximate median age 62 years) urban men who reported exposure to chickens or captive-bred pigeons either professionally or through visits to live poultry markets.[2,3] Patients rapidly develop progressive pneumonia leading to acute respiratory distress syndrome and multiorgan failure.[4] The case fatality rate seems to be roughly 20%,[5] although this early estimated rate will probably prove to be inflated when the denominator increases upon detection of more moderate, mild, or asymptomatic infections through seroepidemiological studies.

In *The Lancet*, Di Liu and colleagues[6] report phylogenetic analyses of the eight gene segments from representatives of the novel H7N9 influenza virus, so as to shed further light on its evolutionary origins. They report that the virus genome resulted from at least three reassortment events, bringing together H7 haemagglutinin and N9 neuraminidase segments in a different constellation from previously reported H7N9 lineages in avian hosts. The H7 gene segment is most closely related to the haemagglutinin gene from H7N3 viruses isolated from ducks in China's Zheijang province, whereas the neuraminidase gene is most closely related to that from H7N9 isolates from Korean ducks and wild birds. The internal gene segment constellation seems to be inherited from H9N2 avian influenza viruses circulating in chickens, but a 2012 H9N2 isolate from a brambling, A/brambling/Beijing/16/2012(H9N2), is the closest relative for the PB2, PB1, and PA segments at the present time.

Intriguingly, one of the novel H7N9 strains is not monophyletic with the other human isolates in the viral nucleoprotein gene, suggesting that other locally circulating segments in poultry have already replaced segments in descendants of the new reassortant viruses. The complex and ongoing reassortment dynamics could serve as a warning of the potential emergence of new viruses and acquisition of other gene segments by this new H7N9 virus (perhaps from locally circulating human or porcine influenza viruses). By contrast with H5, for which all 566 associated human infections since 1997 consistently possessed the N1 neuraminidase subtype (except for some putative H5N2 seroconversions), H7 viruses have already shown tendencies towards genetic promiscuity by partnering with N1, N2, N3, N7, and N9 subtypes, resulting in human infections.[7]

For many H7N9 gene segments, Liu and colleauges[6] report recent common ancestors for the four human isolates, but the closest relatives (eg, in haemagglutinin and neuraminidase) are still divergent from this most recent common ancestor, suggesting that the exact time, location, and host species implicated in the origin of the new H7N9 remain uncertain because of an absence of surveillance data, which is acknowledged by the authors. We can therefore draw a parallel with genetic analyses of H1N1 during the period of early pandemic expansion in 2009,[8] with respect not only to multiple reassortment events in the ancestral history of the virus but also the unsampled history that was discovered, and the associated difficulties in clearly delineating the exact origin of the epidemic.

Hopefully, the intensified surveillance measures and continued sequencing of relevant sample collections will provide further insight into the evolutionary and ecological dynamics of the novel avian influenza A H7N9 virus. Clarification of its circulation history could be particularly important because low pathogenicity in avian hosts probably allowed the virus to spread silently in domestic and wild birds. Containing this hidden epidemic might prove very challenging in view of the magnitude of the domestic and wild bird populations in China.

Liu and colleagues[6] also report mutations in H7N9 strains that could favour high-affinity interaction with human receptors in the upper respiratory tract, a prerequisite for virus transmission by the aerosol route. Although the H7N9 virus might be substantially more easily transmissible from poultry to humans beings than was H5N1, no evidence of sustained person-to-person transmission has been noted. Further monitoring and analyses of human isolates are needed to assess the genetic barrier (if any) to human adaptation. The timing and probability that this H7N9 will acquire the capacity for person-to-person transmission is impossible to estimate. Testing of H7N9 strains in ferrets[9] will help to measure the effect of different mutations on potential transmission via the aerosol route.

H7N9 is an avian influenza virus that rings alarm bells, but seems to ring them more quietly than did H5N1. One reason is that H7N9, by stark contrast with H5N1, does not generate overt morbidity or mortality in poultry, which effectively removes culling as a feasible method to stem bird-to-person transmission, although temporary suspension of live poultry markets in Shanghai seemed to slow the local H7N9 epidemic.[10] Another reason for the subdued response is that governments, supranational organisations, and even media outlets are still reeling from the harsh post-hoc criticism that they received because of the supposedly exaggerated and overmanaged H1N1 pandemic in 2009. However, if H7N9 spreads to other countries or continents, or if sustained person-to-person transmission develops, we should quickly take swift and decisive actions to prevent, quell, and manage an imminent pandemic.

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We declare that we have no conflicts of interest.

1 WHO Disease Outbreak News. Human infection with influenza A(H7N9) virus—update. http://www.who.int/csr/don/2013_04_25/en/index.html (accessed April 28, 2013).
2 Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; published online April 11. DOI:10.1056/NEJMoa1304459.
3 Li A, Zhou L, Zhou M, et al. Preliminary report: epidemiology of the avian influenza A(H7N9) outbreak in China. *N Engl J Med* 2013; published online April 24. DOI: 10.1056/NEJMoa1304617.
4 Chen Y, Liang W, Yang S, et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. *Lancet* 2013; published online April 25. http://dx.doi.org/10.1016/S0140-6736(13)60903-4.
5 European Centre for Disease Prevention and Control. Epidemiological update of 26 April on avian influenza A(H7N9) virus. http://www.ecdc.europa.eu/en/press/news/Lists/News/ECDC_DispForm.aspx?List=32e43ee8-e230-4424-a783-85742124029a&ID=902&RootFolder=%2Fen%2Fpress%2Fnews%2FLists%2FNews (accessed April 28, 2013).
6 Liu D, Shi W, Shi Y, et al. Origin and diversity of novel avian influenza A H7N9 viruses causing human infection: phylogenetic, structural, and coalescent analyses. *Lancet* 2013; published online May 1. http://dx.doi.org/10.1016/S0140-6736(13)60938-1.
7 Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. *Emerg Infect Dis* 2009; **15:** 859–65.
8 Smith GJ, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 2009; **459:** 1122–25.
9 Kupferschmidt K, Enserink M. Chinese H7N9 virus making its way to labs around the world. http://news.sciencemag.org/scienceinsider/2013/04/more-h7n9-infectionsreported.html (accessed April 29, 2013).
10 Mu X. No proof of H7N9 interpersonal transmission. *Xinhua* April 24, 2013. http://news.xinhuanet.com/english/china/2013-04/24/c_132336981.htm (accessed April 29, 2013).