Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

12 Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. *PLoS One* 2010; **5:** e12888.
13 Fayorsey RN, Saito S, Carter RJ, et al. Decentralization of pediatric HIV care and treatment in five sub-Saharan African countries. *J Acquir Immune Defic Syndr* 2013; **62:** e124–e130.
14 Nardell E, Dharmadhikari A. Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. *Int J Tuberc Lung Dis* 2010; **14:** 1233–43.

Age distribution of cases caused by different influenza viruses

As of May 30, 2013, an outbreak[1] of avian influenza A H7N9 virus had caused 132 human cases of influenza in China, most of which resulted in severe disease and 37 of which were fatal.[2] These H7N9 viruses are avian influenza viruses with low pathogenicity. Gene segments are derived from H9N2 viruses of poultry origin and the haemagglutinin and neuraminidase gene segments come from wild-bird origin H7 and N9 viruses, respectively.[1] 71% of 131 reported cases have been in individuals older than 50 years,[3] and thus such patients seem more at risk of severe disease and death than are younger individuals.[4]

The reasons for this disproportionate age distribution are largely unknown. It has been speculated that older individuals might have higher exposure to infected poultry, which could also be the reason why more men than women are affected.[5] However, many patients did not report contact with poultry, the incidence of H7N9 influenza virus infections in poultry seems very low, and the incidence of avian influenza A H5N1 virus infections was higher in younger than in older individuals within the same population, all of which argue against this possible explanation.

Alternatively, elderly people could be more prone to develop severe disease upon infection with avian influenza A H7N9 viruses. Ageing is an important risk factor in viral respiratory tract infections (eg, caused by influenza or severe acute respiratory syndrome coronavirus) and is associated with changes in immune function.[6] In elderly people, these infections can cause severe pneumonia triggered by exacerbated innate host responses, which was confirmed experimentally in aged non-human primates.[7] However, the disease caused by H7N9 viruses resembles that caused by H5N1 viruses, and therefore changes in innate immunity are unlikely to be the only cause of the disproportionate age distribution.

The age distribution of patients infected with H7N9 contrasts with that of the 2009 pandemic influenza A H1N1 virus. This virus was of swine origin and its haemagglutinin gene resembled that of human influenza A H1N1 viruses that circulated before 1950.[8] Therefore, individuals born before 1957 could have been exposed to these viruses earlier in life and developed antibodies or memory B cells, or both, that cross-reacted with the pandemic A H1N1 viruses.[9,10] The older age group were afforded some protection against the pandemic strain via the presence of these cross-reactive antibodies, [11] and were therefore spared compared with younger people during the 2009 pandemic and subsequent influenza seasons in which the virus continued to circulate.

We postulate that interference of pre-existing antibodies with infection of elderly people by pandemic A H1N1 virus might have had negative effects. It might have prevented the induction of recall cross-reactive virus-specific T-cell response, which could contribute to heterosubtypic immunity. Rapid and strong CD4 and CD8 T-cell responses were recorded in individuals infected with the pandemic A H1N1 virus,[12] which might have been absent in older patients as a result of protective pre-existing antibodies to pandemic A H1N1 virus, resulting in higher susceptibility to infection with H7N9 virus (figure). Similarly, yearly vaccination of high-risk patients against seasonal influenza prevented the induction of virus-specific CD8 T-cell responses, which would usually be induced by natural infection with seasonal influenza viruses[13] and was noted in animal models.[14] A possible explanation is that the presence of cross-reactive antibodies predisposed for more severe

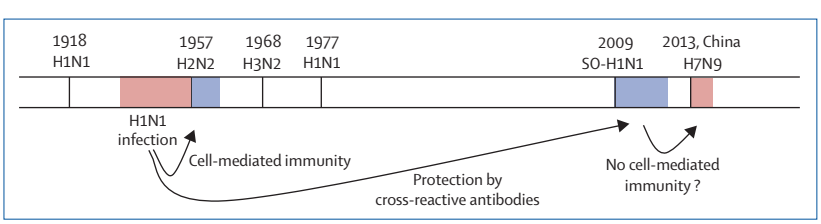

***Figure*: Theoretical effect of immunological imprinting on disease severity in H7N9 avian influenza A virus infections**
SO=swine origin.

disease, a finding that, although not previously noted in influenza, has been reported for some viral diseases.[15]

During the influenza pandemic of 1957, which was caused by the H2N2 subtype, individuals who had previously been infected with the H1N1 virus were less likely to be infected with H2N2 influenza than were those who had not.[16] The low incidence of severe H5N1 infections in elderly compared with younger people might be related to the presence of cross-protective antibodies to neuraminidase that are induced by seasonal influenza A H1N1 viruses.[17]

Overall, we postulate that antibodies to pre-1957 influenza A H1N1 viruses protected elderly people against pandemic A H1N1 virus infection, but consequently affected the development of heterosubtypic immunity and the disease outcome of H7N9 virus infections. The rate and timing of pandemic A H1N1 virus infections might have revealed the differences in H7N9 disease outcome, by contrast with historical infections with seasonal influenza A H3N2 viruses. This counterproductive imprinting of immunity might increase susceptibility to H7N9 virus infection. For that reason, older individuals should be given priority for vaccination if sustained person-to-person transmission of H7N9 viruses emerges. To obtain a better understanding of the role of imprinting of the adaptive immune system in H7N9 disease severity, prospective cohort studies in which cross-reactive T-cell immunity and virus-specific serum antibodies are tested for are imperative before possible wider spread of the virus.

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1 Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; **368:** 1888–97.
2 WHO. Number of confirmed human cases of avian influenza A(H7N9) reported to WHO. http://www.who.int/influenza/human_animal_interface/influenza_h7n9/08_ReportWebH7N9Number.pdf (accessed July 3, 2013).
3 MCEIRS. http://www.cidrap.umn.edu/sites/default/files/public/downloads/topics/mceirs_h7n9_graphs.pdf (accessed July 5, 2013).
4 Arima Y, Zu R, Murhekar M, Vong S, Shimada T. Human infections with avian influenza A(H7N9) virus in China: preliminary assessments of the age and sex distribution. *WPSAR* 2013; **4:** 1–3.
5 Li Q, 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.
6 Meyer KC. The role of immunity in susceptibility to respiratory infection in the aging lung. *Respir Physiol* 2001; **128:** 23–31.
7 Smits SL, de Lang A, van den Brand JM, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. *PLoS Pathog* 2010; **6:** e1000756.
8 Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 2009; **325:** 197–201.
9 Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009; **361:** 1945–52.
10 Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature* 2009; **460:** 1021–25.
11 Skountzou I, Koutsonanos DG, Kim JH, et al. Immunity to pre-1950 H1N1 influenza viruses confers cross-protection against the pandemic swine-origin 2009 A (H1N1) influenza virus. *J Immunol* 2010; **185:** 1642–49.
12 Hillaire ML, van Trierum SE, Bodewes R, et al. Characterization of the human CD8(+) T cell response following infection with 2009 pandemic influenza H1N1 virus. *J Virol* 2011; **85:** 12057–61.
13 Bodewes R, Fraaij PL, Geelhoed-Mieras MM, et al. Annual vaccination against influenza virus hampers development of virus-specific CD8(+) T cell immunity in children. *J Virol* 2011; **85:** 11995–2000.
14 Bodewes R, Fraaij PL, Kreijtz JH, et al. Annual influenza vaccination affects the development of heterosubtypic immunity. *Vaccine* 2012; **30:** 7407–10.
15 Huisman W, Martina BE, Rimmelzwaan GF, Gruters RA, Osterhaus AD. Vaccine-induced enhancement of viral infections. *Vaccine* 2009; **27:** 505–12.
16 Epstein SL. Prior H1N1 influenza infection and susceptibility of Cleveland family study participants during the H2N2 pandemic of 1957: an experiment of nature. *J Infect Dis* 2006; **193:** 49–53.
17 Sandbulte MR, Jimenez GS, Boon AC, Smith LR, Treanor JJ, Webby RJ. Cross-reactive neuraminidase antibodies afford partial protection against H5N1 in mice and are present in unexposed humans. *PLoS Med* 2007; **4:** e59.

Point-of-care testing for community-acquired pneumonia

Community-acquired pneumonia is a life-threatening disease. An estimated 8% of patients are admitted to intensive care and overall estimated 30 day mortality is 4–11%.[1] Many bacteria and viruses cause community-acquired pneumonia (and can co-infect), and the causative pathogen (or pathogens) cannot be predicatively identified by any clinical, radiological, or biological methods.[2] Accordingly, antibiotic treatment is empirical, and guidelines recommend a combination of a β lactam with a macrolide.[2,3] Identification of the causative pathogen is usually delayed because clinical specimens are processed in a core laboratory, which is often in a different centre from the patient and the doctor. Culturing, if done, can also take several days.