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Epidemiology of the Influenza A Virus H5N1 Subtype and Memory of Immunity to the H2N2 Subtype

In their recent paper, Peter Palese and Taia T. Wang proposed a hypothesis to explain how an older circulating subtype of influenza A virus is replaced with a novel subtype (1). They and others also published experimental evidence supporting their hypothesis on the extinction of seasonal H1N1 viruses by the 2009 pandemic H1N1 viruses (2). Although they discussed only the disappearance of seasonal H1N1 and H2N2 subtypes, we think that the same mechanism may be working against the currently circulating H5N1 subtype.

The World Health Organization had reported a skewed age distribution of confirmed H5N1 cases in 2006 (3), and Matthew Smallman-Raynor and Andrew D. Cliff suggested the possibility that persons born before 1969 have immunity to the H5N1 subtype, which may be associated with geographically widespread influenza A events before the late 1960s (they also mentioned other behavioral and biological factors which can account for the observed skewing) (4). An obvious candidate for geographically widespread influenza A events before the late 1960s is the H2N2 pandemic in 1957, in which the seasonal H1N1 subtype, having circulated since 1918, was replaced by the H2N2 subtype (5). Palese and Wang (1) suggested that “the induction of cross-neutralizing antibodies directed against the stalk of the H1 hemagglutinin following infection with the related group 1 virus (H2N2) played a significant role in the protection of older segments of the population from disease in 1957 and in the elimination of the existing seasonal H1N1 virus.” Phylogenetically, the H2 hemagglutinin is closer to H5 hemagglutinin, which also belongs to group 1 (6), than to the H1 hemagglutinin when entire proteins are compared (7) and when the HA2 domains are compared (8). Therefore, the stalk-specific antibodies induced against the H2 subtype from 1957 to 1968 may be more cross-reactive to the H5 subtype and may have rendered the population born before 1968 more resistant to H5N1 subtypes than that born after 1968, who have experienced only seasonal H1N1 and H3N2 subtypes.

The subjects in the Smallman-Raynor and Cliff paper were likely to have been exposed to both subtypes (4); therefore, it is not possible to know the impact of exposure to seasonal H1N1 and H3N2 subtypes on resistance to the H5N1 subtype. However, because the H3 hemagglutinin belongs to group 2, the stalk-specific antibodies produced against H3 are less likely to be cross-reactive to group 1 hemagglutinins, including H5 (although there are reports of monoclonal antibodies in humans which can bind to group 1 hemagglutinins and some, not all, H3 hemagglutinins [9, 10], they are likely to be rarer than group-specific antibodies), suggesting that they do not contribute much to the resistance to H5N1.

Pica et al. showed that natural infection with the 2009 pandemic H1N1 strain boosted the titers of stalk-specific antibodies in humans (2); however, the seasonal vaccine (the inactivated 2008–2009 trivalent vaccine not containing the 2009 pandemic H1N1 hemagglutinin) did not (11). Other groups also found that vaccination with the inactivated 2009 pandemic H1N1 vaccine induced the stalk-specific antibodies efficiently (12–14). Some of the stalk-specific monoclonal antibodies reported to date are

cross-reactive to both 2009 pandemic H1N1 and H5N1 strains (9, 10, 13, 15). Therefore, we speculate that natural infection or vaccination with the pandemic 2009 H1N1 strain may make us more resistant to viruses of the H5N1 subtype because of these stalk-specific antibodies.

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