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Age distribution of cases caused by different influenza viruses

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We read with interest the comment by Rimmelzwaan, Fouchier and Osterhaus explaining different age distribution of cases caused by avian influenza A viruses of the H5N1 and H7N9 subtypes (1). They proposed that the low incidence of severe H5N1 infections in the elderly compared with younger people might be related to the presence of cross-protective antibodies to neuraminidase that had been induced by seasonal influenza A H1N1 viruses. There is another type of cross-reactive antibody which may contribute to the protection against the H5N1 subtype. In contrast to conventional neutralizing antibodies binding to the globular head of the hemagglutinin, which are subtype- or even strain-specific, antibodies binding to the stalk region of the hemagglutinin are broadly neutralizing. Some antibodies to the hemagglutinin stalk are subtype-cross-reactive (2).

Previously Matthew Smallman-Raynor and Andrew D. Cliff suggested a possibility that persons born before 1969 have immunity to the H5N1 subtype, which may have been associated with geographically widespread influenza A events before the late 1960s (3). We proposed that widespread influenza A events before the late 1960s may have been due to the H2N2 pandemic starting in 1957 (4), based on and expanding the hypothesis published by Peter Palese and Taia T. Wang (5). The stalk-specific neutralizing antibodies induced against H2 subtype viruses in 1957–68 may be more cross-reactive to the H5 subtype than those induced against the H1 subtype (the H1, H2 and H5 subtypes belong to Group 1 hemagglutinins, but the H5 subtype is more similar to the H2 subtype than the to the H1 subtype). This may have rendered the population born before 1968 more resistant to the H5N1 subtype than persons born after 1968, who only have experienced seasonal H1N1 and H3N2 subtypes.

Since the H7 subtype belongs to Group 2 hemagglutinins, most stalk-specific neutralizing antibodies induced against H2 subtype are unlikely to be cross-reactive to the H7 subtype and may not have induced more resistance in the older age group against the H7 subtype than the younger age group, resulting in the more typical age distribution of H7N9 subtype as an infectious disease. Although the H3 subtype belongs to the same Group 2 hemagglutinin as the H7, considering that the H3 subtypes have been circulating since 1968, it is difficult to know the impact of antibodies generated against the H3 subtype on the resistance against the H7 subtype. We think our hypothesis is not mutually exclusive with that offered by Rimmelzwaan et al.

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