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Sporadic human cases of swine-origin influenza before 2009 share the Sa epitope

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Recently, Xu et al. provided valuable insight into the structural basis of preexisting immunity to the 2009 H1N1 pandemic influenza virus.[1] They emphasize similarities between the 1918 Spanish flu and the current pandemic virus (e.g., strain CA04) in the critical Sa epitope, while other regions in the sequence have diverged. The authors report that "the antigenic sites of all known human H1 HAs from the 1930s to the present are highly divergent from CA04." While this is true for the selection of sequences analyzed in the report (after 1977 only H1N1 vaccine strains were included), we would like to add that considering all available human H1 HAs from 1900–2008,[2] identifies several sequences from pre-pandemic human infections that are identical to the pandemic CA04 in the very same epitope that is the focus of the authors' study. **Figure 1** reproduces data shown by Xu et al. with the additional human strains included. All of these share the 1918/2009-like epitope and are attributable to sporadic human infections from continuously circulating H1 strains in swine.[2-10] Xu et al. mention the 1976 outbreak among such cases, but the complete list of examples with sequence data available and sharing the 1918/2009-like epitope suggests at least 10 similar incidences during the last 30 years in 3 different regions of the world (**Fig. 1**). As the number of unreported or unsequenced similar cases is unknown, the question arises how much of the preexisting immunity could be attributable to some of these more sporadic human infection events. A possible answer to this difficult question could be extracted from another recent study[11] that estimates that approximately 4% of the US population born after 1980 had preexisting immunity against 2009 H1N1 through previous infections with related strains.

Note

The date >1980 is important as there has been a temporary vaccination effort in the United States for the swine-origin H1N1 outbreak in 1976, which would also result in immunization against 2009 H1N1. Alternative reasons would be cross-immunization through seasonal flu and vaccines or broadly neutralizing antibodies.

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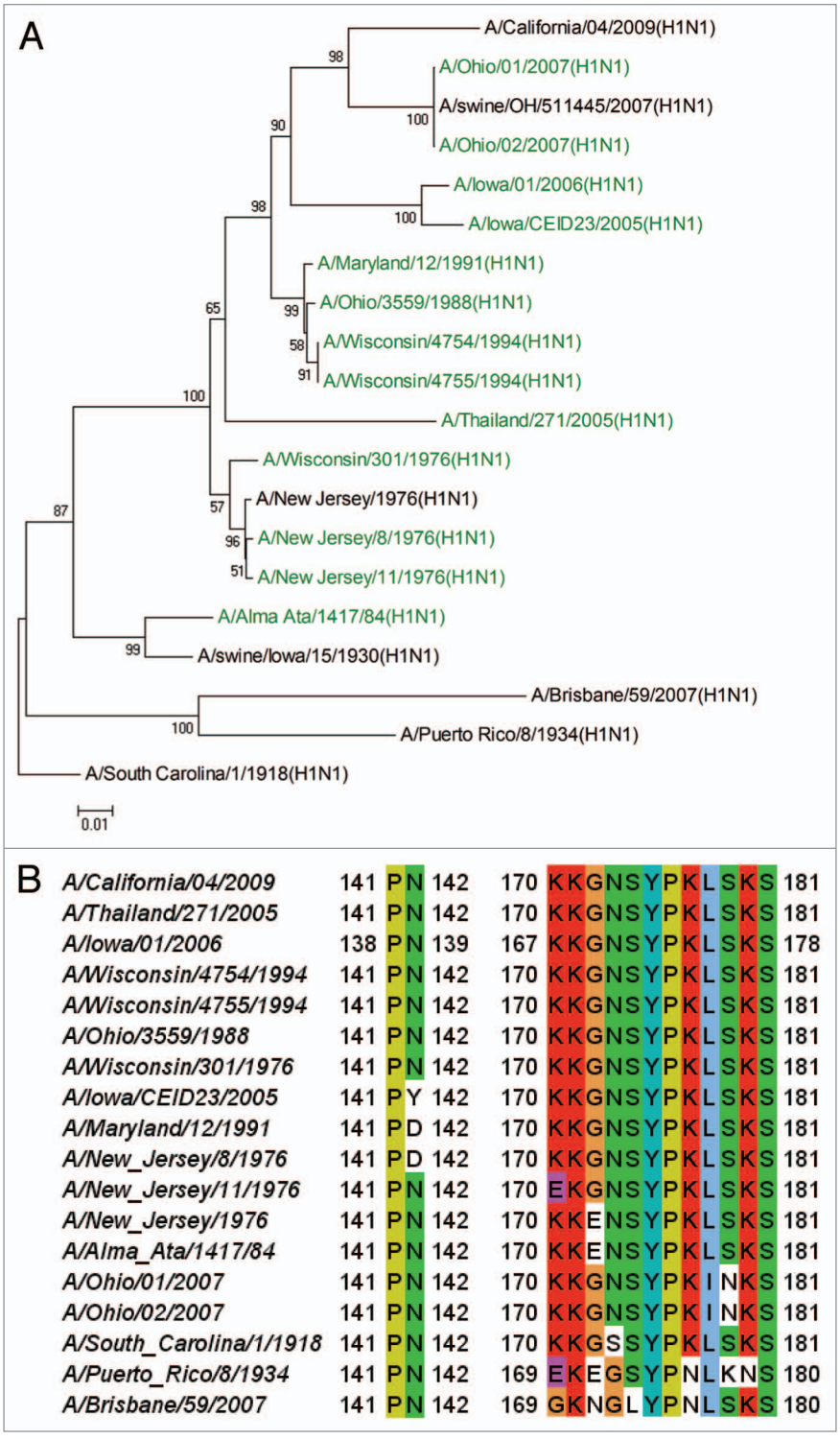

Figure 1 A and B. (A) Phylogenetic tree as in A of Xu et al. with strains of more human infections added and marked green. (B) Alignment of Sa epitope regions (as in C of Xu et al.) including the additional strains. Only the two 2007 Ohio cases have acquired an additional glycosylation site.

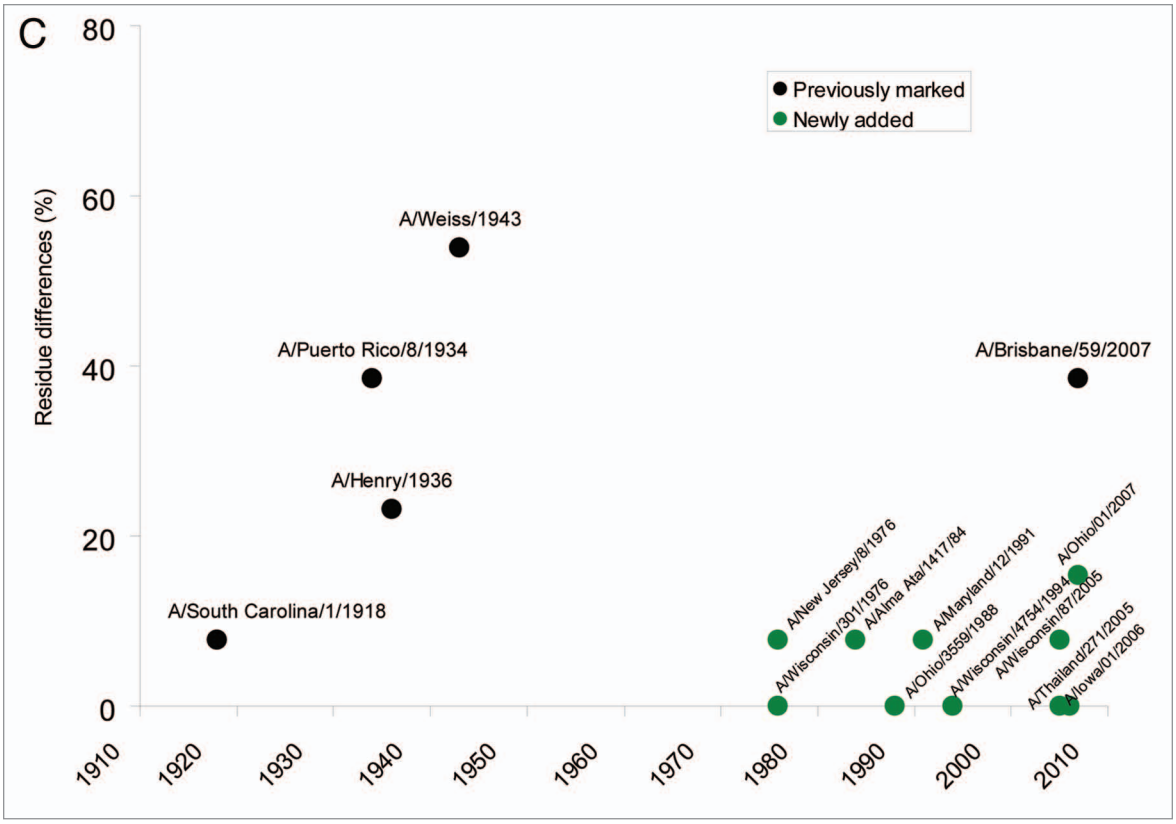

Figure 1 C. (C) Percent residue differences in the Sa epitope versus their temporal occurrence (as in F of Xu et al.). Additional instances of human infections by antigenically related strains are marked green.