

**FIG. W1. Three-dimensional structure of H3 influenza's hemagglutinin showing the mutations that drive designated antigenic drift events (A-I).** The residues and their antigenic binding domains are marked. Seven of nine sets of multiple mutations leading to antigenic drift are in the same antibody-binding sites. Seven of the nine sets of mutations (TABLE 1) that lead to the same antigenic drift are in antibody-binding sites that are the same (e.g., Y155H and K189R, which drive antigenic drift from BK79 to SI87 [C]) or neighboring (e.g., E135K, K145N, and E156K, which all drive antigenic drift from BE89 to BE92 [E]); the other 2 sets are in distant antibody-binding sites (e.g., N145K and G172D, which drive antigenic drift from BE92 to WU95 [F]; and K62E, K156Q, and, E158K, which drive antigenic drift from WU95 to SY97 [G]). The protein structure was visualized by using PyMOL with the H3 HA structure (pdb: 2VIU).

