

Figure S1. Amino acid sequence alignment of reference swine N2 used in N2 antisera generation and antigenic characterization. Gray boxes under the consensus sequence denote putative antibody epitopes extrapolated from human N2. N2-98 lineage sequences are above the black line and N2-02 lineage sequences are below. Mutations in putative epitopes were frequently detected, particularly between the 98 and 02 swine lineages.

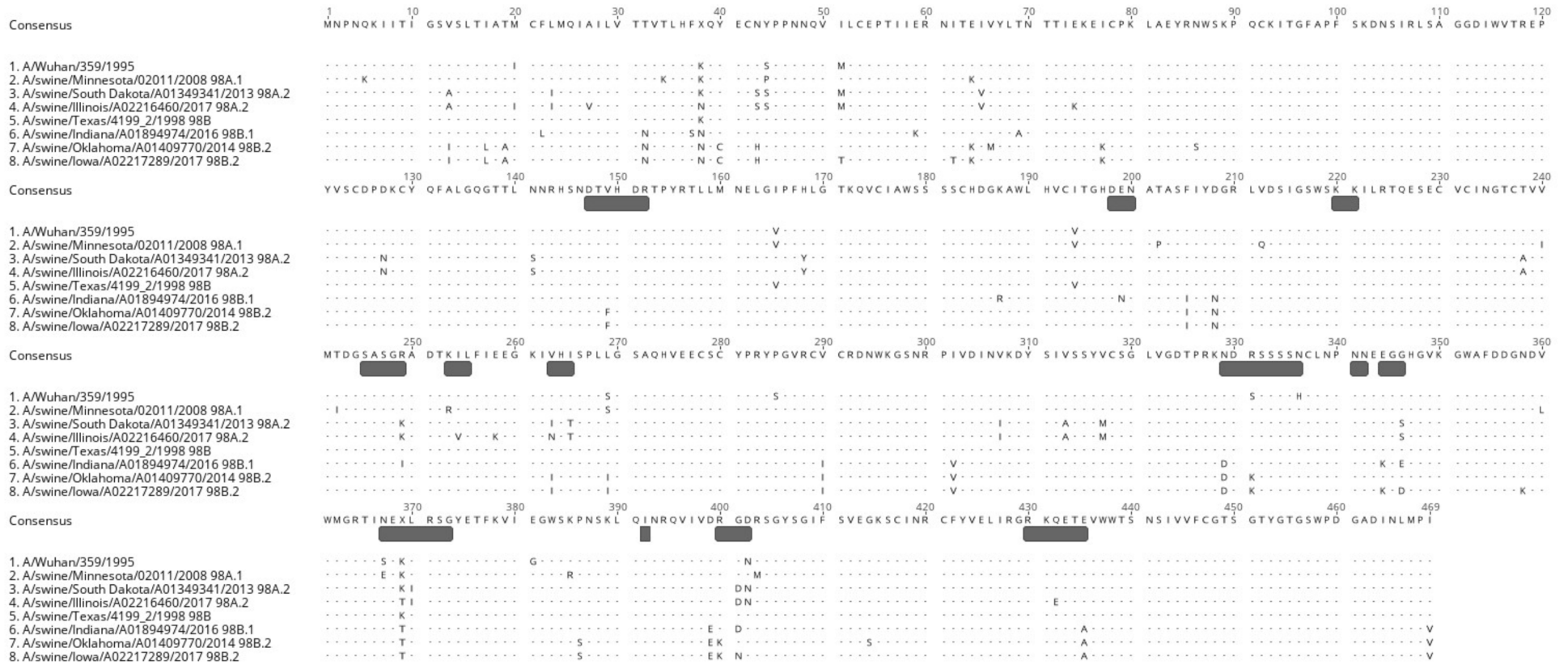


Figure S2. Amino acid sequence alignment of N2-98 lineage reference, contemporary, and human progenitor A/Wuhan/359/1995. Gray boxes under the consensus sequence denote putative antibody epitopes extrapolated from human N2.

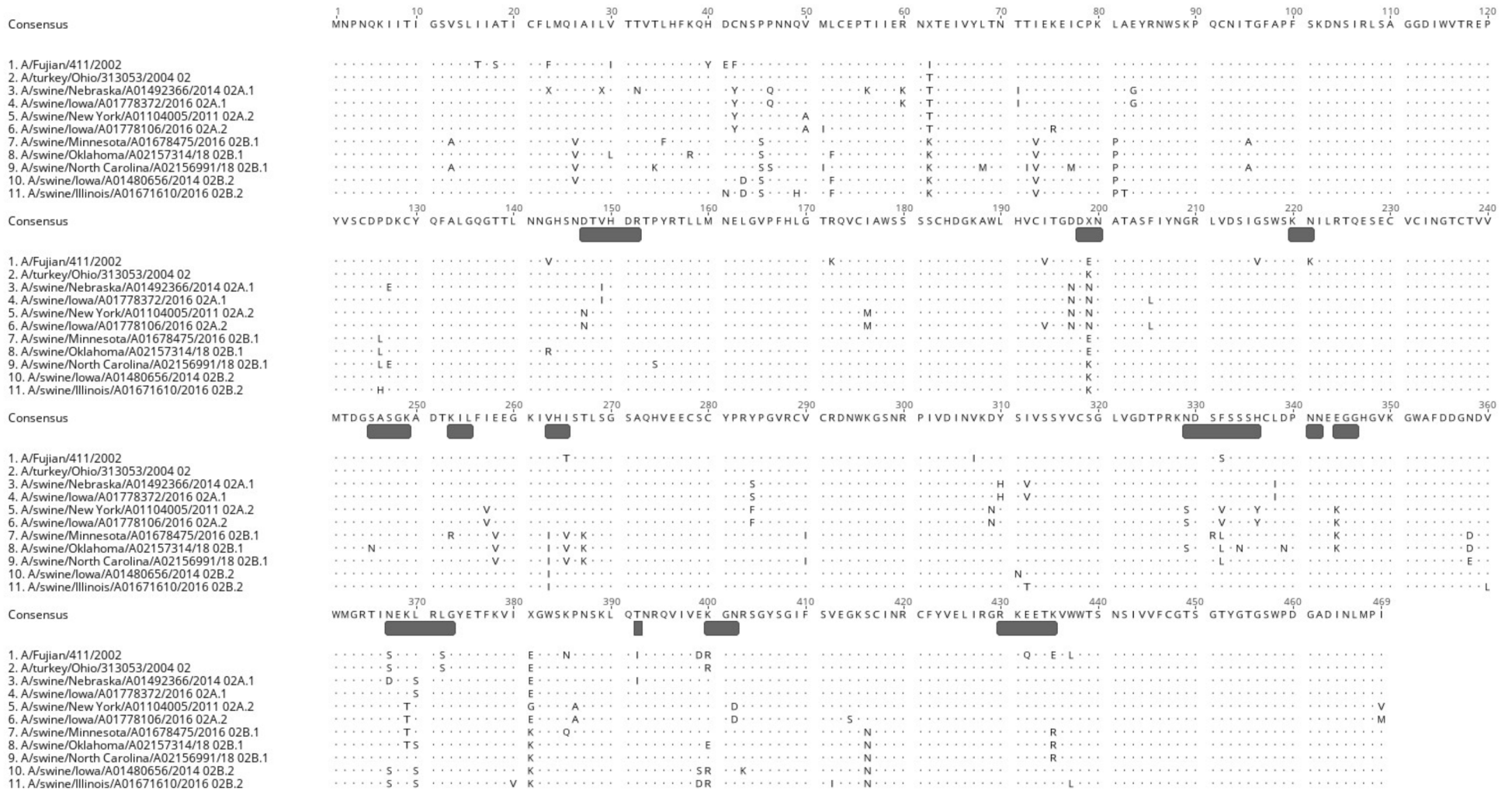


Figure S3. Amino acid sequence alignment of N2-02 lineage reference, contemporary, and human progenitor A/Wuhan/359/1995. Gray boxes under the consensus sequence denote putative antibody epitopes extrapolated from human N2.

## N2 neuraminidase lineage

- Human seasonal
- 1998
  - 1998A
    - 1998A.1
    - 1998A.2
  - 1998B
    - 1998B.1
    - 1998B.2
- 2002
  - 2002A
    - 2002A.1
    - 2002A.2
  - 2002B
    - 2002B.1
    - 2002B.2
- 2016
- ★ Antiserum
- ★ Antigen

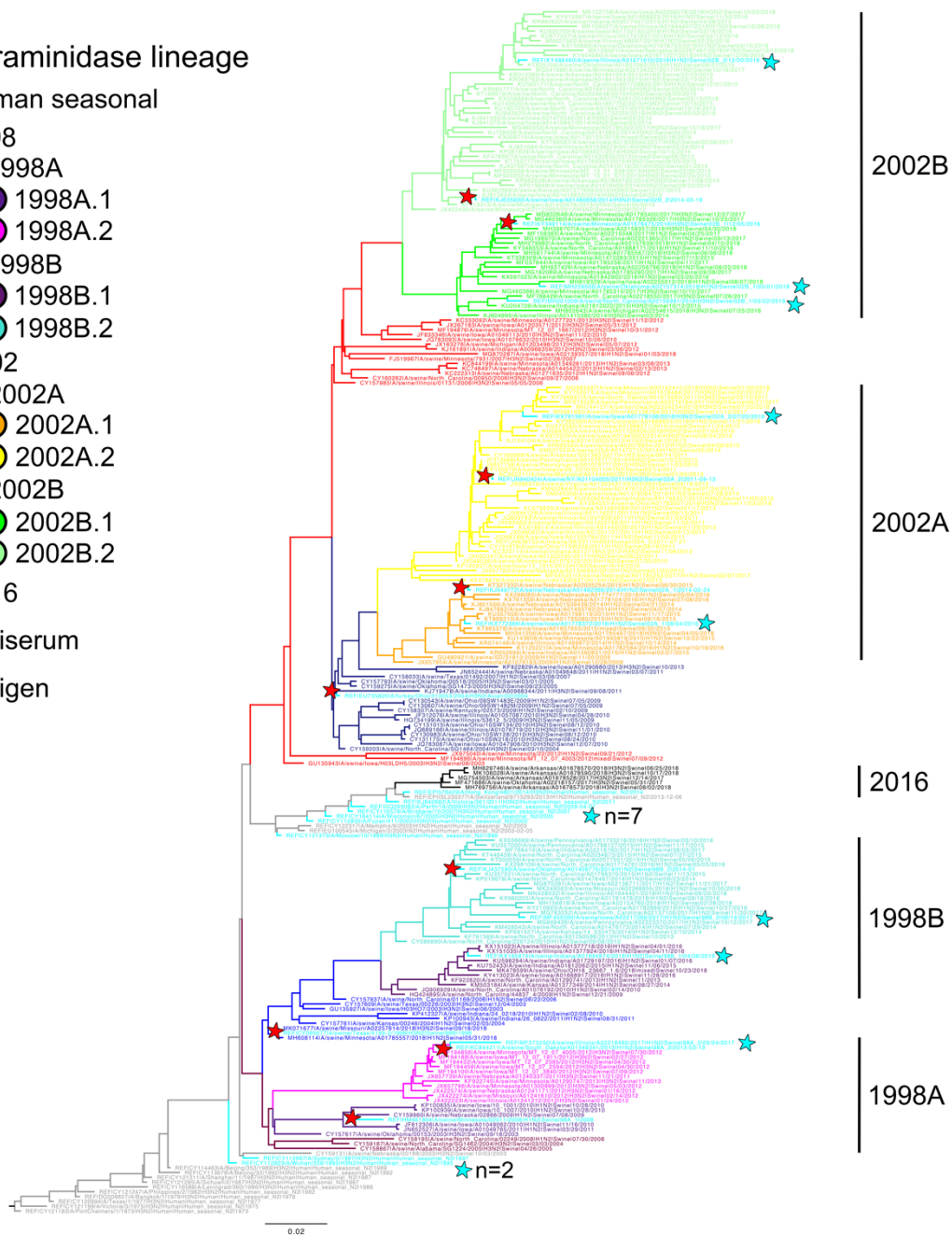


Figure S4. Representative maximum likelihood phylogeny of 250 swine and human N2 NA genes. The two major N2 lineages in swine are the result of independent introductions of N2 from humans to swine and are grouped by 1998 and 2002. Each lineage was divided into multiple statistically supported clades (denoted A, B, 1, 2) for which the branches have been colored. Selected reference and test antigens are annotated by stars and branches are colored cyan; human seasonal N2 NA genes are colored in gray. The tree is rooted on the human seasonal N2 gene A/Port Chalmers/1/1973(H3N2); all branch lengths are drawn to scale, and the scale bar indicates the number of nucleotide substitutions per site. The complete phylogeny with tip labels included is available at <https://github.com/flu-crew/n2-characterization>.