

1 **Supplemental Figure 1**

2 Multiple sequence alignment of HA amino acid residues 59-252 (globular head domain) of
3 all 84 naturally-occurring, non-redundant human H2N2 strains in the Influenza Research
4 Database in the order of the phylogram (Supplemental Figure 2). Residues that belong to
5 the RBD are highlighted in red in the A/Japan/305/1957 (CY014976) sequence at the top.
6 Residues identical to those of this Japan/305 strain are denoted by solid color, green for
7 early H2 strains and blue for late H2 strains. Mutated residues are highlighted in white (or
8 grey for conservative mutations). Residues that have been identified as contact residues of
9 the human H2 mAbs 8F8, 8M2, or 2G1 are annotated with the mAb name in grey at the top.

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	60	65	70	75	80	85	90	95A	100	105	110	115																																																
A/Japan/305/1957 (CY014976)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Japan/305/1957 (AY209953)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Japan/305/1957 (CY044325)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Japan/305/1957 (DQ508841)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/El Salvador/2/1957 (AF270716)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Japan/305 MA12/1957 (CY087800)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/7/1957 (AF270720)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Chile/13/1957 (AY209952)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/El Salvador/2/1957 (HM204767)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Krasnodar/101/1959 (CY032253)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/RI/5/1957 (AF270718)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/2/1958 (CY020317)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/22/1957 (CY021805)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/El Salvador/2 Q226L/1957 (HM204775)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/26/1957 (CY020381)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/3/1958 (CY021069)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/4/1958 (CY020373)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/1/1958 (CY021813)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/6/1958 (AF270723)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Guiyang/1/1957 (CY032269)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/RI/5+/1957 (AF270722)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/20/1957 (CY022013)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Sao Paolo/3/1959 (AF270725)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/1/1959 (CY020541)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Sao Paolo/1/1961 (AY209957)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Albany/1/1960 (CY021933)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Ohio/2/1959 (AF270727)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Philippines/2/1960 (AY209954)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Victoria/1 5681/1959 (AF270726)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Kayano/1957 (AB056699)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Adachi/2/1957 (AB432937)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Ann Arbor/6/1960 (AF270721)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Malaya/16/1958 (AF270724)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Moscow/1019/1965 (CY031603)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Ann Arbor/23/1957 (CY031579)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Netherlands/001M/1958 (CY077741)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E	N	P	R	D	G	L	C	Y	P	G	S	F	N	D	Y	E	E	L	K	H	L	L	S	S	V	K
A/Yale/1/1961 (AY209958)	L	E	L	G	D	C	S	I	A	G	W	L	L	G	N	P	E	C	D	R	L	L	S	V	P	E	W	S	Y	I	M	E	K	E																										

	116A		120	123		130	8M2 8F8	135	140	145	150	155	2G1	160	165	170		
	B	C																
A/Japan/305/1957 (CY014976)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Japan/305/1957 (AY209953)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Japan/305/1957 (CY044325)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Japan/305/1957 (DQ508841)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/El Salvador/2/1957 (AF270716)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Japan/305 MA12/1957 (CY087800)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/7/1957 (AF270720)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Chile/13/1957 (AY209952)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/El Salvador/2/1957 (HM204767)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Krasnodar/101/1959 (CY032253)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/RI/5/1957 (AF270718)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/2/1958 (CY020317)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/22/1957 (CY021805)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/El Salvador/2 Q226L/1957 (HM204775)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/26/1957 (CY020381)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/3/1958 (CY021069)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/4/1958 (CY020373)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1958 (CY021813)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/6/1958 (AF270723)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Guiyang/1/1957 (CY032269)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/RI/5+/1957 (AF270722)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/20/1957 (CY022013)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Sao Paolo/3/1959 (AF270725)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1959 (CY020541)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Sao Paolo/1/1961 (AY209957)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1960 (CY021933)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Ohio/2/1959 (AF270727)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Philippines/2/1960 (AY209954)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Victoria/15681/1959 (AF270726)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Kayano/1957 (AB056699)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Adachi/2/1957 (AB432937)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Ann Arbor/6/1960 (AF270721)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Malaya/16/1958 (AF270724)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Moscow/1019/1965 (CY031603)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Ann Arbor/23/1957 (CY031579)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/001M/1958 (CY077741)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Yale/1/1961 (AY209958)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/056H1/1960 (CY077786)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/England/1/1961 (AY209955)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/60/1962 (AY209960)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Japan/170/1962 (AY209959)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Tokyo/3/1967 (AY209987)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Taiwan/1/1962 (AY209961)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1965 (AY209970)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Berlin/3/1964 (CY032237)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Potsdam/2/1965 (CY032245)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/6/1967 (CY020389)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/3/1967 (CY020405)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/4/1967 (CY021997)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/9/1967 (CY020517)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Ann Arbor/7/1967 (AY209978)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Berkeley/1/1968 (CY033473)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1968 (CY021021)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Panama/1/1967 (AY209983)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Cottbus/1/1964 (CY032261)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Pittsburgh/2/1965 (AY209973)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Kumamoto/1/1965 (AY209971)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Izumi/5/1965 (D13579)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Canada/1/1966 (AY209976)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Tashkent/1046/1967 (CY032277)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Berkeley/1/1966 (AY209974)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Cordoba/522/1967 (AY209979)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Montevideo/2208/1967 (AY209986)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Georgia/1/1967 (CY033980)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Georgia/1/1967 (AY209981)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Johannesburg/567/1967 (AY209982)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Johannesburg/617/1967 (CY032285)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Panama/1/1966 (AY209977)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/California/1/1966 (AY209975)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Poland/5/1967 (AY209984)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/England/10/1967 (AY209980)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Taiwan/1/1967 (AY209985)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/England/12/1964 (AY209967)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Murakami/4/1964 (AY209968)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/New Jersey/3/1965 (AY209972)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Korea/426/1968 (CY031595)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Taiwan/1/1964 (AY209969)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/56/1963 (CY035078)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/65/1963 (AY209966)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Georgia/1/1963 (AY209964)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Netherlands/001K1/1963 (CY077733)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/North Carolina/1/1968 (CY031587)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Albany/1/1963 (AY209963)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T
A/Great Lakes/3/1963 (AY209965)	H	F	E	K	V	K	I	L	P	K	D	R	W	T	Q	H	T	T

A/Japan/305/1957 (CY014976)
 A/Japan/305/1957 (AY209953)
 A/Japan/305/1957 (CY044325)
 A/Japan/305/1957 (DQ508841)
 A/El Salvador/2/1957 (AF270716)
 A/Japan/305 MA12/1957 (CY087800)
 A/Albany/7/1957 (AF270720)
 A/Chile/13/1957 (AY209952)
 A/El Salvador/2/1957 (HM204767)
 A/Krasnodar/101/1959 (CY032253)
 A/RI/5/1957 (AF270718)
 A/Albany/2/1958 (CY020317)
 A/Albany/22/1957 (CY021805)
 A/El Salvador/2 Q226L/1957 (HM204775)
 A/Albany/26/1957 (CY020381)
 A/Albany/3/1958 (CY021069)
 A/Albany/4/1958 (CY020373)
 A/Albany/1/1958 (CY021813)
 A/Albany/6/1958 (AF270723)
 A/Gulyang/1/1957 (CY032269)
 A/RI/5+/1957 (AF270722)
 A/Albany/20/1957 (CY020213)
 A/Sao Paolo/3/1959 (AF270725)
 A/Albany/1/1959 (CY020541)
 A/Sao Paolo/1/1961 (AY209957)
 A/Albany/1/1960 (CY021933)
 A/Ohio/2/1959 (AF270727)
 A/Philippines/2/1960 (AY209954)
 A/Victoria/15681/1959 (AF270726)
 A/Kayano/1957 (AB056699)
 A/Adachi/2/1957 (AB432937)
 A/Ann Arbor/6/1960 (AF270721)
 A/Malaya/16/1958 (AF270724)
 A/Moscow/1019/1965 (CY031603)
 A/Ann Arbor/23/1957 (CY031579)
 A/Netherlands/001M/1958 (CY077741)
 A/Yale/1/1961 (AY209958)
 A/Netherlands/056H1/1960 (CY077786)
 A/England/1/1961 (AY209955)
 A/Netherlands/60/1962 (AY209960)
 A/Japan/170/1962 (AY209959)
 A/Tokyo/3/1967 (AY209987)
 A/Taiwan/1/1962 (AY209961)
 A/Albany/1/1965 (AY209970)
 A/Berlin/3/1964 (CY032237)
 A/Potsdam/2/1965 (CY032245)
 A/Albany/6/1967 (CY020389)
 A/Albany/3/1967 (CY020405)
 A/Albany/4/1967 (CY021997)
 A/Albany/9/1967 (CY020517)
 A/Ann Arbor/7/1967 (AY209978)
 A/Berkeley/1/1968 (CY033473)
 A/Albany/1/1968 (CY021021)
 A/Panama/1/1967 (AY209983)
 A/Cottbus/1/1964 (CY032261)
 A/Pittsburgh/2/1965 (AY209973)
 A/Kumamoto/1/1965 (AY209971)
 A/Izumi/5/1965 (D13579)
 A/Canada/1/1966 (AY209976)
 A/Tashkent/1046/1967 (CY032277)
 A/Berkeley/1/1966 (AY209974)
 A/Cordoba/522/1967 (AY209979)
 A/Montevideo/2208/1967 (AY209986)
 A/Georgia/1/1967 (CY033980)
 A/Georgia/1/1967 (AY209981)
 A/Johannesburg/567/1967 (AY209982)
 A/Johannesburg/617/1967 (CY032285)
 A/Panama/1/1966 (AY209977)
 A/California/1/1966 (AY209975)
 A/Poland/5/1967 (AY209984)
 A/England/10/1967 (AY209980)
 A/Taiwan/1/1967 (AY209985)
 A/England/12/1964 (AY209967)
 A/Murakami/4/1964 (AY209968)
 A/New Jersey/3/1965 (AY209972)
 A/Korea/426/1968 (CY031595)
 A/Taiwan/1/1964 (AY209969)
 A/Netherlands/56/1963 (CY035078)
 A/Netherlands/65/1963 (AY209966)
 A/Georgia/1/1963 (AY209964)
 A/Netherlands/001K1/1963 (CY077733)
 A/North Carolina/1/1968 (CY031587)
 A/Albany/1/1963 (AY209963)
 A/Great Lakes/3/1963 (AY209965)

175	180	185	190	195	200	205	210	215	220	225	230																																															
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N	K	R	S	T	P	E	I	A	T	R	P	K	V	N	G	L	G	R	M	E	F	S	W
Q	M	L	I	I	W	G	V	H	H	P	N	D	E	T	E	Q	R	T	L	Y	Q	N	V	G	T	Y	V	S	V	G	T	S	T	L	N																							

	235	240	245	250
A/Japan/305/1957 (CY014976)	T	L	L	D
A/Japan/305/1957 (AY209953)	T	L	L	D
A/Japan/305/1957 (CY044325)	T	L	L	D
A/Japan/305/1957 (DQ508841)	T	L	L	D
A/EI Salvador/2/1957 (AF270716)	T	L	L	D
A/Japan/305 MA12/1957 (CY087800)	T	L	L	D
A/Albany/7/1957 (AF270720)	T	L	L	D
A/Chile/13/1957 (AY209952)	T	L	L	D
A/EI Salvador/2/1957 (HM204767)	T	L	L	D
A/Krasnodar/101/1959 (CY032253)	T	L	L	D
A/RI/5/1957 (AF270718)	T	L	L	D
A/Albany/2/1958 (CY020317)	T	L	L	D
A/Albany/22/1957 (CY021805)	T	L	L	D
A/EI Salvador/2 Q226L/1957 (HM204775)	T	L	L	D
A/Albany/26/1957 (CY020381)	T	L	L	D
A/Albany/3/1958 (CY021069)	T	L	L	D
A/Albany/4/1958 (CY020373)	T	L	L	D
A/Albany/1/1958 (CY021813)	T	L	L	D
A/Albany/6/1958 (AF270723)	T	L	L	D
A/Guiyang/1/1957 (CY032269)	T	L	L	D
A/RI/5+/1957 (AF270722)	T	L	L	D
A/Albany/20/1957 (CY022013)	T	L	L	D
A/Sao Paolo/3/1959 (AF270725)	T	L	L	D
A/Albany/1/1959 (CY020541)	T	L	L	D
A/Sao Paolo/1/1961 (AY209957)	T	L	L	D
A/Albany/1/1960 (CY021933)	T	L	L	D
A/Ohio/2/1959 (AF270727)	T	L	L	D
A/Philippines/2/1960 (AY209954)	T	L	L	D
A/Victoria/15681/1959 (AF270726)	T	L	L	D
A/Kayano/1957 (AB056699)	T	L	L	D
A/Adachi/2/1957 (AB432937)	T	L	L	D
A/Ann Arbor/6/1960 (AF270721)	T	L	L	D
A/Malaya/16/1958 (AF270724)	T	L	L	D
A/Moscow/1019/1965 (CY031603)	T	L	L	D
A/Ann Arbor/23/1957 (CY031579)	T	L	L	D
A/Netherlands/001M/1958 (CY077741)	T	L	L	D
A/Yale/1/1961 (AY209958)	T	L	L	D
A/Netherlands/056H1/1960 (CY077786)	T	L	L	D
A/England/1/1961 (AY209955)	T	L	L	D
A/Netherlands/60/1962 (AY209960)	T	L	L	D
A/Japan/170/1962 (AY209959)	T	L	L	D
A/Tokyo/3/1967 (AY209987)	T	L	L	D
A/Taiwan/1/1962 (AY209961)	T	L	L	D
A/Albany/1/1965 (AY209970)	T	L	L	D
A/Berlin/3/1964 (CY032237)	T	L	L	D
A/Potsdam/2/1965 (CY032245)	T	L	L	D
A/Albany/6/1967 (CY020389)	T	L	L	D
A/Albany/3/1967 (CY020405)	T	L	L	D
A/Albany/4/1967 (CY021997)	T	L	L	D
A/Albany/9/1967 (CY020517)	T	L	L	D
A/Ann Arbor/7/1967 (AY209978)	T	L	L	D
A/Berkeley/1/1968 (CY033473)	T	L	L	D
A/Albany/1/1968 (CY021021)	T	L	L	D
A/Panama/1/1967 (AY209983)	T	L	L	D
A/Cottbus/1/1964 (CY032261)	T	L	L	D
A/Pittsburgh/2/1965 (AY209973)	T	L	L	D
A/Kumamoto/1/1965 (AY209971)	T	L	L	D
A/Izumi/5/1965 (D13579)	T	L	L	D
A/Canada/1/1966 (AY209976)	T	L	L	D
A/Tashkent/1046/1967 (CY032277)	T	L	L	D
A/Berkeley/1/1966 (AY209974)	T	L	L	D
A/Cordoba/522/1967 (AY209979)	T	L	L	D
A/Montevideo/2208/1967 (AY209986)	T	L	L	D
A/Georgia/1/1967 (CY033980)	T	L	L	D
A/Georgia/1/1967 (AY209981)	T	L	L	D
A/Johannesburg/567/1967 (AY209982)	T	L	L	D
A/Johannesburg/617/1967 (CY032285)	T	L	L	D
A/Panama/1/1966 (AY209977)	T	L	L	D
A/California/1/1966 (AY209975)	T	L	L	D
A/Poland/5/1967 (AY209984)	T	L	L	D
A/England/10/1967 (AY209980)	T	L	L	D
A/Taiwan/1/1967 (AY209985)	T	L	L	D
A/England/12/1964 (AY209967)	T	L	L	D
A/Murakami/4/1964 (AY209968)	T	L	L	D
A/New Jersey/3/1965 (AY209972)	T	L	L	D
A/Korea/426/1968 (CY031595)	T	L	L	D
A/Taiwan/1/1964 (AY209969)	T	L	L	D
A/Netherlands/56/1963 (CY035078)	T	L	L	D
A/Netherlands/65/1963 (AY209966)	T	L	L	D
A/Georgia/1/1963 (AY209964)	T	L	L	D
A/Netherlands/001K1/1963 (CY077733)	T	L	L	D
A/North Carolina/1/1968 (CY031587)	T	L	L	D
A/Albany/1/1963 (AY209963)	T	L	L	D
A/Great Lakes/3/1963 (AY209965)	T	L	L	D

18 **Supplemental Figure 2**

19 Phylogram of all 84 naturally-occurring, non-redundant human H2N2 HA sequences in the
20 Influenza Research Database based on the protein sequences of residues 59-252 (globular
21 head domain) of the HA1 subunit (MacVector 12.0.1). The phylogram branches are colored
22 green for early H2 strains and blue for late H2 strains.

