

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.

10



	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



	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/El 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/El 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/El 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.

