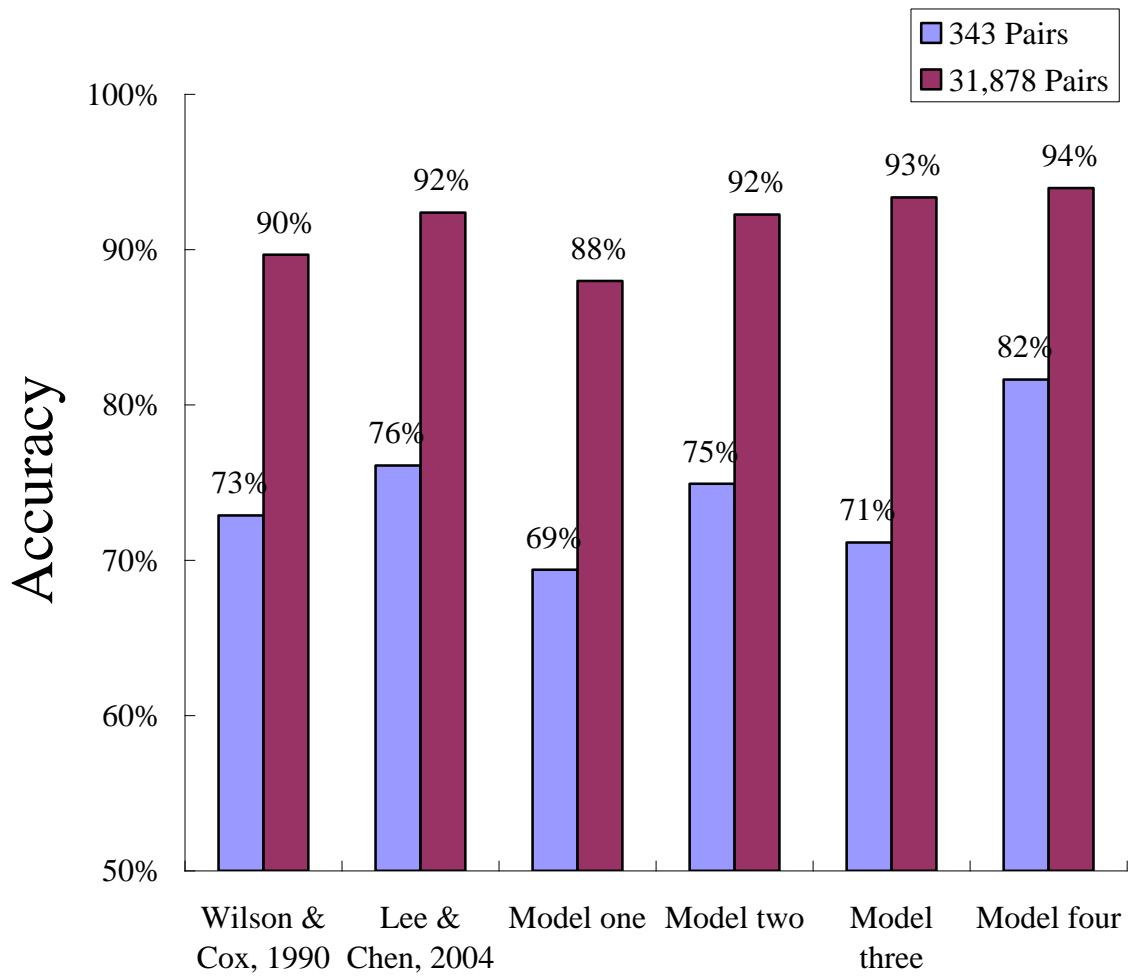


Supplementary Figure S1 : The three HA-antibody complex structures. PDB codes are (A) 1KEN [1], (B) 2VIR [2], and (C) 1QFU [3].



Supplementary Figure S2 : Compare our method with other two methods on predicting antigenic variants on two data sets.

Supplementary Table S1 : The number of HI assays and number of sequences in Smith's dataset and WER strains from 1968 to 2009

Year	HI-assay data set	Smith's data set [4]	WER strain ¹
1968	0	4	A/Hong Kong/1/68
1969	0	3	A/Hong Kong/1/68
1970	1 [5]	2	A/Hong Kong/1/68
1971	2 [5]	4	A/Hong Kong/1/68
1972	2 [5]	5	A/Hong Kong/1/68
1973	2 [5]	4	A/England/42/72
1974	3 [5]	5	A/Port Chalmers/1/73
1975	6 [5]	3	A/Port Chalmers/1/73
1976	7 [5]	6	A/Victoria/3/75
1977	4 [5]	5	A/Victoria/3/75
1978	0	0	A/Texas/1/77
1979	0	0	A/Texas/1/77
1980	6 [5]	2	A/Bangkok/1/79
1981	0	1	A/Bangkok/1/79
1982	3 [5]	4	A/Bangkok/1/79
1983	5 [5], 23[6]	1	A/Phillipines/2/82
1984	0	1	A/Phillipines/2/82
1985	3 [5]	4	A/Phillipines/2/82
1986	9 [5]	2	A/Christchurch/4/85, A/Mississippi/1/85
1987	3 [5]	3	A/Leningrad/360/86
1988	17 [5]	4	A/Sichuan/2/87
1989	0	16	Si/87; Sh/87
1990	10 [5]	5	A/Shanghai/11/87
1991	5 [5]	17	A/Beijing/353/89
1992	5 [5]	45	A/Beijing/353/89
1993	21 [5]	43	A/Beijing/32/92
1994	6 [5]	10	A/Shangdong/9/93
1995	3 [5], 20 [7]	15	A/Johannesburg/33/94
1996	12 [5]	10	A/Johannesburg/33/94
1997	28 [8]	9	A/Wuhan/359/95
1998	3 [5]	4	A/Wuhan/359/95; A/Sydney/5/97
1999	2 [5]	3	A/Sydney/5/97
2000	0	1	A/Moscow/10/99 ²
2001	11 [9]	3	A/Moscow/10/99
2002	0	3	A/Moscow/10/99
2003	11[5], 20 [10]	6	A/Moscow/10/99
2004	4 [5], 17 [10]	0	A/Fujian/411/2002
2005	14 [5], 1 [10]	0	A/California/7/2004
2006	11 [5], 9 [10]	0	A/California/7/2004; A/Wisconsin/67/2005
2007	3 [5], 31 [11]	0	A/Wisconsin/67/2005; A/Brisbane/10/2007
2008	0	0	A/Brisbane/10/2007
2009	0	0	A/Brisbane/10/2007
Total	343 pairs	253 sequences	

¹ WER strain is the dominant virus in influenza season reported by WHO.

² The widely used vaccine strain A/Panama/2007/99 was used instead in following years.

Supplementary Table S2 : The list of 64 selected critical positions

List of critical positions	
Epitope A	122,124,126,131,133,135,137,140,143,144,145,146
Epitope B	128,155,156,157,158,159,160,164,186,188,189,193,196,197,198
Epitope C	50,53,54,275,276,278,307
Epitope D	121,172,174,201,207,213,216,217,230,242,244,248
Epitope E	62,63,75,78,82,83,260,262
Other area	2,3,9,25,31,199,202,222,225,326

Supplementary Table S3 : The 13 antigenic variants without changed epitopes

Virus A	Virus B	Type (A to B) ¹	Type (B to A) ²	HD	Epitope A	Epitope B	Epitope C	Epitope D	Epitope E
A/Alaska/10/95	A/Idaho/4/95	V	S	3	145	165	312		
A/Alaska/10/95	A/Wuhan/359/95	V	S	5	135	165, 194	275		262
A/Alaska/10/95	A/Hongkong/55/95	V	S	7	135, 138	165	275	167, 226	262
A/Alaska/10/95	A/Shanghai/9/95	V	S	7	135	165, 193, 194	275	226	262
A/Anhui/1239/2005	A/Wisconsin/67/2005	V	S	5	122, 138	160			
A/Fujian/140/2000	A/Chile/6416/2001	V	S	12	144	186, 194	273	226, 246, 247	
A/Hong_Kong/1/94	A/Guangdong/25/93	V	S	8	124		47, 299	96, 216, 219, 226	92
A/Panama/2007/99	A/Chile/6416/2001	V	S	7	144	186		246	
A/Wellington/1/2004	A/Singapore/68/2004	V	S	9	145	189	50	226, 227	94
A/Wellington/1/2004	A/Victoria/513/2004	V	S	5	145	186, 190		167, 226	
A/Wellington/1/2004	A/Wisconsin/19/2004	V	S	5	138, 145	186	278	226	
A/Fujian/140/2000	A/NewYork/55/2001	V	V	12	144	186, 194	273	226, 229, 247	
A/Victoria/3/75	A/Victoria/112/76	V	V	2				229	

¹ the antigenic type of virus B relative to antisera against virus A.

² the antigenic type of virus A relative to antisera against virus B.

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