

# Supporting Information

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## SI Text

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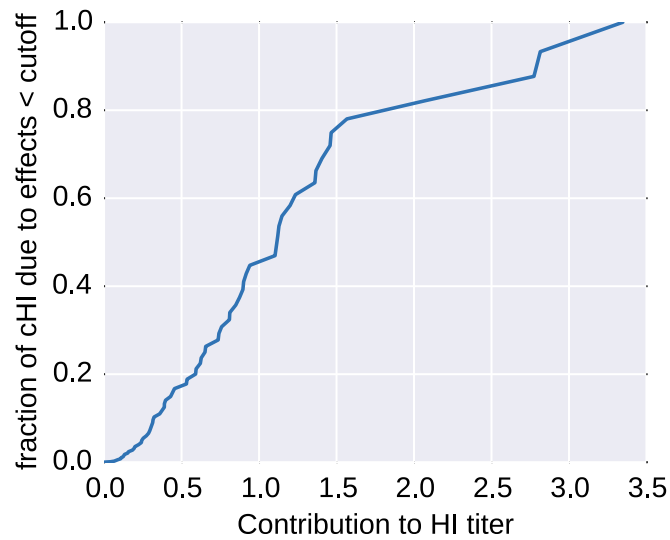
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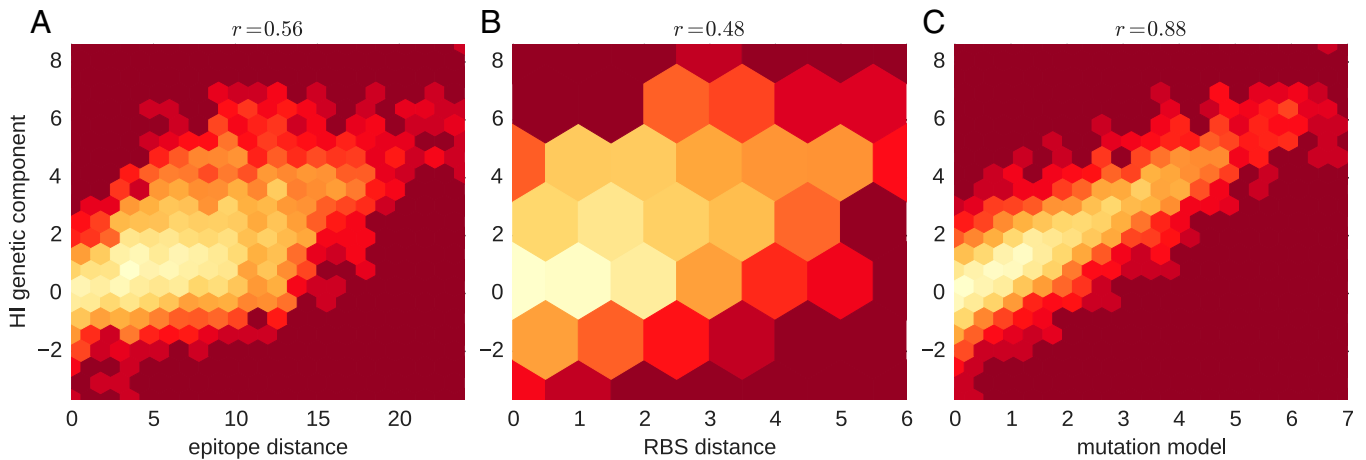
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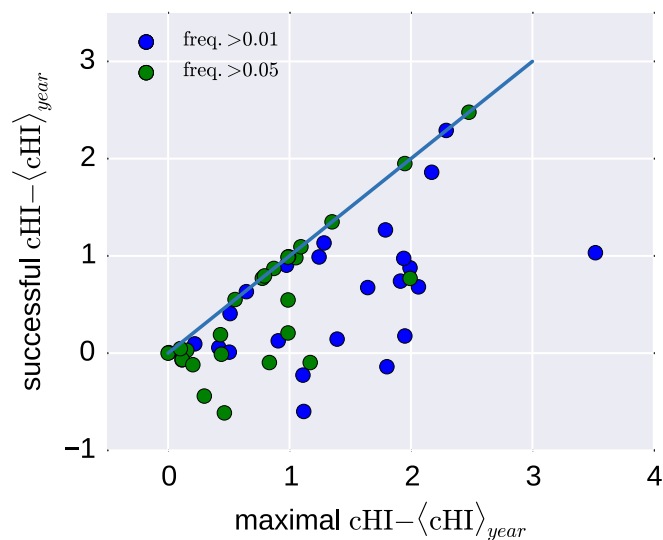


**Fig. S1.** Contributions of small and large effect substitution to antigenic evolution. About half of antigenic change is attributed to mutations with effects smaller than one unit. The figure shows the fraction antigenic change by common mutations with effects smaller than the cutoff on the horizontal axis.



**Fig. S2.** Determinants of corrected HI titers  $H_{a\beta} - v_a - p\beta$  (y axis) of A(H3N2) viruses. (A) Correlation of corrected HI titers  $H_{a\beta} - v_a - p\beta$  with the number of substitutions at mapped epitope sites between reference and test virus. Similarly, B shows this correlation for the distance at receptor binding sites, and C shows the correlation with the genetic component  $D_{ab}$  of the substitution model. Neither epitope or RBS distance explain much of the titer variation (Pearson correlation coefficient above the panels).





**Fig. S3.** Success versus antigenic advancement. In many years, the most antigenically advanced clade (highest cHI) is not the clade dominating the next season. The figure shows the maximally observed centered cHI vs. the centered cHI of the successful clade for each year from 1990 to 2014.

**Table S1.** Virus, antisera, and parameter count for the different time intervals and influenza virus lineages

Lineage	Time interval	Model	Number of viruses	Number of test viruses	Number of ref viruses	Number of antisera	Number of HI titers	Number of genetic parameters	Number of s nonzero genetic parameters
H3N2	3 y	tree	1,985	720	15	31	3,626	235	56
H3N2	3 y	mutation	1,985	720	15	31	3,626	44	24
H3N2	6 y	tree	2,658	1,442	31	74	10,676	472	146
H3N2	6 y	mutation	2,658	1,442	31	74	10,676	94	44
H3N2	12 y	tree	2,502	1,772	69	233	15,925	610	231
H3N2	12 y	mutation	2,502	1,772	69	233	15,925	143	73
H3N2	20 y	tree	3,283	1,935	98	299	17,490	698	266
H3N2	20 y	mutation	3,283	1,935	98	299	17,490	225	105
H1N1pdm09	7 y	tree	2,441	908	8	12	2,776	296	62
H1N1pdm09	7 y	mutation	2,441	908	8	12	2,776	60	18
Vic	6 y	tree	1,929	303	4	9	534	131	23
Vic	6 y	mutation	1,929	303	4	9	534	12	5
Vic	12 y	tree	1,425	400	16	61	2,501	176	53
Vic	12 y	mutation	1,425	400	16	61	2,501	30	19
Vic	20 y	tree	1,676	471	26	87	2,792	206	64
Vic	20 y	mutation	1,676	471	26	87	2,792	44	22
Yam	3 y	tree	1,572	77	2	5	153	31	8
Yam	3 y	mutation	1,572	77	2	5	153	2	2
Yam	6 y	tree	1,750	304	9	20	1,304	121	28
Yam	6 y	mutation	1,750	304	9	20	1,304	34	12
Yam	12 y	tree	1,384	352	15	52	2,751	147	39
Yam	12 y	mutation	1,384	352	15	52	2,751	44	17
Yam	20 y	tree	1,811	422	24	72	2,789	188	57
Yam	20 y	mutation	1,811	422	24	72	2,789	70	25

**Table S2. The 55 largest inferred antigenic effects of substitutions in HA1 for A(H3N2) in the past 30 y as inferred by the substitution model in overlapping 10 y intervals**

Substitutions	1985–1995	1990–2000	1995–2005	2000–2010	2005–2016
K156E*	—	3.4	—	—	—
K158N/N189K*	—	—	—	2.59	3.28
C1R <sup>*,†</sup>	—	3.23	—	—	—
K189N*	—	—	—	2.96	2.45
S262N	—	2.48	0.0	—	0.05
K158R*	—	—	—	1.95	2.01
C2 <sup>*,†</sup>	—	—	1.98	—	—
K135G	1.95	1.95	—	—	—
C1 <sup>*,†</sup>	—	1.94	—	—	—
N145K*	1.91	0.0	0.48	0.53	—
K140E	—	—	1.59	1.33	—
K193N*	1.56	—	—	—	—
H155Y/R189K*	1.55	—	—	—	—
I186S	1.54	—	—	—	—
V186G	—	—	—	0.0	1.52
Y155H/K189R*	1.48	—	—	—	—
K145N*	0.0	0.0	1.45	1.2	—
S193F/D225N*	—	—	—	1.4	—
S133D/E156K*	—	1.37	—	—	—
T135G	—	1.34	—	—	—
R189S*	1.28	0.93	—	—	—
C3 <sup>†</sup>	1.27	—	—	—	—
T262N	1.25	0.35	—	—	—
S157L	0.09	0.7	—	—	1.23
E190D	0.0	1.21	—	—	—
N121T	—	—	1.2	—	—
K135T	—	1.19	—	—	—
K156E/D190E*	1.18	—	—	—	—
S133D	1.16	—	—	—	—
T135K	—	0.0	1.16	—	—
K140I	—	—	—	1.15	1.1
Q156H*	—	—	1.14	0.75	—
K62E/N276K	—	—	1.11	—	—
G186S	—	—	1.07	—	—
N144K	—	—	—	1.06	0.0
L226V	—	0.22	1.06	—	—
K144D	—	—	—	—	1.06
M260I	—	—	—	1.05	0.0
F159Y*	—	—	0.25	0.39	1.04
S193N*	1.03	—	0.46	0.0	—
S189R*	—	0.98	—	—	—
T212S	—	—	—	—	0.98
K135E	0.94	0.88	—	—	—
T212A	—	—	—	0.94	0.59
C4 <sup>*,†</sup>	—	—	0.92	0.15	—
K156H*	—	—	0.91	—	—
R142G	—	—	0.91	0.32	0.23
M242I	—	—	0.91	—	—
Y159F*	—	—	0.91	0.81	0.0
I112V/S193F*	—	—	—	—	0.88
N145S*	—	—	—	0.21	0.88
F159S*	—	—	—	—	0.88
L157S/S189R*	0.87	—	—	—	—
S159Y*	0.0	—	—	—	0.85
K144N	—	—	—	—	0.85

When several substitutions always occurred together, a combined effect is shown. Columns involving substitutions at Koel 7 sites are marked with an asterisk. A dash indicates the absence of the substitution in a particular time interval. The substitutions are sorted by the maximum across time intervals.

<sup>†</sup>C1: K62E, V144I, K156Q, E158K, V196A, N276K; C1R: E62K, N121T, S124G, N133D, R142G, I144V, Q156K, K158E, A196V, K276N, i.e., largely the reverse of cluster C1; C2: S124G, N133D, I144V, Q156K, K276N a subset of cluster C1; C3: K82E, E83K, A131T, R299K; C4: I25L, Q75H, T131A, T155H.

## Other Supporting Information Files

[Dataset S1 \(TSV\)](#)

[Dataset S2 \(TSV\)](#)

[Dataset S3 \(TSV\)](#)

[Dataset S4 \(TSV\)](#)

[Dataset S5 \(TSV\)](#)