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Quantifying Influenza Vaccine Efficacy and Antigenic Distance

Vishal Gupta, **David J. Earl**, and **Michael W. Deem**

Departments of Bioengineering and Physics & Astronomy, Rice University, 6100 Main Street—MS 142, Houston, TX 77005–1892

Abstract

We introduce a new measure of antigenic distance between influenza A vaccine and circulating strains. The measure correlates well with efficacies of the H3N2 influenza A component of the annual vaccine between 1971 and 2004, as do results of a theory of the immune response to influenza following vaccination. This new measure of antigenic distance is correlated with vaccine efficacy to a greater degree than are current state-of-the-art phylogenetic sequence analyzes or ferret antisera inhibition assays. We suggest that this new measure of antigenic distance be used in the design of the annual influenza vaccine and in the interpretation of vaccine efficacy monitoring.

1 Introduction

Annual influenza epidemics are responsible for the deaths of 250000 to 500000 people worldwide and cause illness in 5 to 15% of the total population each year [1]. The total direct and indirect costs associated with influenza in the USA are roughly $10 billion [2], and the economic cost of an influenza pandemic is estimated to be between $71–167 billion [3] in the USA alone. Vaccination is the primary method employed to prevent infection by influenza and its associated complications. Antigenic change, combined with the high transmission rate of influenza strains, means that the vaccine must be redesigned annually, currently based upon phylogenetic, experimental, and epidemiological analysis.

The effectiveness of the annual influenza vaccine varies from year to year due to changes in the identity of the circulating influenza strains. Typically, three strains are included in the annual vaccine, with these three strains chosen to be as similar as possible to those projected to be the most prominent circulating strains in the upcoming influenza season. Currently, the vaccine contains H3N2 and H1N1 influenza A components and an influenza B component. Since the mutation rate of the influenza virus is rather high, vaccine efficacies are rarely 100%, and are more typically 30 – 60%, against influenza-like illness. As significant as the estimated worldwide mortality is, it rises by another factor of 160% [4] to 260% [5] if influenza-induced complications to patients with other conditions are included, and the influenza vaccine on average significantly reduces such excess mortality [6]. Vaccine efficacy can even be negative, however, due to original antigenic sin [7–9], the tendency for antibodies produced in response to exposure to influenza vaccine antigens to suppress the creation of new, different antibodies in response to exposure to new versions of the

Correspondence should be addressed to: M. W. Deem, mwdeem@rice.edu, tel: 713–348–5852, fax: 713–348–5811.

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influenza virus. The efficacy of the annual influenza vaccine, and whether original antigenic sin may occur, depends sensitively on how similar the vaccine and circulating viral strains are. Current state of the art measures of antigenic distance are based on ferret antisera hemagglutinin inhibition assays [10–12], and these distances are assumed to correlate well with vaccine efficacies in humans. However, to our knowledge no such good correlation has ever been shown for an experimental or theoretical measure of antigenic distance. In addition to its annual value, a reliable measure of antigenic distance would provide valuable extra time if preparation and rush production of a modified vaccine is necessary to stem the spread of a newly emerged influenza strain [13]. We here provide a quantitative definition of the difference between dominant epitope regions in the vaccine and circulating strain and show that this definition of antigenic distance correlates well with human influenza vaccine efficacy over the last 35 years.

2 Methods

Our theory models the response of an immune system not subject to immunosenescence. Therefore, we limited consideration to experimental studies of vaccine efficacy for 18 to 64 year old subjects in all years since sequencing began, when the H3N2 subtype of influenza A was the predominant virus, and where epidemiological data on vaccine efficacy exists. We focus on the H3N2 strain because it is the most common strain and is responsible for significant morbidity and mortality and due to the abundance of available crystallographic, genetic, and epidemiological data. Our approach, however, is general. As is customary, we restrict attention to the hemagglutinin protein, against which neutralizing antibodies are generated [14]. Shown in figure 1 is the hemagglutinin protein for the A/Fujian/411/2002 strain with the epitope regions highlighted.

Our theory of the immune response to vaccination and disease uses the generalized $N K$ model [9] to calculate affinity constant values for the immune response to an antigen following vaccination. In this theory, the natural order parameter to distinguish between the vaccine strain and the circulating strain is the fraction of amino acids that differ in the dominant epitope region. The model considers the diversity of an individual's antibody repertoire and includes interactions within the antibody and between the antibody and the antigen. Here, the binding constant is determined as $K = \exp(a - b\langle U \rangle)$, where $a = 18.56$ and $b = 1.67$ are found from a comparison of the dynamics of the model with experiment [9], and U is the energy function for an antibody [9].

To apply the theory to a candidate vaccine and circulating strain, the sequences and identity of the dominant epitope must be known. The sequences and identities of the vaccine and circulating strains for each year were taken from Ref. [15]. The definition of the five epitopes, or surface regions that are recognized by human antibodies, in the H3N2 hemagglutinin protein were also taken from Ref. [15]. The dominant epitope, or the epitope that induces the most significant immune response, for a particular circulating strain in a particular year was taken as that which had the largest fractional change in amino acid sequence relative to the vaccine strain [16–19]. We use as our definition of antigenic distance p_{epitope}, where

$$p_{\text{epitope}} = \frac{\text{number of amino acid differences in the dominant epitope}}{\text{total number of amino acids in the dominant epitope}}. \quad (1)$$

An excel spreadsheet to calculate p_{epitope} is available [20].

The difference between the vaccine strain and the circulating strain is defined in the model by p_{epitope}, eq. 1. The vaccine efficacy, E, was assumed to correlate with the binding constant as $E = a \ln[K_{\text{secondary}}(p_{\text{epitope}})/K_{\text{primary}}]$, where the constant a is chosen so that a perfect match between the vaccine and circulating strain leads to 45% vaccine efficacy (which matches historical data, see table 1), K_{primary} is the binding constant for the primary immune response, and $K_{\text{secondary}}$ is the binding constant for the secondary immune response following vaccination. The theory is entirely predictive, with no fitted parameters save for the determined constant a. For example, the point at which the vaccine efficacy becomes negative is independent of the value of a.

3 Results

Shown in figure 2 and table 1 are the experimental vaccine efficacies and the efficacies predicted by the theory as a function of p_{epitope}. Vaccine efficacies are taken from the literature [21–35] and defined as

$$(u-v)/u, \quad (2)$$

where u is the influenza-like illness rate of unvaccinated individuals, and v is the influenza-like illness rate of vaccinated individuals. While the epidemiological estimates of u and v contain statistical noise, these are the best estimates available of vaccine efficacy in humans. The statistical mechanical model captures the essential physics of the immune response to influenza vaccination and demonstrates the value of using p_{epitope} to define the degree of antigenic drift. Consideration of antigenic drift of the dominant epitope follows from immunoassays and crystallographic data that show only the epitope regions are significantly involved in immune recognition [36]. When the antigenic drift, p_{epitope}, in the dominant epitope is greater than 0.19, according to historical records, or 0.22, according to theory, the vaccine efficacy becomes negative (see figure 2). This regime is to be avoided. For example, in the 1997/1998 northern hemisphere influenza season, when the Sydney/5/97 strain became widespread, $p_{\text{epitope}} = 0.238$, and the vaccine efficacy was −17 % [30]. The only data point that falls significantly off the theory is that for the 1989/1990 epidemic [37], in which it is likely that multiple circulating strains were present, including influenza B strains [38,25].

When the vaccine efficacy is compared to the sequence difference of the entire hemagglutinin protein,

$$p_{\text{sequence}} = \frac{\text{number of amino acid differences in the sequence}}{\text{total number of amino acids in the sequence}}, \quad (3)$$

one current measure of antigenic drift used to construct phylogenetic relationships between circulating strains for the WHO February report [39], the correlation is far less apparent. These data are shown in figure 3 and table 1. Since much of the protein is inaccessible to antibodies or simply not recognized by human antibodies, drift in much of the protein sequence is not correlated with vaccine efficacy.

When the vaccine efficacy is compared to the antigenic distance derived from ferret antisera [11,12], the dominant current measure of antigenic drift used to confirm phylogenetic strain analysis [39], the correlation is again less apparent. These data are shown in figure 4 and table 1. It appears that the ferret antisera experiments capture no more information than does the analysis with p_{sequence}. A ferret-derived antigenic distance of zero does not always guarantee that the two strains are identical. For example, for the 1996/1997 vaccine strain of A/Nanchang/933/95 and circulating strain of A/Wuhan/359/95, the ferret-derived antigenic distance was zero, whereas, $p_{\text{epitope}} = 0.095$, and the vaccine efficacy was 28% in the northern hemisphere [32] and 11% the next year in the southern hemisphere [31]. These values are much lower than the average for a perfect match between vaccine and circulating strains, which is 45%.

4 Discussion

Vaccine design is done under considerable time pressure. At present, the WHO and national health agencies in the northern hemisphere determine the components of the annual flu vaccine between February and April. The vaccine is then produced by growing virus in hen's eggs, and it is distributed in September after regulatory tests in mid-July [40]. Data collection relating to the effectiveness of the vaccine can begin in October, and by January a very good measure of the season's vaccine has been obtained. The availability of high-growth reassortments from egg-cultured strains imposes additional constraints on the choice of possible vaccine strains. Given the constraints imposed by the biology and manufacturing process, one wishes to choose the strain that provides the best possible match to the anticipated circulating strain for the following season.

There are two ways in which p_{epitope} can be used to improve vaccine development. The first is identification of "like" strains. Due to constraints of the manufacturing process, very often it is not feasible to produce in large quantity the exact strain of influenza that is desired for the vaccine. In this case, a similar, "like" strain is chosen from several possibilities. The value of p_{epitope} can be used to quantify how close each of the "like" strains is to the desired vaccine strain. The second way in which p_{epitope} can be used is identification of the strains desired to be included in the vaccine. That is, given a list of potential circulating strains, each with probabilities of outbreak for the upcoming year, which vaccine strain minimizes the weighted distance from the potential circulating strains? The value of p_{epitope} can be used to define distance, and so to help choose the closest vaccine strain to the potential circulating strains. The value of p_{epitope} might also help to design custom DNA-based vaccines that are as close as possible to a set of potential circulating strains. By applying the approach to the other strains of influenza through knowledge of the epitope regions, the value of p_{epitope} can also quantify distance or "likeness" in other H*x*N*y* strains of influenza A or in influenza B strains.

We believe that the antigenic distance between strains would profitably be defined by world health professionals as $p_{epitope}$ (figure 2), in addition to or rather than by sequence distance (figure 3) or by ferret antisera assays (figure 4). Of importance to note is that the immune response is non-monotonic and non-linear in the antigenic distance, *i.e.* original antigenic sin or negative vaccine efficacy exists only for an intermediate antigenic distance. In this regime, the vaccine can induce a greater degree of susceptibility to flu-like illness in vaccinated individuals relative to unvaccinated individuals. This negative efficacy has occurred 26% of the time for circulating H3N2 strains in the last 33 years (5 of the 19 data points in table 1, figure 2 and figure 3 are negative). Thus, original antigenic sin can occur not only if an individual's flu shot is not updated on an annual basis, but also even if an individual's flu shot is updated yearly. The original antigenic sin regime is to be avoided both for the immunological consequences and for the negative impact of such a vaccine on public health policy acceptance. Our theory quantifies where the regime lies and lends additional credence to the experimental measurements of such negative vaccine efficacies. While negative efficacies have often been thought to be experimental error (and appear to be noise in figures 3 and 4), they are not. Negative efficacies appear only for large values of $p_{epitope}$ (see figure 2).

As an example of how our theory can be used to help guide public health policy, we apply it to the 2004/2005 northern hemisphere flu season. By using $p_{epitope}$ as the definition of antigenic distance, one may be quantitative about which strains will *a priori* be most protective, and so should be chosen for inclusion in the annual vaccine. For example, to combat the A/Fujian/411/2002 strain that was predominant in the 2003–2004 influenza epidemic, the FDA Advisory Council decided to use A/Wyoming/3/2003, a strain termed 'antigenically equivalent' to A/Fujian/411/2002, as the H3N2 component of the 2004–2005 vaccine [41]. Our analysis yields $p_{epitope} = 0.095$ between these two strains, suggesting that the vaccine will have an efficacy of roughly 20% for influenza-like illness against the Fujian strain (see figure 2), and that these strains are not antigenically equivalent. Conversely, for A/Kumamoto/102/02 (ISDN38180), another available H3N2 component [42], we find $p_{epitope} = 0$ versus A/Fujian/411/2002, suggesting this component would provide superior protection to Fujian than would the Wyoming strain.

Continuing this example of how our theory can be used in vaccine design, we show in figure 5 the calculated $p_{epitope}$ values and vaccine efficacies between recent influenza A H3N2 vaccine components and circulating strains. Many isolates from the 2004/2005 flu season have been A/Fujian/411/2002-like strains [43]. Another circulating strain that began to emerge in late 2004 is A/California/7/2004, and an A/California/7/2004-like strain is recommended as the influenza A component of the 2005/2006 northern hemisphere vaccine by the WHO [44], suggesting that this is an important strain to consider as an example. For individuals who received a vaccination in 2003/2004 (the A/Panama/2007/99 strain) and who were not exposed to the Fujian strain, their protection against the Fujian strain is low, and their protection against the California strain is predicted to be in the region of original antigenic sin. For individuals who were vaccinated in the 2004/2005 season (the A/Wyoming/3/2003 strain), their protection against the Fujian strain is moderate, but their protection against the California strain is again predicted to be in the region of original

antigenic sin. For individuals who were exposed to the Fujian strain in 2003/2004 or 2004/2005, their protection against the California strain is predicted to be just in the region of original antigenic sin. The 2005 southern hemisphere vaccine strain was A/Wellington/1/2004. Our analysis yields $p_{epitope} = 0.143$ between Wellington and California indicating the vaccine will provide a low level of protection against the California strain. These findings suggest that production of a new vaccine strain to combat A/California/7/2004 in the next flu season is essential. Persons who received a flu vaccine in 2003/2004 and/or 2004/2005 should be particularly encouraged to receive a flu shot in 2005/2006, as they may be more susceptible to this new strain than if they had not received their flu shot in the previous 2 years.

In order to calculate the antigenic distance optimally, the dominant human epitope in each strain is needed. In the present approach, the dominant human epitope for a particular circulating strain in a particular year was defined as the epitope that had the largest fractional change in amino acid sequence relative to the vaccine strain. The identity of the dominant human epitope is not currently measured. Measurement of which epitope is dominant for humans for each vaccine and circulating strain should increase the predictive ability of our approach, beyond that in figure 2. More epidemiological studies relating antigenic drift to vaccine efficacy are needed [45] and would help guide the management of health resources during the flu season. Since substantial costs are associated with lost work due to influenza among those in the 18–64 age bracket, large studies of this age range are both important and informative, due to lack of immunosenescence. Continuous measurement and sequencing of the dominant circulating strains during the flu season, combined with the theory of figure 2, should enable better prediction of the severity of the annual flu season and better design of the subsequent year's vaccine.

More generally, our results have implications for the design of vaccines to combat rapidly mutating viral diseases that are controlled by antibody responses. We suggest that antigenic drift in the dominant epitope, $p_{epitope}$, will provide a prediction measure of efficacy for such vaccines. This quantitative measure of efficacy may then be used to determine the frequency and nature of vaccine redesign that is necessary.

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Appendix: The Generalized N K Model

Our theory of the immune response to vaccination and disease uses the generalized *N K* model [9] to calculate affinity constant values for the immune response to an antigen following vaccination. In this theory, the natural order parameter to distinguish between the vaccine strain and the circulating strain is the fraction of amino acids that differ in the dominant epitope region, p_{epitope}. The model considers the diversity of an individual's antibody repertoire and includes interactions within the antibody and between the antibody and the antigen. Here, the binding constant is determined as $K = \exp(a - b\langle U \rangle)$, where $a = -18.56$ and $b = 1.67$ are found from a comparison of the dynamics of the model with experiment [9], and U is the energy function for an antibody and is defined as

$$U=\sum_{i=1}^{M} U_{\alpha_i}^{\text{sd}}+\sum_{i>j=1}^{M} U_{ij}^{\text{sd}-\text{sd}}+\sum_{i=1}^{P} U_i^{\text{c}}. \quad (4)$$

The parameters within the generalized block *N K* model represent the number of secondary structures and the total size of the variable region [9]. We have $L = 5$ different subdomain energy functions of the *N K* form

$$U_{\alpha_i}^{\text{sd}}=\frac{1}{[M(N-K+1)]^{1/2}}\sum_{j=1}^{N-K+1}\sigma_{\alpha_i}(a_j,a_{j+1},\ldots,a_{j+K-1}), \quad (5)$$

where a_j is the amino acid type of the *j*th amino acid in the subdomain, and α_i is the type of the *i*th subdomain. As in previous studies, we consider the case where the range of the interactions within a subdomain is specified by $K = 4$ and there are $N = 10$ amino acids in each subdomain [46]. Here σ_{α_i} is a quenched Gaussian random number with zero mean and a variance of unity, and it is different for each value of its argument for each of the L subdomain types, α_i. The interaction energy between secondary subdomain structures is given by

$$U_{ij}^{\text{sd}-\text{sd}}=\left[\frac{2}{DM(M-1)}\right]^{1/2}\times\sum_{k=1}^{D}\sigma_{ij}^{(k)}\left(a_{j_1}^{(i)},\ldots,a_{j_{K/2}}^{(i)};a_{j_{K/2+1}}^{(j)},\ldots a_{j_K}^{(j)}\right). \quad (6)$$

Here $M = 10$ is the number of antibody secondary structural subdomains. We consider $D = 6$ interactions between secondary structures [46]. The zero-mean, unit-variance Gaussian $\sigma_{ij}^{(k)}$ and the interacting amino acids, $j_1, \ldots, j_K$, are selected at random for each interaction (i, j, k). In our model, $P = 5$ amino acids contribute directly to an antigen binding event, where the chemical binding energy of each amino acid is given by

$$U_i^c = \frac{1}{\sqrt{P}} \sigma_i(a_i), \quad (7)$$

where the zero-mean, unit-variance Gaussian σ_i and the contributing amino acid, i, are chosen at random.

To model the immune system dynamics, we use 30 rounds of point mutation and selection to evolve our antibody sequences, which corresponds to an immune response of approximately 10 days. For each round of selection we conduct 0.5 point mutations per antibody sequence and amplify the best 20% of antibody sequences to form the starting population for the next round of selection. The secondary immune response following vaccination uses evolved memory sequences as well as naive cells, whereas the primary immune response uses only naive cells [9].

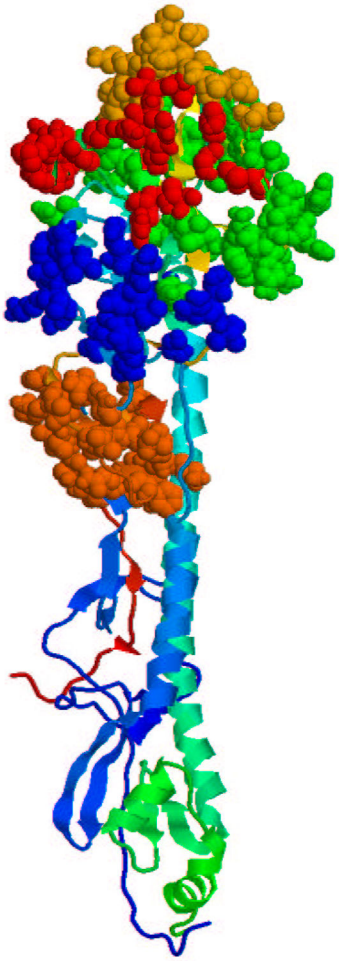

Fig. 1.

Hemagglutinin protein for the A/Fujian/411/2002 strain. Highlighted are the A (red), B (orange), C (brown), D (green), and E (blue) epitopes [15]. The rest of the protein is shown in ribbon format.

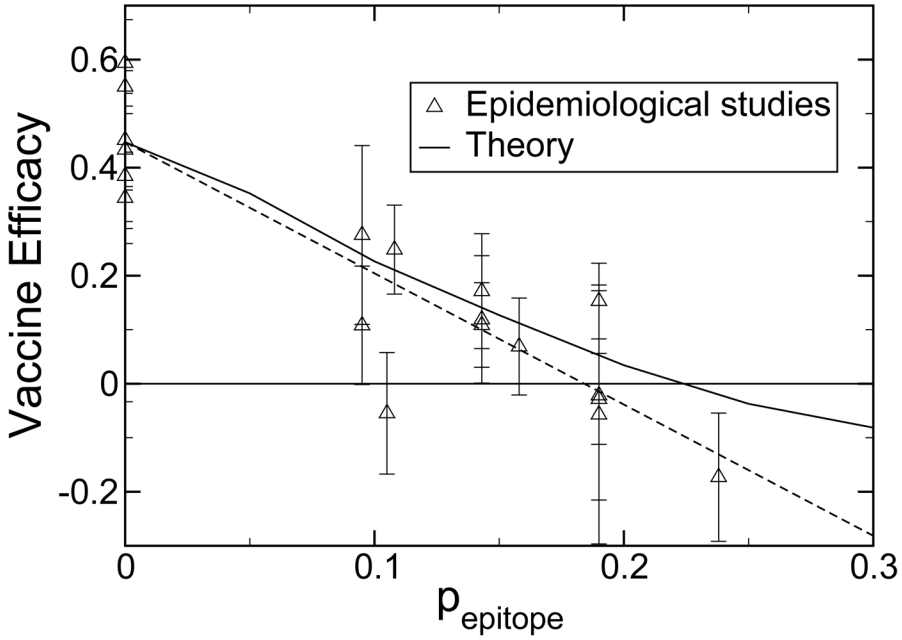

Fig. 2.

Vaccine efficacy for influenza-like illness as a function of p_{epitope} as observed in epidemiological studies and as predicted by theory. Also shown is a linear least squares fit to the data (long dashed, $R^2 = 0.81$). Error bars are one standard error, ε, calculated as described in Table 1.

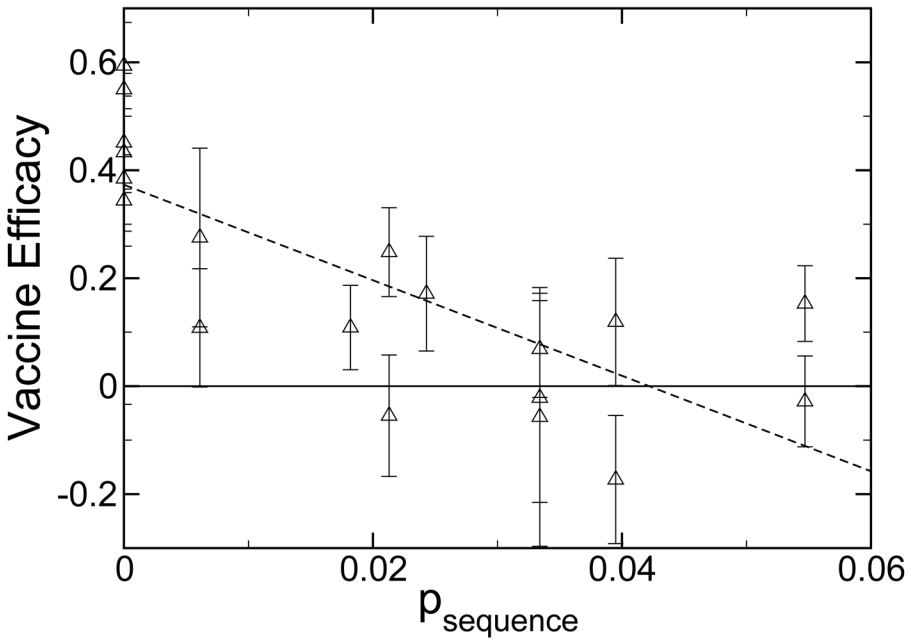

Fig. 3.

Vaccine efficacy as observed in epidemiological studies for influenza-like illness as a function of p_{sequence} (see eq. 3). Also shown is a linear least squares fit to the data (long dashed, $R^2 = 0.59$). The epidemiological data shown in this figure are the same as in figure 2. Only the definition of the *x*-axis is different.

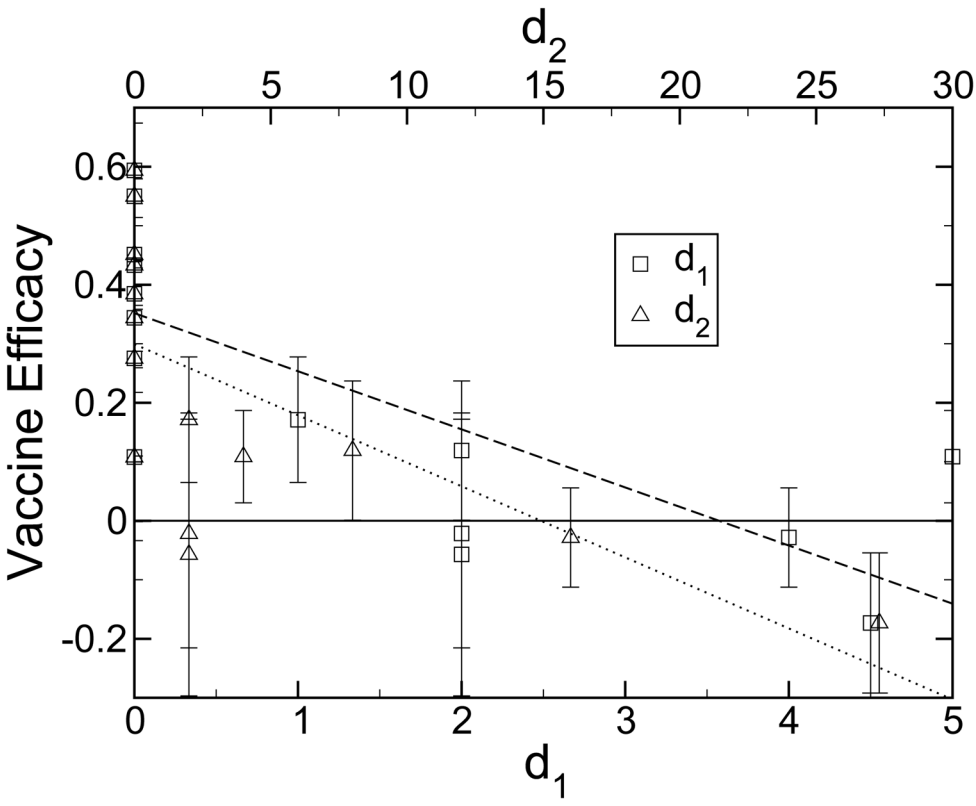

Fig. 4.

Vaccine efficacy for influenza-like illness as a function of two measures of antigenic distance, d_1 [11] and d_2 [12], derived from ferret antisera experiments. Experimental data were collected from a variety of sources [11,39,47,49,50,48,52,51]. Results were averaged when multiple hemagglutination inhibition (HI) studies had been performed for a given year. These HI binding assays measure the ability of ferret antisera to block the agglutination of red blood cells by influenza viruses. Also shown are linear least squares fits to the d_1 (long dashed, $R^2 = 0.57$) and d_2 (short dashed, $R^2 = 0.43$) data. The epidemiological data shown in this figure are the same as in figure 2. Only the definition of the x-axis is different.

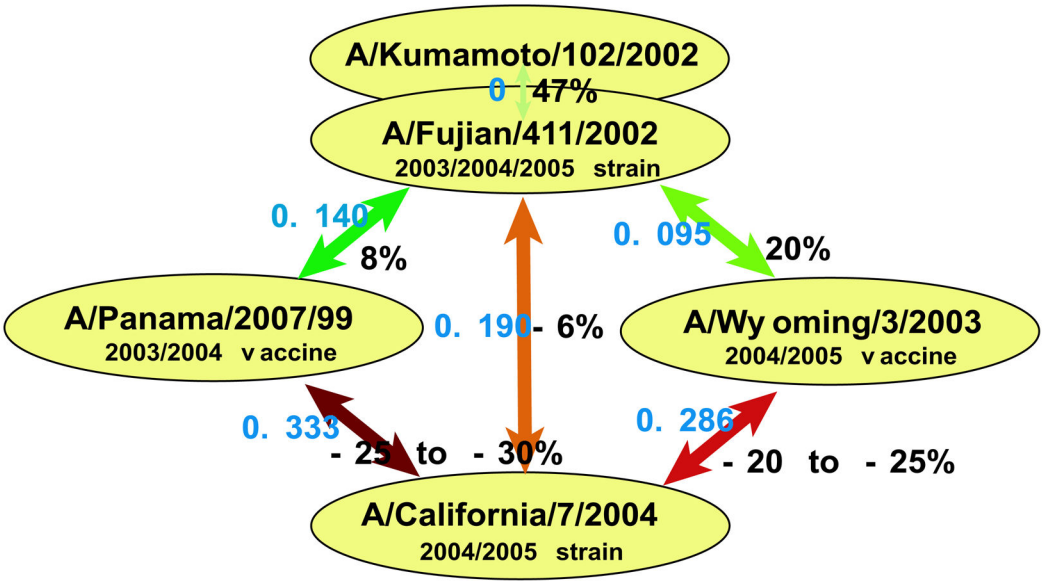

Fig. 5.

p_{epitope} (blue) and estimated vaccine efficacy (black) from figure 2 between components used in the 2003/2004 and 2004/2005 vaccinations and circulating strains in the 2004/2005 season.

Table 1

Summary of results. The table includes the identities and accession numbers of the vaccine and circulating strains for each of the years since 1971 that the H3N2 virus has been the predominant influenza virus and for which vaccine efficacy data are available. Vaccine efficacy is taken from the literature [21–35] and defined by eq. 2. Where more than one study exists for the same influenza season, the efficacy results are averaged. The dominant epitope is predicted by our theory for all seasons where the vaccine and circulating strains are not a match. The p_{epitope} and p_{sequence} values are calculated using eq. 1 and eq. 3, respectively. Two measures of antigenic distance from ferret antisera assays, d_1 [11] and d_2 [12], are determined from the literature [11,39,47,49,50,48,52,51]. Where more than one antisera assay has been performed, the calculated distances are averaged. Error bars are calculated assuming binomial statistics for each data set: $\varepsilon^2=[\sigma_v^2/u^2/N_v+(v/u^2)^2\sigma_u^2/N_u]$, where $\sigma_v^2=v(1-v)$ and $\sigma_u^2=u(1-u)$. If two sets of data are averaged in one year, then $\varepsilon^2=\varepsilon_1^2/4+\varepsilon_2^2/4$.

Year	Vaccine Strain	Circulating Strain	Vaccine Efficacy	Dominant Epitope	p_{epitope}	p_{sequence}	d_1	d_2	N_u	N_v
1971–72	Aichi/2/68 (V01085)	HongKong/1/68 (AF201874)	7 % [21]	A	0.158	0.033			25202	26317
1972–73	Aichi/2/68 (V01085)	England/42/72 (AF201875)	15 % [21]	B	0.190	0.055			26130	26779
1973–74	England/42/72 (ISDNENG72)	PortChalmers/1/73 (AF092062)	11 % [21]	B	0.143	0.018	5 [11]	4 [11]	26536	28158
1975–76	PortChalmers/1/73 (AF092062)	Victoria/3/75 (ISDNVIC75)	−3 % [21]	B	0.190	0.055	4 [47]	16 [47]	25591	29247
1984–85	Philippines/2/82 (AF233691)	Mississippi/1/85 (AF008893)	−6 % [22]	B	0.190	0.033	2 [48]	2 [48]	241	171
1985–86	Philippines/2/82 (AF233691)	Mississippi/1/85 (AF008893)	−2 % [23,24]	B	0.190	0.033	2 [48]	2 [48]	253, 91	153, 88
1987–88	Leningrad/360/86 (AF008903)	Shanghai/11/87 (AF008886)	17 % [23,25]	B	0.143	0.024	2 [48]	1 [48]	145, 1064	121, 1060
1989–90	Shanghai/11/87 (AF008886)	England/427/88 (AF204238)	−5 % [25]	A	0.105	0.021			1016	1016
1992–93	Beijing/32/92 (AF008812)	Beijing/32/92 (AF008812)	59 % [26]		0.0	0.0	0 [49]	0 [49]	131	131
1993–94	Beijing/32/92 (AF008812)	Beijing/32/92 (AF008812)	38 % [24]		0.0	0.0	0 [49]	0 [49]	12	26
1994–95	Shangdong/9/93 (Z46417)	Johannesburg/33/94 (AF008774)	25 % [27]	A	0.108	0.021			424	422
1995–96	Johannesburg/33/94 (AF008774)	Johannesburg/33/94 (AF008774)	45 % [28]		0.0	0.0	0 [50,51]	0 [50,51]	652	684
1996–97	Nanchang/933/95 (AF008725)	Wuhan/359/95 (AF008722)	28 % [32]	B	0.095	0.006	0 [50,51]	0 [50,51]	2978	273
1997	Nanchang/933/95 (AF008725)	Wuhan/359/95 (AF008722)	11 % [31]	B	0.095	0.006	0 [50,51]	0 [50,51]	299	294
1997–98	Nanchang/933/95 (AF008725)	Sydney/5/97 (AJ311466)	−17 % [30]	B	0.238	0.040	4.5 [50,52]	27.3 [50,52]	554	576
1998–99	Sydney/5/97 (AJ311466)	Sydney/5/97 (AJ311466)	34 % [30]		0.0	0.0	0 [39,50]	0 [39,50]	596	582
1999–00	Sydney/5/97 (AJ311466)	Sydney/5/97 (AJ311466)	43 % [34]		0.0	0.0	0 [39,50]	0 [39,50]	324	342
2001–02	Panama/2007/99 (ISDNCDA001)	Panama/2007/99 (ISDNCDA001)	55 % [33]		0.0	0.0	0 [39,50]	0 [39,50]	982	968
2003–04	Panama/2007/99 (ISDNCDA001)	Fujian/411/2002 (ISDN38157)	12 % [35]	B	0.143	0.040	2 [39]	8 [39]	402	1000