Modeling the effects of updating the influenza vaccine on the efficacy of repeated vaccination

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Abstract

Background: The accumulated wisdom is to update the vaccine strain to the expected epidemic strain only when there is at least a 4-fold difference [measured by the hemagglutination inhibition (HI) assay] between the current vaccine strain and the expected epidemic strain. In this study we investigate the effect, on repeat vaccinees, of updating the vaccine when there is a less than 4-fold difference. Methods: Using a computer model of the immune response to repeated vaccination, we simulated updating the vaccine on a 2-fold difference and compared this to not updating the vaccine, in each case predicting the vaccine efficacy in first-time and repeat vaccinees for a variety of possible epidemic strains. Results: Updating the vaccine strain on a 2-fold difference resulted in increased vaccine efficacy in repeat vaccinees compared to leaving the vaccine unchanged. Conclusions: These results suggest that updating the vaccine strain on a 2-fold difference between the existing vaccine strain and the expected epidemic strain will increase vaccine efficacy in repeat vaccinees compared to leaving the vaccine unchanged.

Keywords: original antigenic sin, vaccine efficacy, antigenic distance.

Introduction

Generally, the influenza vaccine strain is updated when there is at least a 4-fold difference in HI titer between the existing vaccine strain and the expected epidemic strain. Public health recommendations are for individuals in high-risk groups to be revaccinated annually [1]; thus, vaccine efficacy in repeat vaccinees is particularly important. However, the efficacy of repeated vaccination has been difficult to determine definitively: Meta-analysis has shown a statistically significant heterogeneity in the efficacy of repeated vaccination in serology-based field trials [2], and different studies have draw different conclusions as to the effectiveness of repeated vaccination [3, 4]. To explain this heterogeneity, we introduced the "antigenic distance" hypothesis [5] which states that prior exposure to influenza virus or vaccine can influence the subsequent response depending upon the degree of cross-reactivity among the antigens used in the vaccines and the epidemic influenza strains in each study year (Figure 1). Using a computer, we showed that this hypothesis offered a parsimonious explanation for the observed variation in repeated vaccination within and between the Hoskins[3] and Keitel[4] repeated vaccination studies (Figure 2). Here we use the antigenic distance hypothesis, and the same computer model, to reason quantitatively about the effects, on repeat vaccinees, of updating the vaccine strain on a less than 4-fold difference.

Methods

The computer model consists of B cells, plasma cells, memory B cells, antibodies, and antigens. The model captures the essence of the primary and secondary humoral immune response, and the cross-reactive immune response. More details of the model can be found in [5], full details can be found in the supplemental material of [5] at http://www.pnas.org/, and the software for the simulator is available from http://www.santafe.edu/ dsmith/software/PNAS-model.html.

The computer experiment simulated two influenza seasons. A control group of 200 simulated individuals received no vaccinations and was challenged with replicating virus 2 months into the second influenza season. Four first-time vaccination groups, each of 200 simulated individuals, were vaccinated at the start of the second influenza season, and were challenged 2 months into the second influenza season with either homologous virus, or virus 2- 4- or 8-fold different from the vaccine strain. Sixteen repeated vaccination groups, each of 200 simulated individuals, all received the same "vaccine1" (v1) strain at the start of the first influenza season. At the start of the second influenza season, eight of the sixteen groups were vaccinated with the same strain as used for the first vaccination, and the other eight groups received a "vaccine2" (v2) strain that was 2-fold different[1] from the vaccine1 strain. All sixteen repeat vaccination groups were challenged 2 months into the second influenza season with replicating virus up to 4-fold different from each of the vaccine strains (Figure 3). In all cases, the vaccine dose was 1,000 "units" of non-replicating virus, and the epidemic dose was 500 units of replicating virus.

If the viral load exceeded 1,500 units it was deemed to have passed a "disease threshold" and the simulated individual was considered symptomatic. The attack rate within a group was defined as the proportion of the group in which the viral load exceeded the disease threshold. Vaccine efficacy was defined as $1 - (ar_{vac}/ar_{nonvac})$, where ar_{vac} is the attack rate in a vaccinated group and ar_{nonvac} is the attack rate in the non-vaccinated control. Two sample z-tests were used to compare proportions. Two-tailed testing was used for p values.

Results

The attack rate in the non-vaccinated control was 1.0.[2] Attack rates in first-time vaccinees were 0.0, 0.02, 0.55, and 0.83 for homologous, 2-fold, 4-fold, and 8-fold differences, respectively, between the vaccine strain and the actual epidemic strain. Efficacies in repeat vaccinees when the vaccine was updated, and when it was not updated, and for various actual epidemic strains, are shown in Figure 3. Ratios of efficacy in repeat vaccinees to efficacy in first-time vaccinees ranged from 0.49 to 3.00 (Figure 3).

Updating the vaccine on a 2-fold difference between the existing epidemic strain and the expected

[1] 2- 4- and 8-fold differences corresponds to "antigenic distances" 1, 2, and 3 respectively in [5].

[2] Each simulated individual was challenged with a large dose of virus, resulting in higher attack rates than in influenza vaccine field trials

epidemic strain resulted in higher predicted vaccine efficacy in repeat vaccinees in all cases compared to when the vaccine was not updated ($p < 0.01$ in all cases other than in the case when the actual epidemic strain was the same as the vaccine1 strain). Efficacies when the vaccine was not updated were dependent only on the antigenic distance between the vaccine strain and the actual epidemic strain. When the vaccine was updated to the expected epidemic strain, efficacies in repeat vaccinees depended on the antigenic distances between the actual epidemic strain and both vaccine1 and vaccine2 strains. Repeat vaccine efficacy was higher when there was a triangular configuration between the three strains (for example, when the actual epidemic strain was 4-fold different from both the vaccine1 and vaccine2 strains, and vaccine1 and vaccine2 strains were 2-fold different from each other). Vaccine efficacy in repeat vaccinees exceeded that in first-time vaccinees in some groups ($p < 0.01$) when the vaccine was updated to the expected epidemic strain, and not at all when the vaccine was not updated.

Somewhat surprisingly, for actual epidemic strains closer to vaccine1 than to the expected epidemic strain (strains to the left of vaccine1 in Figure 3), the predicted efficacy in repeat vaccinees was higher ($p < 0.01$) when the vaccine was updated than when it remained unchanged—even though leaving the vaccine unchanged would result in a vaccine strain closer to those actual epidemic strains.

Discussion

Updating the vaccine when there is a 2-fold difference between the existing vaccine strain and the expected epidemic strain gave a higher vaccine efficacy in repeat vaccinees than leaving the vaccine unchanged (Figure 3). It is similarly advantageous to update the vaccine on a 4-fold or more difference (data not shown). These results support the current strategy to update the vaccine strain on a 4-fold or more difference between the existing vaccine strain and the expected epidemic strain. Moreover, these results suggest that also updating the vaccine on a 2-fold difference will increase vaccine efficacy in repeat vaccinees compared to leaving the vaccine unchanged.

Influenza epidemics occur most years, and public health recommendations are for at-risk individuals to be revaccinated annually. Thus, optimizing the vaccine efficacy for a single year by updating the vaccine strain to an expected epidemic strain 2-fold from the existing vaccine is not necessarily the best strategy over multiple years. For example, an advantage of only updating the vaccine when there is at least a 4-fold difference is that there will be less "negative interference" (antigenic sin effect [6, 7]) from prior vaccinations. Thus, keeping the vaccine unchanged trades off reduced efficacy in repeat vaccinees in the year when the vaccine did not change, for increased efficacy in the subsequent year. To fully assess the tradeoffs for repeat vaccinees in updating the vaccine or not requires examining the effects over multiple years (manuscript in preparation).

A difficulty of updating the vaccine strain on a 2-fold difference in HI titer is that the resolution and reliability of the HI assay are such that only at least a 4-fold difference between strains has typically been considered significant. Beyer and Masurel [8], and Lapedes and Farber [9], have used mathematical techniques to address some of the inherent difficulties in obtaining accurate measurements of antigenic distance from HI data. These techniques are investigated further in a manuscript in preparation.

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Figure Captions

Figure 1. An illustration of the antigenic distance hypothesis. These *Shape space* diagrams are a way to illustrate both the affinities of multiple B cells/antibodies to multiple antigens, and also the antigenic distances among multiple antigens [10]. In these diagrams, the affinity between a B cell or antibody ($\times$) and an antigen (•) is represented by the distance between them. Similarly, the distance between antigens is a measure of how similar they are antigenically. (a) B cells with sufficient affinity to be stimulated by an antigen lie within a *ball of stimulation* centered on the antigen. Thus, a first vaccine (vaccine1) creates a population of memory B cells and antibodies within its ball of stimulation. (b) Cross-reactive antigens have intersecting balls of stimulation, and antibodies and B cells in the intersection of their balls—those with affinity for both antigens—are the cross-reactive antibodies and B cells. The antigen in a second vaccine (vaccine2) will be partially eliminated by pre-existing cross-reactive antibodies (depending on the amount of antibody in the intersection), and thus the immune response to vaccine2 will be reduced [6, 7]. (c) If a subsequent epidemic strain is close to vaccine1, it will be cleared by pre-existing antibodies. (d) However, if there is no intersection between vaccine1 and the epidemic strain, there will be few pre-existing cross-reactive antibodies to clear the epidemic strain quickly, despite two vaccinations. Note, in the absence of vaccine1, vaccine2 would have produced a memory population and antibodies that would have been protective against both the epidemic strains in panels c and d. For an antigen with multiple epitopes (such as influenza) there would be a ball of stimulation for each epitope. Figure taken from [5], copyright (1999) National Academy of Sciences, U.S.A., used with permission.

Figure 2. The observed and predicted vaccine efficacy in repeat vaccinees relative to the efficacy in first-time vaccinees. The prediction of relative efficacy had good correlation with the observed data ($r = 0.87$, $p = 0.01$); however, the model did not accurately predict absolute vaccine efficacies, suggesting additional variation in each vaccine not accounted for in the model (discussed further in [5]). Figure taken from [5], copyright (1999) National Academy of Sciences, U.S.A., used with permission.

Figure 3. Predictions from the model for vaccine efficacy in repeat vaccinees (given V_1 and V_2), and in parenthesis, relative efficacy compared to that in first-time vaccinees (given V_2 only), for two vaccine2 strain choices given a variety of actual epidemic strains (hollow circles) up to 4-fold from both vaccine strains. There was a 2-fold difference between the existing vaccine (V_1) and the expected epidemic strain (E_e) in both panels a and b.

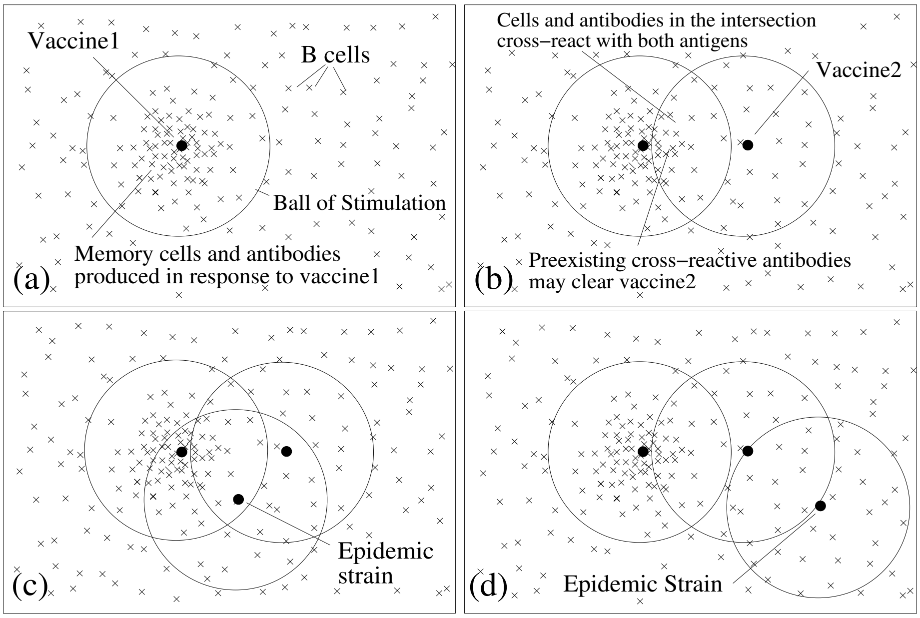

Vaccine1
B cells
Ball of Stimulation
Memory cells and antibodies
produced in response to vaccine1
(a)
Cells and antibodies in the intersection
cross−react with both antigens
Vaccine2
Preexisting cross−reactive antibodies
may clear vaccine2
(b)
Epidemic
strain
(c)
Epidemic Strain
(d)

Figure 1:

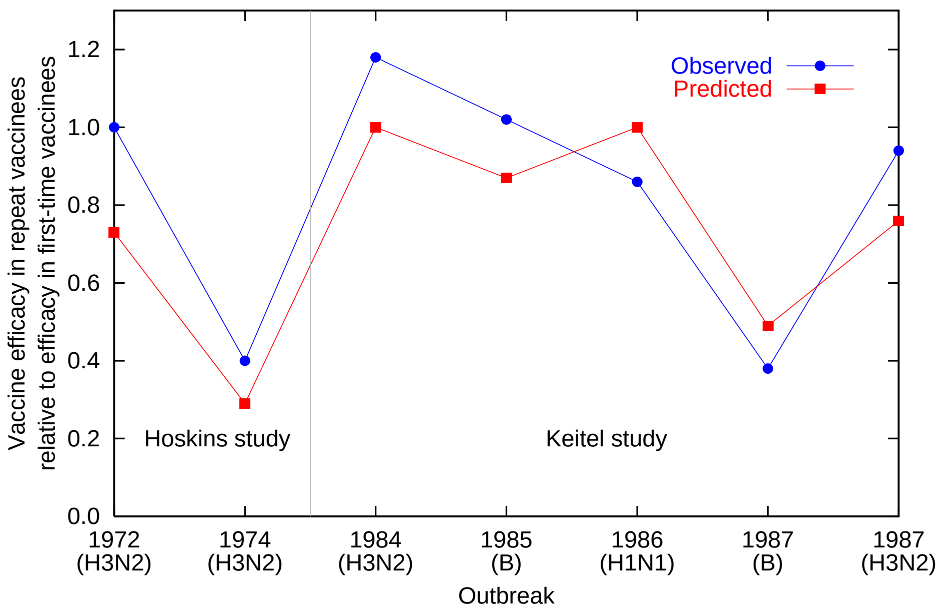
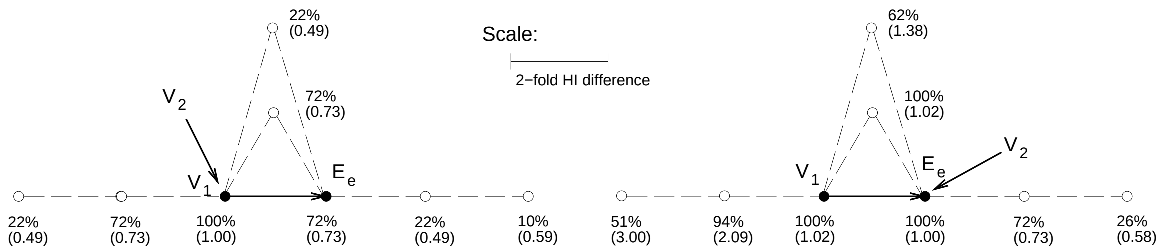

Observed
Predicted
Vaccine efficacy in repeat vaccinees relative to efficacy in first-time vaccinees
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Hoskins study
Keitel study
1972 (H3N2)
1974 (H3N2)
1984 (H3N2)
1985 (B)
1986 (H1N1)
1987 (B)
1987 (H3N2)
Outbreak

Figure 2:



(a) Vaccine strain stays the same

(b) Vaccine updated to expected epi strain

Figure 3: