LA-UR-98-2924

Title: MODELING THE EFFECTS OF ANNUAL INFLUENZA VACCINATION

CONF-981019--

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Submitted: Proc. IEEE. Intl. Conf. on Systems, Man and Cybernetics
San Diego, CA
October 1998

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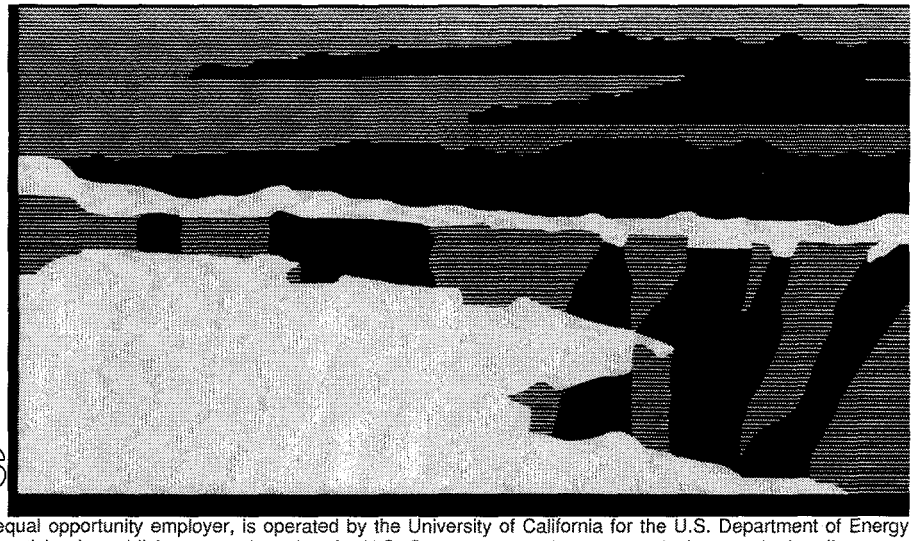

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Modeling the Effects of Annual Influenza Vaccination

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Abstract

Although influenza vaccine efficacy is 70-90% in young healthy first-time vaccinees, the efficacy in repeat vaccinees has varied considerably. In some studies, vaccine efficacy in repeat vaccinees was higher than in first-time vaccinees, whereas in other studies vaccine efficacy in repeat vaccinees was significantly lower than in first-time vaccinees and sometimes no higher than in unvaccinated controls. It is known that the closeness of the antigenic match between the vaccine strain and the epidemic virus is important for vaccine effectiveness. In this study we show that the antigenic differences between a first vaccine strain and a second vaccine strain, and between the first vaccine strain and the epidemic strain, might account for the observed variation in attack rate among two-time vaccinees.

Introduction

Antigenic drift of the influenza virus exposes the human population to new but related influenza variants on an annual basis. Thus, components of the influenza vaccine are updated, sometimes yearly, to maintain a reasonable correspondence between the vaccine and epidemic strains. Public heath recommendations are for annual vaccination of the at-risk individuals [1]. Millions of people in the United States receive annual influenza vaccination; the major categories are the elderly, persons at high risk of death or severe illness with influenza infection, and health care workers.

Vaccine efficacy in young healthy first-time vaccinees is 70-90% [2, 3, 4]. However, efficacy in individuals who have been vaccinated multiple times (repeat-vaccinees) has varied considerably. In some studies the attack rate in repeat vaccinees has been the same as in unvaccinated controls, while the attack rate in first-time vaccinees have been in the usual 70-90% range [5, 4]. In other studies the attack rate among repeat vaccinees have sometimes been higher and sometimes lower than among first-time vaccinees [6, 7, 8, 9]. Duration of illness and mortality appear to be lower in repeat-vaccinees [4, 10]. These variations between first-time and repeat vaccinees are not well understood.

It is known that the closeness of the antigenic match between the vaccine strain and the epidemic virus is important for vaccine effectiveness—this is why components of the vaccine are updated as the antigen drifts. In this study we investigate whether the antigenic differences between a first vaccine strain and a second vaccine strain, and between the first vaccine strain and the epidemic strain, can account for the observed variation in attack rate among two-time vaccinees. We previously reported that a prior infection could affect vaccine efficacy [19]. Here we consider a prior vaccination, and set up the timing of the vaccinations to correspond to annual influenza vaccinations.

The experiments reported here were performed *in machina*. Like any model system, a computer model trades off accuracy for controllability, observability, speed, and lower cost. Consequently, as with any model system (whether animal, *in vitro*, or computer) care must be taken to understand the limitations of the model, and when interpreting the results. The model has been validated by replicating existing experiments, and parameters of the model have been derived from data important in the cross-reactive immune response [11].

Introduction to the model

Antibody-antigen binding is a complex physical-chemical process involving, among other things, shape and charge complementarity, hydrogen bonding, hydrophobic interactions, and van der Waals interactions. Imagine, for illustrative purposes, that these binding properties could be described by some number of parameters [12]; for the pur-

Category	Num. Groups	Num. in each group	Vaccine 1 (year 1) (dose on day 0)	Vaccine 2 (year 2) (dose on day 365)	Epidemic challenge (year 2 flu season) (dose on day 425)
(a) No vaccines	1	40			500
(b) Vaccine 1 only	8	80	1,000		500
(c) Vaccine 2 only	1	80		1,000	500
(d) Vaccines 1 and 2	31	40-42	1,000	1,000	500

Table 1: The timing and dose of simulated vaccinations and epidemic challenge. Each category corresponds to a different vaccine strategy, and each group within a category corresponds to different antigenic distances among the vaccine and epidemic strains. Each individual was challenged with epidemic virus two months into the second influenza season. (a) One group was never vaccinated. (b) Eight groups were vaccinated in year one—each group corresponded to challenge with a different epidemic strain with the vaccine1-epidemic strain antigenic distance varying from 0 to 7. (c) One group was vaccinated in year two and challenged with an epidemic strain antigenic distance 2 from the vaccine2 strain. (d) Thirty-one groups were vaccinated in years one and two—each group corresponded to different combinations of vaccine1-vaccine2 antigenic distances from 0 to 7 and vaccine1-epidemic strain antigenic distances 0 to 7, the vaccine2-epidemic strain antigenic distance was 2.

poses of illustration let us assume two parameters. These two parameters could then be used as x,y-coordinates to locate antibodies and antigens in a two-dimensional *shape space* (Figure 1a). Further, imagine that the affinity between an antigen and antibody depends on the distance between them. In such a space, B cells with sufficient affinity to be stimulated by an antigen lie within a *ball of stimulation* centered on the antigen (Figure 1a). Further, cross-reactive antigens will have intersecting balls of stimulation, and the antibodies and B cells in the intersection of their balls—those with affinity for both antigens—are the cross-reactive antibodies and B cells (Figure 1b).

Such shape space diagrams can be used to think about annual vaccination against influenza. A first vaccine (vaccine1) creates a population of memory B cells and antibodies within its ball of stimulation (Figure 2a). A second vaccine (vaccine2), if its ball of stimulation overlaps vaccine1, will be mostly eliminated by preexisting antibodies from the intersection of the balls of stimulation of the two antigens. Stimulation of all naive B cells in the ball of stimulation of vaccine2 is reduced because of the clearance of vaccine2 by the cross-reactive antibodies (Figure 2b). If a subsequent epidemic strain is close to vaccine1, it too will be eliminated by preexisting antibodies (Figure 2c). However, if the ball of stimulation of the epidemic strain does not overlap vaccine1, then there will be little protection (Figure 2d). Note, that in the absence of vaccine1, vaccine2 would have produced a memory population and antibodies that would have been protective against both the epidemic strains of Figures 2c and d. These diagrams provide the basis of a possible explanation of why vaccine efficacy is highly variable in multiple vaccinees while it is consistently high in first-time vaccinees.

These two-dimensional shape space diagrams are illustrative, but it is clear that the complexities of real antigen and antibody binding characteristics cannot be described by just two parameters. The actual number of parameters required is not known. We have calculated that a shape-space using twenty parameters, each of which can take on one of four values, results in a space that has some biological relevance [11]. It might be useful (though perhaps misleading) to think of these twenty parameters as a binding site of twenty amino acids, and the four values of each "amino acid" as properties such as charge and hydrophobicity. In this space, the distance between two antigens is measured by *mutation* distance, i.e. the number of changes in the parameters describing one antigen required to make the parameters identical to those of the second antigen. Similarly, the distance between an antibody and an antigen is the number of mutations required to make the antibody a perfect match for the antigen. This measurement of the distance between antigens by their mutation distance allows a quantization of the usual antigenic difference as antigenic *distance* which we define as the mutation distance between our string representation of antigens. Antigenic distances can vary between 0 and 20, where a distance of 0 implies antigenic identity, and a distance of 7 or more implies no cross-reactivity.

The computer model includes B cells, plasma cells, antibodies, memory B cells, and antigens. The model is agent based, and in that sense similar to [13]. More details of the model can be found in [14].

Materials and Methods

Experimental design. The experiment considered four categories of individuals: (a) those never vaccinated, (b) those who received a "vaccine1" at the start of the first influenza season and were not vaccinated for the second season, (c) those not vaccinated for the first influenza season but who received "vaccine2" at the start of the second season, and (d) those who received a vaccine1 at the start of the first influenza season and vaccine2 at the start of the second. All simulated individuals were challenged with an epidemic strain two months into the second influenza season. The epidemic strain was always antigenic distance two from the vaccine2 strain. Individuals vaccinated only at the start of the first season (category b) were further split into eight groups with each group having a different vaccine1-epidemic strain antigenic distance. Sim-

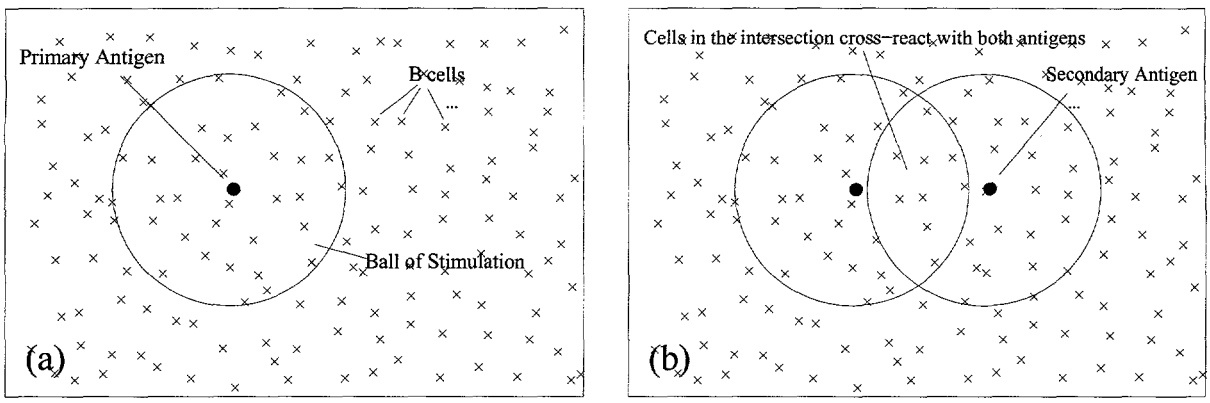

Figure 1: In these *shape space* diagrams, the position of B cells (×) and antigens (•) is determined by a parameterization of their binding characteristics, and the distance between a B cell and an antigen is a measure of their affinity for each other. (a) B cells with sufficient affinity to be stimulated by an antigen lie within a *ball of stimulation* centered on the antigen. (b) Cross-reactive antigens have intersecting balls of stimulation, and antibodies and B cells within the intersection of their balls—those with affinity for both antigens—are the cross-reactive antibodies and B cells.

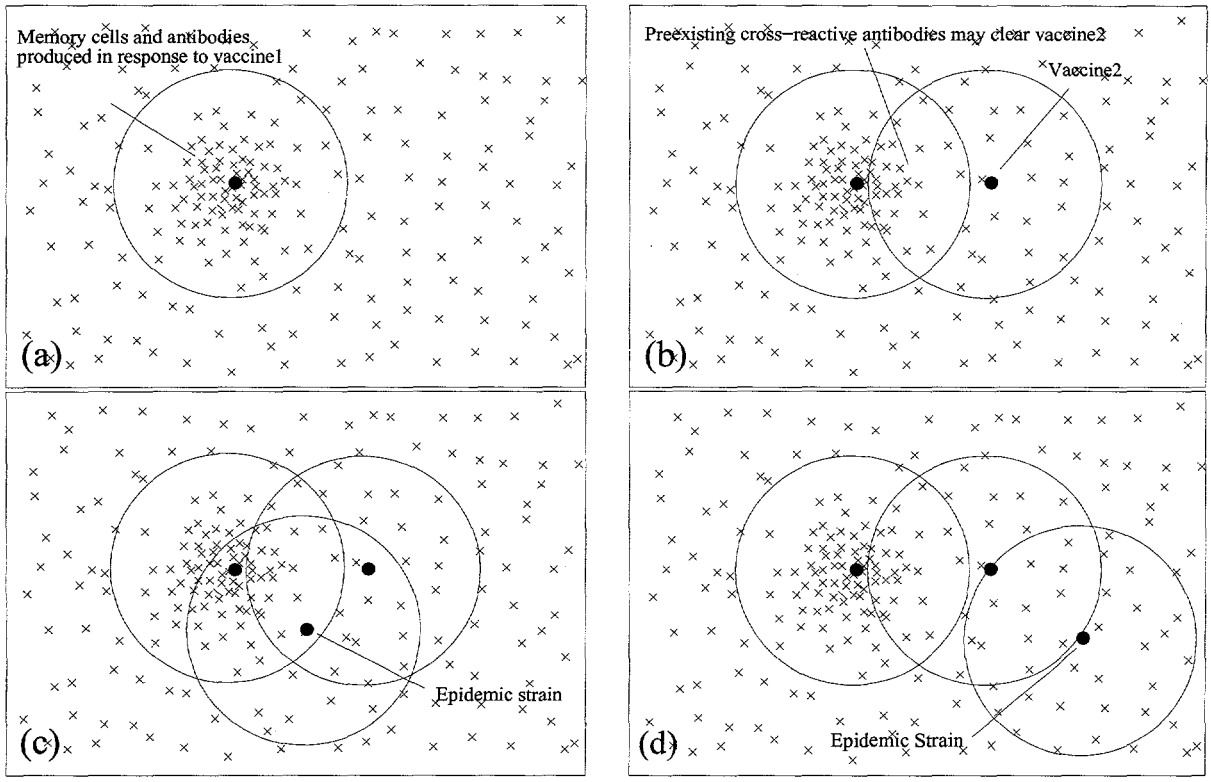

Figure 2: Cross-reactivity with an earlier vaccine (vaccine1) can cause a second vaccine (vaccine2) to fail. (a) A first vaccine (vaccine1) creates a population of memory B cells and antibodies within its ball of stimulation. (b) A second vaccine (vaccine2) will be mostly eliminated by preexisting antibodies; stimulation of all naive B cells in its ball of stimulation will be reduced. (c) If a subsequent epidemic strain is close to vaccine1, it will be cleared by preexisting antibodies. (d) If there is no intersection between vaccine1 and the epidemic strain, there will be no preexisting antibodies to clear the epidemic strain quickly.

ilarly, the twice-vaccinated (category d) were split into 31 groups with different vaccine1-epidemic strain, and different vaccine1-vaccine2 antigenic distances. Dosage and timing of the vaccinations and epidemic challenge are summarized in Table 1. If the viral load exceeded 1,500 units it was deemed to have passed a "disease threshold" and the simulated individual was considered symptomatic. Every simulated individual was exposed to epidemic virus, and the attack rate within a group was defined as the proportion of the group in which the maximum viral load exceeded the disease threshold.

Vaccine and epidemic strains. The same epidemic strain was used for all challenges. Similarly, the same vaccine strain ("vaccine2") was used for all vaccinations at the start of the second influenza season. Thirty-one different vaccine strains ("vaccine1") were used for vaccinations at the start of the first influenza season. Keeping the epidemic and vaccine2 strains constant allows us to simulate individuals with different vaccination histories being vaccinated with the same strain and challenged with the same epidemic virus. The vaccine strains were nonreplicating.

Results

Table 2 shows the experimental attack rate in each experimental and control group. Each member of each group was challenged with epidemic virus 2 months into the second simulated influenza season. Challenging each member of a group gives higher attack rates than those observed in field trials of influenza vaccines because in the field trials some members of a group might not be exposed to influenza. The experimental attack rate was 1.0 in the group that was never vaccinated. The experimental attack rate was 0.58 in the group vaccinated once at the start of the second influenza season. Experimental attack rates varied from 0.04 to 1.0 in groups vaccinated once at the start of the first influenza season—the attack rate depended on the vaccine1-epidemic strain antigenic distance. Experimental attack rates varied from 0.0 to 0.83 in groups vaccinated twice, once before the first influenza season, and again before the second season—the attack rate depended on the vaccine1-vaccine2 antigenic distance, and the vaccine1-epidemic strain antigenic distance (the vaccine2-epidemic strain distance distance was fixed at 2).

An additional year between vaccination and challenge increased the experimental attack rate from 0.58 to 0.89 for first time vaccinees when the vaccine-epidemic strain antigenic distance was 2 (Table 2). This was due to decay of the quantity of cross-reactive antibodies (data not shown).

In all groups that received vaccine1, it always lowered experimental attack rates to receive vaccine2. This can be seen by comparing the attack rates across a row Table 2 (a row corresponds to groups in which the vaccine1-epidemic strain antigenic distance was the same).

Experimental attack rates in groups that received vaccine1 and vaccine2 (Table 2) were sometimes lower, and sometimes higher, than that in the group that received only vaccine2—even though the timing, dose, and vaccine2-epidemic strain antigenic distance were identical. This interference of vaccine1 on the apparent efficacy of vaccine2 can be split into two factors. The first factor is a "negative interference" in which vaccine2 is partially eliminated by preexisting cross-reactive antibodies produced in response to vaccine 1, and in which vaccine2 preferentially stimulates memory clones produced in response to vaccine1. Negative interference is greater when the vaccine1-vaccine2 antigenic distance is small—this can be seen in rows of Table 2. An example of negative interference of vaccine1 on vaccine2 is shown in Figure 3. The second factor is a "positive interference" in which the epidemic strain is cleared by preexisting cross-reactive antibodies produced in the immune response to vaccine1, and boosted by the immune response to vaccine2. Positive interference is greater when the vaccine1-epidemic strain antigenic distance is smaller–this trend can be seen in columns of Table 2. An example of positive interference is shown in Figure 4.

Discussion

Our results indicate that for individuals vaccinated in two successive years, the antigenic distances of the first vaccine to the second vaccine, and of the first vaccine to the epidemic strain, can significantly affect experimental attack rates. These results offer an explanation for the contradictory findings in field trials of annual influenza vaccination. When the vaccine1-vaccine2 antigenic distance was small, vaccine1 *negatively interfered* with vaccine2, clearing it before it induced an immune response, and thus inhibited production of potentially protective antibodies against the subsequent epidemic strain. However, when the vaccine1-epidemic strain antigenic distance was small, vaccine1 *positively interfered* with the epidemic strain because antibodies produced by the immune response to vaccine1 cross-reacted with the epidemic strain and helped to clear it. Thus, experimental attack rates varied in annual vaccinees depending on the combination of negative and positive interference induced by vaccine1 which in turn depended on the vaccine1-vaccine2 and vaccine1-epidemic strain antigenic distances.

The observed reduction in the immune response to the second vaccination, due to partial elimination of the vaccine by preexisting cross-reactive antibodies, has also been reported for influenza vaccines in humans [15]. The amount of reduction appears to be proportional to the amount of circulating antibodies [16, 17].

In our model system, when the vaccine was the same in both years (homologous vaccine), the second vaccination

Vaccine1 to epidemic strain antigenic distance	Vaccine1 only	Vaccine1 and vaccine2							
		Vaccine1 to vaccine 2 antigenic distance							
		0	1	2	3	4	5	6	7
0	0.04			0.00					
1	0.52		0.07	0.05	0.02				
2	0.89	0.79	0.31	0.31	0.12	0.17			
3	0.95		0.83	0.43	0.48	0.27	0.43		
4	0.98			0.79	0.50	0.44	0.28	0.47	
5	1.00				0.56	0.49	0.45	0.40	0.38
6	1.00					0.60	0.62	0.43	0.53
7	1.00						0.52	0.59	0.53

Table 2: A summary of the experimental attack rate in each group. Exposure to the epidemic challenge, without prior vaccination, caused disease in all cases (experimental attack rate 1.0). Experimental attack rates varied from 0.04 to 1.0 when the vaccine was given 1 year 2 months before the epidemic challenge, depending on the antigenic distance between the vaccine and epidemic strains. The experimental attack rate was 0.58 when the vaccine was given 2 months before the epidemic challenge. Experimental attack rates varied between 0.0 to 0.83 when the epidemic challenge came after two annual vaccinations.

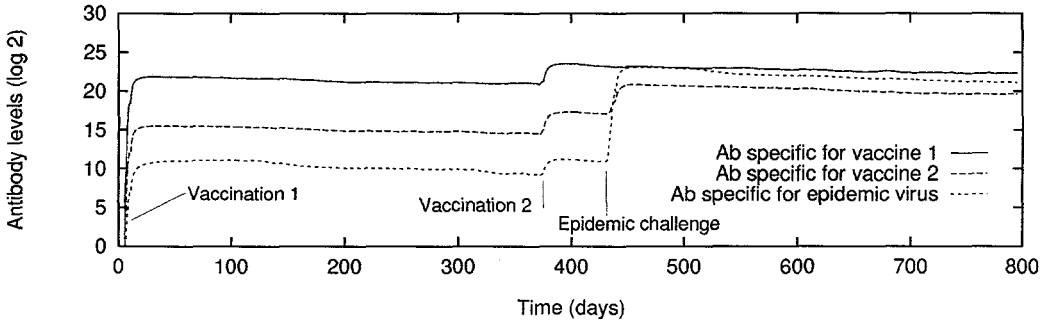

Figure 3: An example of negative interference of vaccine1 on vaccine2. The experiment shown is from the group in which the vaccine2-epidemic strain antigenic distance was 2, the vaccine1-epidemic strain antigenic distance was 4, and the vaccine1-vaccine2 antigenic distance was 2. In this example, the immune response to vaccine1 produced antibodies that were moderately cross-reactive with vaccine2 but only slightly cross-reactive with the epidemic virus. When vaccine2 was injected, much of it was eliminated by preexisting cross-reactive antibodies (data not shown), and the 8-fold increase in antibody levels to vaccine1, vaccine2, and the epidemic virus was predominantly caused by stimulation of memory clones generated by the immune response to vaccine1 (data not shown). Although the antibody level to the epidemic strain increased, it remained below protective levels, and the epidemic challenge caused disease.

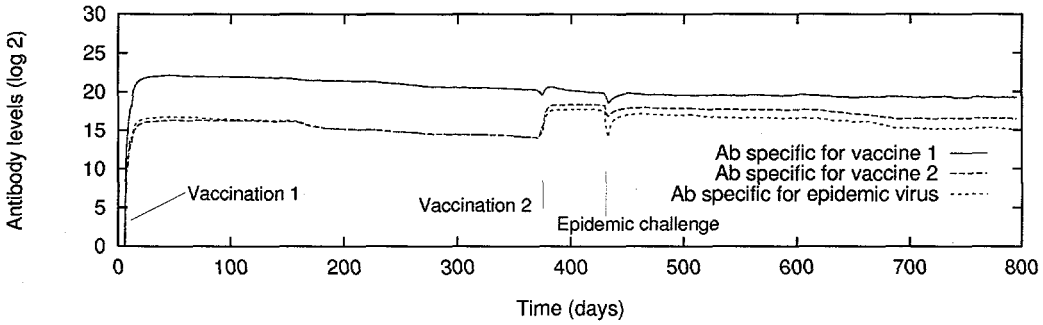

Figure 4: An example of negative interference of vaccine1 on vaccine2, and positive interference by vaccine1 on the epidemic virus. The experiment shown is from the group in which the vaccine2-epidemic strain antigenic distance was 2, the vaccine1-epidemic strain antigenic distance was 2, and the vaccine1-vaccine2 antigenic distance was 2. The immune response to vaccine1 produced antibodies that were moderately cross-reactive to both vaccine2 and the epidemic virus. Vaccine2 was mostly eliminated by preexisting cross-reactive antibodies (data not shown), however there was also a 16-fold increase in antibody levels specific to the vaccine2 and epidemic strains. The antibody levels specific to the epidemic virus were above the protective level and the epidemic virus was cleared by pre-existing antibodies without causing disease, and without stimulating a *de novo* immune response that increased antibody levels.

failed to elicit a significant rise in antibody levels, and this, coupled with the antibodies having fallen below protective levels, resulted in a high experimental attack rate. Failure of such homologous strain vaccination to boost after 2 weeks [16] and after 6 months [18] has also been seen in human trials. However, in the latter study titers had not fallen below protective levels. We have previously performed simulations, similar to those reported here, but in which antibody levels returned close to zero levels before revaccination [19]. In those experiments a homologous second vaccination provided good protection; here it does not. Thus, our results depend on the persistence of antibodies and whether that persistence remains above protective levels. In humans, antibody persistence appears to be different for different influenza antigens; for example, it has been found that antibody persistence was lower for the H1N1 component compared with the H3N2 and B components of a trivalent vaccine [18].

Wet biology is, of course, never as simple as *in machina* biology—our model system abstracts away many details of the immune system and influenza virology and pathology, and factors known to have an effect on influenza vaccination and pathogenesis are ignored by the model, including age, virus virulence, vaccine immunogenicity, and immunocompetance. However, even given the simple nature of the model, our experimental results appear to reflect some of the complex phenomena observed in field trials of influenza vaccine, and offer an explanation of apparently contradictory results in trials of annual vaccination against influenza.

Our major result is that the antigenic distance between a prior vaccine and a subsequent vaccine, and the antigenic distance between the prior vaccine and a subsequent epidemic virus, can significantly influence the protection offered by annual vaccination. Wet experiments are required to test the significance of our results. Our results suggest that field trials of influenza vaccines should record the vaccination history and prior infection history of study volunteers. Our results also suggest that if a choice is available among otherwise equivalent vaccine strain candidates, that a strain as far as possible from the previous vaccine strain would be most effective in previously vaccinated individuals.

Acknowledgments

The authors gratefully acknowledge the ongoing support of the Santa Fe Institute and its Joseph P. and Jeanne M. Sullivan Foundation program in theoretical immunology. This work was also supported by ONR (N00014-95-1-0364), NSF (IRI-9157644), and the Los Alamos National Laboratory LDRD program. Portions of this work were performed under the auspices of the U.S. Department of Energy. We also acknowledge discussions with Nancy Arden, Nancy Cox, Henrietta Hall, Jacqueline Katz, and Alexander Klimov. DJS also acknowledges a graduate internship at the Santa Fe Institute, and the University of New Mexico Computer Science Department AI and Digital Equipment Fellowships, and the help of Ron Hightower, Stan Lee, Mihaela Oprea, Francesca Shrady, Paul Stanford, and Bernhard Sulzer.

References

[1] CDC. Prevention and control of influenza: recommendations of the advisory committee on immunization practices (ACIP). *Morbidity and Mortality Weekly Report*, 45, 1996.

[2] F. M. Davenport. Control of influenza. *Med. J. Aust.*, (Supplement):33–38, 1973.

[3] T. W. Hoskins, J. R. Davis, A. Allchin, C. L. Miller, and T. M. Pollock. Controlled trial of inactivated influenza vaccine containing the A/HongKong strain during an outbreak of influenza due to the A/England/42/72 strain. *Lancet*, ii:116–120, 1973.

[4] B. J. Feery, M. G. Evered, and E. I. Morrison. Different protection rates in various groups of volunteers given subunit influenza virus vaccine in 1976. *J. Inf. Dis.*, 139:237–241, 1979.

[5] T. W. Hoskins, J. R. Davis, A. J. Smith, C. L. Miller, and A. Allchin. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. *Lancet*, i:33–35, 1979.

[6] G. Meiklejohn. Viral respiratory disease at lowry air force base in denver, 1952-1982. *J. Infect. Dis.*, 148:775–784, 1983.

[7] G. Meiklejohn, R. A. Zajac, and M. E. Evans. Influenza at lowry air force base in denver, 1982-1986. *J. Infect. Dis.*, 156:649–651, 1987.

[8] W. A. Keitel, T. R. Cate, and R. B. Couch. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *Am. J. Epidemiol.*, 127:353–364, 1988.

[9] W. A. Keitel, T. R. Cate, R. B. Couch, L. L. Huggins, and K. R. Hess. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine*, 15:1114–1122, 1997.

[10] A. H. Ahmed, K. G. Nicholson, and J. S. Nguyen-Van Tam. Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. *Lancet*, 346:591–595, 1995.

[11] D. J. Smith, S. Forrest, R. R. Hightower, and A. S. Perelson. Deriving shape space parameters from immunological data. *J. Theor. Biol.*, 189:141–150, 1997.

[12] A. S. Perelson and G. F. Oster. Theoretical studies of clonal selection: Minimal antibody repertoire size and reliability of self-non-self discrimination. *J. Theor. Biol.*, 81:645–670, 1979.

[13] P. E. Seiden and F. Celada. A model for simulating cognate recognition and response in the immune system. *J. Theor. Biol.*, 158:329–357, 1992.

[14] D. J. Smith. *The Cross-Reactive Immune Response: Analysis, Modeling, and Application to Vaccine Design*. PhD Thesis, University of New Mexico, NM, 1997.

[15] C. H. L. Howells, A. D. Evans, and C. Vessilinova-Jenkins. *Lancet*, i:1436, 1973.

[16] D. Hobson, F. A. Baker, and R. L. Curry. Effect of influenza vaccines in stimulating antibody in volunteers with prior immunity. *Lancet*, ii:155–156, 1973.

[17] H. L. Robinson, C. A. Boyle, D. M. Feltquate, M. J. Morin, J. C. Santoro, and R. G. Webster. DNA immunization for influenza virus studies using hemagglutinin- and nucleoprotein-expressing DNAs. *J. Infect. Dis.*, 176 (Supplement 1):50–55, 1997.

[18] R. D. Powers, F. G. Hayden, J. Samuelson, and J. M. Gwaltney Jr. Immune response of adults to sequential influenza vaccination. *J. Med. Virol.*, 14:169–175, 1984.

[19] D. J. Smith, S. Forrest, D. H. Ackley, and A. S. Perelson. Modeling the effects of prior infection on vaccine efficacy. In *IEEE Intnl. Conf. on Systems, Man, and Cybernetics*, pages 363–368, Orlando, Florida, 1997. IEEE.