Modeling the Effects of Prior Infection on Vaccine Efficacy*†

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Abstract

We performed computer simulations to study the effects of prior infection on vaccine efficacy. We injected three antigens sequentially. The first antigen, designated the *prior*, represented a prior infection or vaccination. The second antigen, the *vaccine*, represented a single component of the trivalent influenza vaccine. The third antigen, the *epidemic*, represented challenge by an epidemic strain. For a fixed vaccine to epidemic strain cross-reactivity, we generated prior strains over a full range of cross-reactivities to the vaccine and to the epidemic strains. We found that, for many cross-reactivities, vaccination, when it had been preceded by a prior infection, provided more protection than vaccination alone. However, at some cross-reactivities, the prior infection reduced protection by clearing the vaccine before it had the chance to produce protective memory. The cross-reactivities between the prior, vaccine and epidemic strains played a major role in determining vaccine efficacy. This work has applications to understanding vaccination against viruses such as influenza that are continually mutating.

Introduction

Continual and rapid antigenic change is a property of many viruses, including influenza virus, human immunodeficiency virus, and hepatitis C virus. As a result of their high mutation rate, thousands of strains of these viruses coexist in a *species swarm* (or *quasispecies*) [1]. Vaccination against species swarms is difficult because of the need to provide broad immunity to the many strains, and because new strains are constantly emerging. In the case of influenza, for example, a worldwide network of surveillance centers identifies hundreds of influenza strains each year. Current public heath practice uses a trivalent vaccine against the three major influenza species swarms currently circulating. Year to year it is typically necessary to change at least one component of the vaccine to keep up with the evolution of the species swarm. Influenza vaccine efficacy and virus virulence varies; in a bad flu season it is not unheard of for 20% of the residents of an elderly persons nursing home to die from the effects of influenza, despite yearly vaccination. In part this is due to the effects of the species swarm and, as we investigate below, possibly due to the effects of prior infection (or vaccination) interfering with the current vaccination.

The effect of prior infection (or vaccination) on vaccine efficacy has not been throughly investigated. [2] and [3] established that the immune response to influenza was dominated by recall of immunological memory to prior influenza infections. Most of the experiments that followed this work were performed with two antigens [4, 5]. However, to study the effect of prior infection on vaccine efficacy, at least three responses need to be studied—the prior infection, the vaccination, and the epidemic challenge [6]. In the case of three antigens, and considering say only eight degrees of cross-reactivity between any two antigens, there are hundreds of combinations of the cross-reactivities between the three antigens. The hundreds of combinations, and the necessity to have sufficient replicates of each experiment, necessitates thousands of exper-

*To appear in: *Proc. IEEE Intnl. Conf. on Systems, Man, and Cybernetics,* Orlando, Florida.

†This paper contains excerpts from a more detailed version to be published in the biology literature.

iments for a comprehensive survey.

Because of the difficulty of conducting this many experiments *in vivo*, we have built a computer model to perform the experiments *in machina*. An advantage of *in machina* experiments is that a large number can be performed and analyzed relatively cheaply and quickly. A disadvantage is that the computer model might not faithfully represent important aspects of the immune system and thus give misleading results. The model has been validated by replicating existing experiments and has shown good, *qualitative*, agreement. Parameters of the model have also been chosen to match immunological data important for modeling the cross-reactive immune response [7]. All the experiments reported here were done *in machina*. The predictions from the experiments are testable with a much smaller number of *in vivo* experiments.

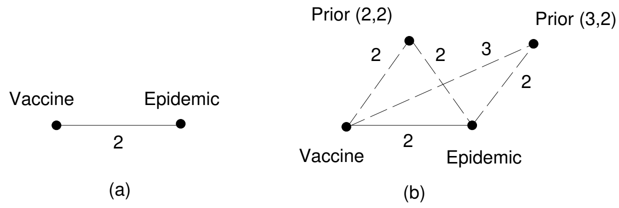

Figure 1: (a) The antigenic distance between the vaccine and epidemic strains was fixed for all the experiment at two units. (b) 31 different prior strains were generated at different antigenic distances to the vaccine and epidemic strains (two shown).

Materials and Methods

The computer simulation is a simplified model of the vertebrate humoral immune system. It consists of B cells, plasma cells, antibodies, memory B cells, and antigens. T cell help is modeled implicitly by assuming that it is available whenever necessary. Each B cell, plasma cell and memory B cell is modeled as a separate entity within the simulation. In this way the model is *agent based* and similar to that of [8]. Because of the large number of antibodies in a real immune system, each antibody in the model corresponds to a large number of real antibodies, similarly each antigen in the model corresponds to a large number of real antigens. B cell, antibody, and antigen receptors are modeled as strings of symbols that can loosely be thought of as the amino acids of a binding site. When antigens are introduced into the simulation, B cells have a chance to bind the antigens depending on their affinity. B cells with antigen bound are stimulated to divide, and on division have some chance of mutation in their antibody receptor, and some chance to differentiate into a memory or plasma cell. Plasma cells secrete antibodies, which have a chance to bind antigens. If antigens have above a threshold number of antibodies bound they are removed from the simulation.

B cell, antibody and antigen receptors are made up of 20 symbols, where each symbol corresponds to one of four equivalence classes of amino acids. In the model, receptor sequence and shape are equivalent, and affinity is a function of the number of symbols that are complementary between receptors. We choose an affinity cut-off for clonal selection when receptors have less than 15 complementary symbols. This parameter selection was chosen to correspond to immunological data [7] and gives the following properties: a potential repertoire of 10^{12} B cells, a 1 in 10^5 chance of a B cell responding to a particular antigen [9, 10, 11], and with an expressed repertoire of 10^7 B cells [12, 13, 14] two antigens cease being cross-reactive when they have more than about 35% sequence difference [15, 16]. Instead of referring to the percentage sequence difference between antigens, we refer to the *antigenic distance* between antigens which we define as the number of symbols in which the antigen's receptors differ. Thus, for receptors of length 20, there are 21 possible antigenic distances between antigens and any two antigens that are separated by an antigenic distance greater than or equal to seven (35% sequence difference) are not cross-reactive. Thus, effectively, there are eight degrees of cross-reactivity in our model corresponding to antigenic distances zero through seven.

To study the effect of a prior infection on vaccine efficacy we held the cross-reactivity between the vaccine and epidemic strains constant and varied the cross-reactivities of the prior to the vaccine and epidemic strains (Figure 1). The epidemic dose and replication rate were chosen (500 units of epidemic strain, replicating every six hours) so that, with high probability, an unvaccinated simulated organism would become diseased when challenged. The vaccine dose and strain were chosen (1,000 units of inactivated vaccine, antigenic distance two from the epidemic strain) to have about 50% efficacy against the epidemic challenge. Antigens at all combinations of antigenic distances to the vaccine and epidemic were generated for use as *prior* strains. In total 31 different prior strains were generated.

Ten control groups and 31 experimental groups were injected with combinations of prior, vaccine and epidemic strains according to Table 1. The timing of the injections of the prior, vaccine and epidemic strains was such that antibody titers were close to pre-injection levels before the next injection. For the controls (groups 1-10) 120 replications were performed, and for the experiments (groups 11-41) 250 replications were performed in each group. A "disease threshold" was set at 2,500 units and if the viral load exceeded it the simulation was stopped. During

Group	Purpose	Prior infection (replicating) (dose on day 5)	Vaccine (non replicating) (dose on day 75)	Epidemic infection (replicating) (dose on day 145)
1	control			500
2	control		1,000	500
3-10	control	200*		500
11-41	experiment	200†	1,000	500

Table 1: The timing and dosage of the prior infection, vaccination, and epidemic infection is shown for the 41 groups. *Groups 3-10 received a prior infection at antigenic distances zero through seven respectively from the epidemic strain. †Groups 11-41 received a prior infection with different combinations of antigenic distances between zero and seven from the vaccine and epidemic strains. The correspondence between group and antigenic distances is shown in Figure 2.

each experiment the viral load, and antibody titers and affinities for each antigen, were measured every six hours. In addition, prior to each injection, and at the peak of each response, the number, affinity for each antigen, and clonal history of each B cell involved in the response were recorded.

Results and Discussion

The model exhibited classical behavior of cross-reactive memory in the response to the vaccine after the prior infection, and in response to the epidemic challenge after the prior infection and vaccination: the strength of each cross-reactive response increased as the antigenic distance between antigens decreased (Figure 2c, [16]), the number of cross-reactive memory cells increased as the antigenic distance between the antigens decreased (Table 2 and [17]), and the number of new memory cells produced in response to a cross-reactive antigen was reduced by the cross-reactive memory to previous antigens (Table 2 and [4]). This last phenomenon is sometimes called *original antigenic sin* [4].

Protection against epidemic challenge decreased as the antigenic distance between the prior and epidemic strains increased, for a constant antigenic distance between the prior and vaccine strains (columns of Figure 2d). This was because memory of the prior infection was more cross-reactive with the epidemic strain when the prior and epidemic strains were closer, while the effect of original antigenic sin between the prior and vaccine strains was constant.

Protection against epidemic challenge was lowest when the antigenic distance between the prior and vaccine strains was lowest, for a constant antigenic distance between the prior and epidemic strains (rows of Figure 2d). This was because the closer the prior strain was to the vaccine, the greater the effect of original antigenic sin in reducing the number of memory cells produced by the vaccination, and thus reducing the protection provided by the vaccination (Figure 3 and Table 2). This suggests that given a choice of strains to use as a vaccine, the one that is farthest from the prior strain will be least affected by original antigenic sin, and would thus be a good choice (assuming it is also a good choice because it is expected to be close to the epidemic strain).

Prior infection sometimes decreased vaccine efficacy below the situation when there was vaccination without prior infection (groups 24, 29, and 34, on the upper diagonal of Figure 2d). This occurred because the prior infection was far enough from the epidemic strain to provide little protection, but close enough to the vaccine strain to cause original antigenic sin and reduce the effectiveness of the vaccination (Figure 3 and Table 2). These situations occurred when the differences between the vaccine and epidemic strains were at different locations in the receptor than the differences between the prior and vaccine strains—so called *accumulative* mutations [18], and when the prior and epidemic strains were only moderately cross-reactive. Although only five of the 31 experimental groups have only accumulative mutations between the prior, vaccine and epidemic strains, these groups are more likely to occur in practice because, early in the evolutionary history of a subspecies, there are more residues that have not been mutated than ones that have, and thus more chance that a mutation at a random residue will be accumulative rather than sequential. For example, the major epidemic strains of H3N2 influenza, from its emergence in 1968 until 1980, had only accumulative mutations from the A/Hong Kong/8/68 reference strain [18], although this might also be due to other factors.

Vaccination always increased protection against the epidemic challenge, because even if the vaccine was close to the prior strain, and was reduced in effectiveness by

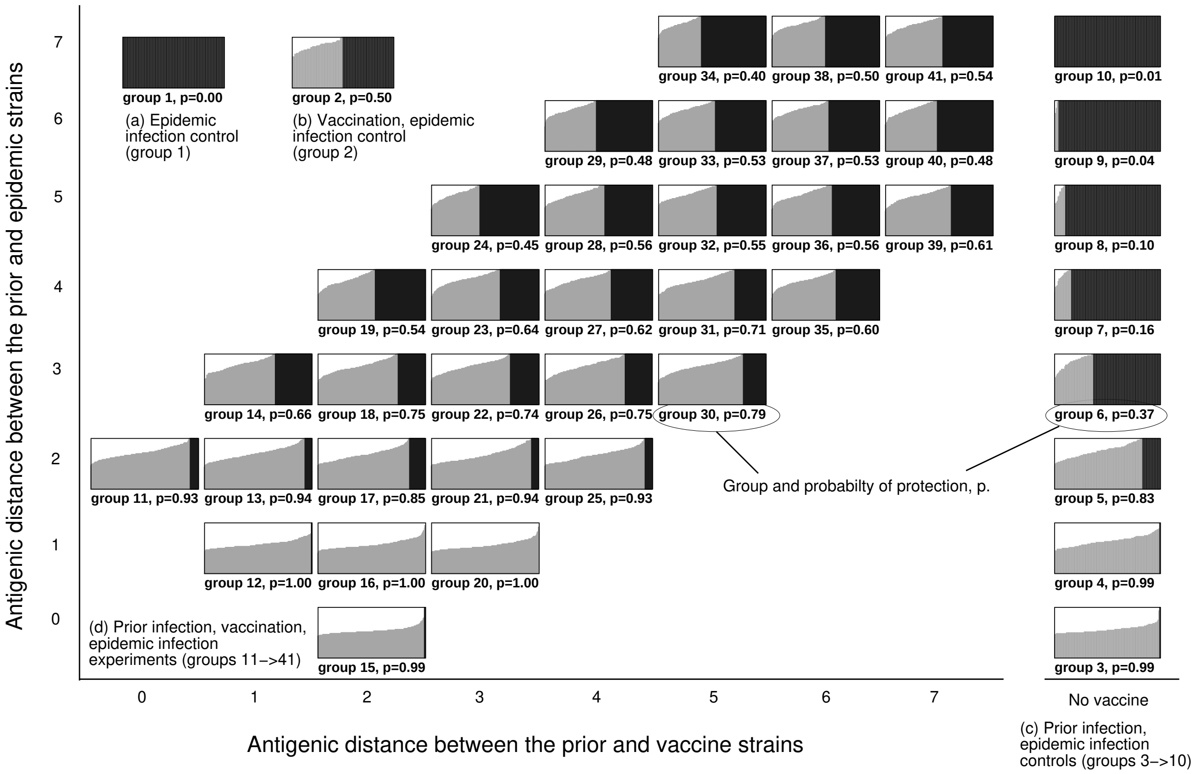

Figure 2: A summary of the maximum viral load of the epidemic strain in each experiment. Each subplot is comprised of 250 vertical lines (120 for the control groups), the height of each vertical line indicates the maximum viral load during an experiment. The 250 experiments in each group (120 in the control groups) are plotted in order of increasing maximum viral load. Viral loads above the disease threshold are plotted in black, thus, the width of the black region indicates the frequency of disease in each group. (a) Exposure to the epidemic challenge, without prior infection or vaccination, caused disease in all cases. (b) Vaccine efficacy was, by design, 50% against the epidemic infection when there was no prior infection. (c) The frequency of disease due to a epidemic challenge after there had been a prior infection was proportional to the antigenic distance between the prior and epidemic strains. (d) The vaccine efficacy against the epidemic challenge, after there had been a prior infection, varied from 40 to 100% depending on the antigenic distances between the prior strain and the vaccine and epidemic strains. The timing of the injections of the prior, vaccine and epidemic strains was such that antibody titers had returned to pre-injection levels before the next injection.

original antigenic sin, it still generated some new memory cells that potentially cross-reacted with the epidemic strain. The vaccination also increased protection by boosting the memory cells, produced by the prior infection, that cross-reacted with the vaccine and epidemic strains.

Among the memory cells that cross-reacted with the epidemic strain, there were a greater proportion originally generated by the prior infection than by the vaccination, when there was at least moderate cross-reactivity between the prior and epidemic strains (data not shown). This was because of original antigenic sin reducing the number of new memory cells produced by the vaccine, and because the vaccination boosted the memory cells, produced by the prior infection, that cross-reacted with the vaccine and epidemic strains. This is in partial agreement with the report by [19] that responses to influenza were dominated recall of prior infections. In our model however, once the prior and epidemic strains had little or no cross-reactivity, antibodies specific to the vaccine dominated the response to the epidemic infection.

We have shown the effects of cross-reactive memory and original antigenic sin in the context of three antigens, and investigated how they can lead to vaccine failure. Vaccine efficacy in the absence of prior infection was designed to be 50%. In the presence of prior infection, vaccine efficacy ranged from 40 to 100% depending on the antigenic distances between the prior strain and the vaccine and epidemic strains (for a fixed vaccine to epidemic strain antigenic distance). Even though the prior infection sometimes decreased the effectiveness of the vaccination, protection against an epidemic challenge was always increased by the vaccination. Extrapolating these results to the case

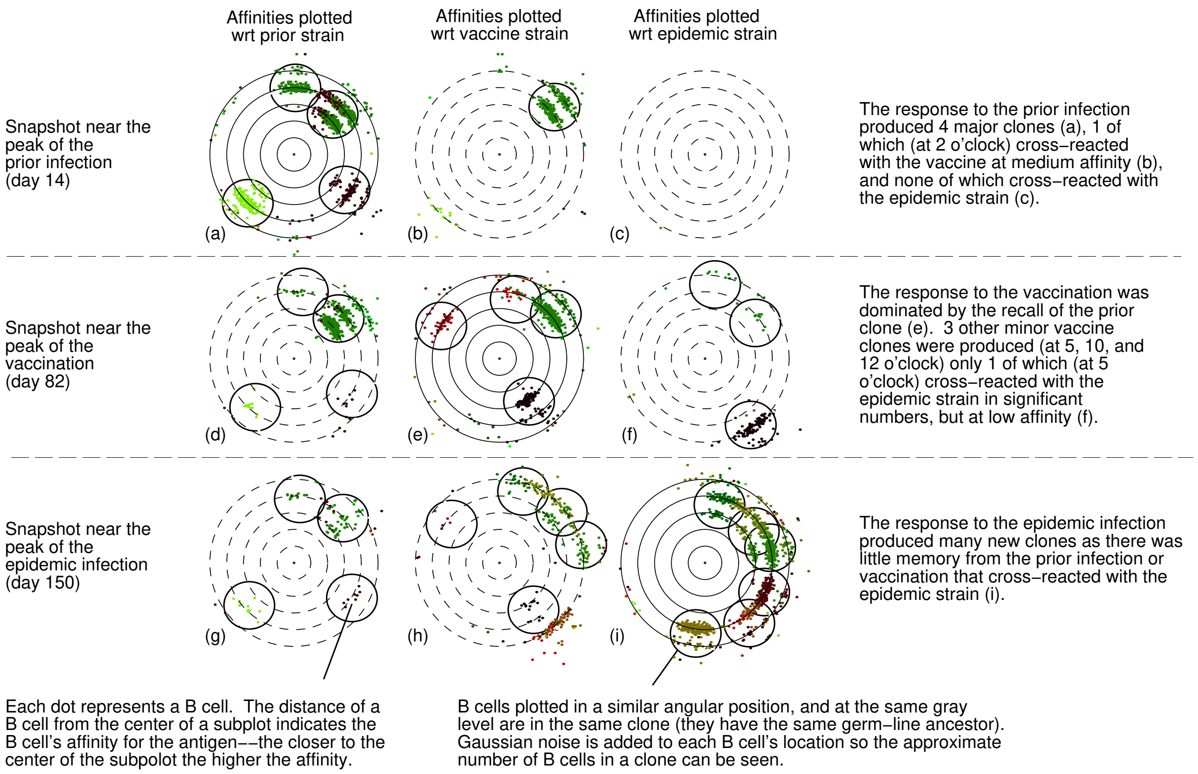

Figure 3: An example of original antigenic sin causing vaccine failure. Experiment 81 of group 24 is shown, in which the prior strain was distance five from the epidemic strain and distance three from the vaccine strain. The major prior clone, that cross-reacted with the vaccine, dominated the vaccine response and prohibited the generation of new clones by the vaccine that might have been cross-reactive with the epidemic strain. Because there were few memory clones from the prior infection or vaccination that cross-reacted with the epidemic strain, the response to the epidemic infection was like a primary response and the maximum viral load exceeded the disease threshold.

Prior to vaccine distance	% prior x-reacts w/ vaccine	% vaccine generated (vs control)	Probability of protection
3	12%	66%	45%
4	5%	79%	56%
5	1%	94%	55%
6	0%	96%	56%
7	0%	100%	61%

Table 2: A cellular analysis of the row of Figure 2d in which the antigenic distance of the prior to epidemic strains was five, and the antigenic distance between the prior and vaccine strains varied between three and seven. When the prior was closest to the vaccine, a larger percentage of memory B cells, that were generated by the prior infection, cross-reacted with the vaccine. This led to a lower percentage of new memory cells generated by the vaccination compared to a control that had no prior infection. This lower number of new memory cells reduced the protection against the epidemic challenge.

where the prior infection is a prior vaccination, we can say that in the model, vaccination improves protection against the next challenge, but depending on antigenic distances between the antigens, might reduce the effectiveness of subsequent vaccination. Performing these experiments *in machina* was useful because of the large number of experiments necessary, however the predictions now need to be checked by a smaller number of *in vivo* experiments. Knowledge of the effects of different antigenic distances between the antigens might lead to more effective influenza vaccines by allowing prior infection or prior vaccination to be taken into account in the vaccine strain selection process.

Acknowledgments

The authors gratefully acknowledge the ongoing support of the Santa Fe Institute and its Joseph P. and Jeanne M. Sullivan program in theoretical immunology. DJS also acknowledges the University of New Mexico Computer Science Department AI fellowship and Digital Equipment Fellowship, and the help of

Patrik D'haeseleer, Ron Hightower, Terry Jones, Andrew Kosoresow, Stan Lee, Wendell Miller, Ronald Moore, Mihaela Oprea, Francesca Shrady, Paul Stanford, Jason Stewart, Bernhard Sulzer, and Carla Wofsy. Portions of this work were performed under the auspices of the U.S. Department of Energy. This work was also supported by ONR (N00014-95-1-0364), NSF (IRI-9157644), and the Los Alamos National Laboratory LDRD program. This paper was written while Forrest was visiting the MIT Artificial Intelligence Laboratory.

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