Supplemental Information

1 Model Assumptions

Assumptions for the one-epitope model.

Model variables are the two states of an antigen (free antigen and antigen bound to antibody), B cells specific for the antigen and antibodies secreted by the B cells with the following assumptions:

1. Antigen: Free antigen can bind to antibody in accord with mass action and the rate constant k. As antibody-antigen affinities are high we neglect dissociation rate. Antigen decays at rate d_A, and we assume that this is not substantially affected by binding to antibody. In reality there are two opposing forces, antigen binding to antibody enhances uptake by Fc receptor mediated phagocytosis on macrophages (increasing d_A) and it also sequesters antigen on follicular dendritic cells (lowering d_A).
2. B cells: B cells are stimulated by free antigen and proliferate as described by the term $\frac{sBH_f}{\phi+H_f}$. Antibody binding to antigen prevents it from binding to and stimulating the B cell. We encapsulate all B cell subpopulations into B. Since the concentration of secreted antibody is much greater than membrane bound antibody on B cells we neglect the term for removal of antigen by binding to B cells.
3. Antibody: B cells secrete antibody at rate a and it decays at rate d_A. Antibody binds to free antigen at rate kAH_f mentioned in (2) above.
4. Other: We assume that CD4 T cell help is not rate limiting, and we do not consider affinity maturation.

Additional assumptions for the multi-epitope influenza model

1. We consider only vaccination with the HA antigen of influenza. We do not initially consider responses to replicating virus as it introduces an additional feedback into the system because of the interaction between replication and clearance by immunity. However, we expect that this can be indirectly explored in our model by changing the dose of the antigen.
2. We consider head and stem with two potentially variable epitopes on the head and one conserved epitope on the stem.
3. We assume sterical interference in antibody responses to the head epitopes but not interference between stem-specific and head-specific antibody responses as stem and head are widely spatially separated.

2 Model parameter ranges and outcomes

Model parameter	Symbol	Value	Range
Rate constant for antibody binding	k ($\mathrm{AU}^{-1}\mathrm{day}^{-1}$)	0.01	$0.01 - 1$
Decay rate of antigen	d_H (day^{-1})	0.5	$0.25 - 1$
Max. prolif rate of B cells	s (day^{-1})	1	$1 - 2$
Antigen for 1/2 max. prolif of B cells	ϕ (AU)	10	$1 - 50$
Antibody production rate	a (day^{-1})	0.1	$0.09 - 0.11$
Decay rate of antibody	d_A (day^{-1})	0.1	$0.09 - 0.11$

Model parameters such as decay rate of antibody (d_A) has been relatively accurately estimated *in vivo* [**?**] and we don't expect much variation. The maximum effective proliferation rate of B cells (s) was set in the range $s = 1 - 2$ which corresponds to division times between 1 and 0.5 days. The mean value of a was obtained by rescaling the concentration of antibodies so as to have $A \approx B$ at equilibrium, and we would expect little variation between individuals. Biological ranges for the antigen for half-maximum proliferation (ϕ) and decay rate of antigen (d_H) were estimated to allow the duration of antigenic stimulation for B cells to encompass range of 3 to 14 days. Our model is robust to the value of the rate constant for antibody binding provided $k > 0.01$ which is needed for rapid binding of antibodies to the antigen compared with the duration of the response. We note that we have rescaled the concentrations of antigen, B cells and antibodies as described in the main text and for their concentration we use the scaled or arbitrary unit (AU). 1 AU is defined as initial concentration or density of antigen-specific B cells (and antibodies due to rescaling $a = d_a$) at "naive" state. The concentration of antibodies and antigens is scaled so that $B \approx A$ at equilibrium. The unit of time is a day.

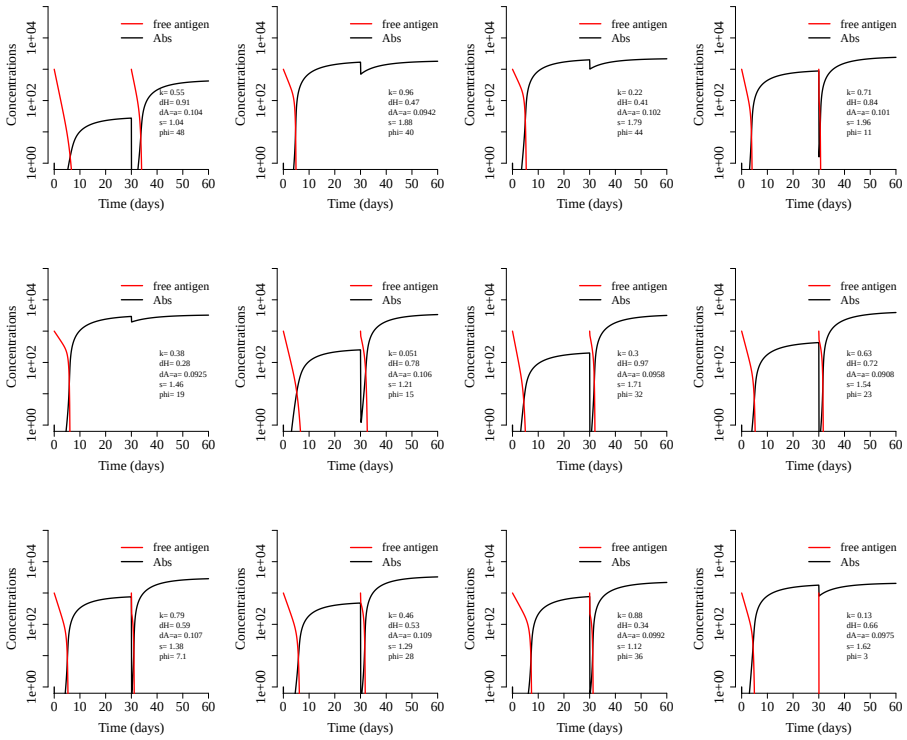
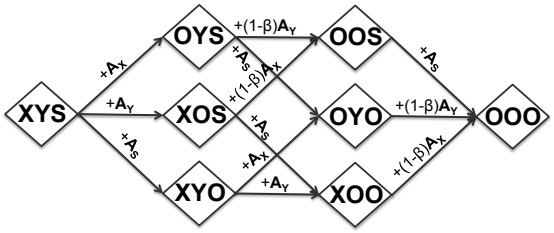


Figure 1: We illustrate how the main qualitative result showing that epitope masking reduces the magnitude of antibody boosting during secondary responses is robust to changes in parameters in the one-epitope model. We used Latin hypercube sampling (LHS) [**?**], with the ranges of each model parameter shown in the table. The antigen is shown in red and the antibody response in black.

3 Three-epitope model for influenza



$$
\begin{aligned}
\frac{dH_{XYS}}{dt} &= -kH_{XYS}(A_X + A_Y + A_S) - d_H H_{XYS} \\
\frac{dH_{OYS}}{dt} &= k(H_{XYS}A_X - H_{OYS}((1-\beta)A_Y + A_S)) - d_H H_{OYS} \\
\frac{dH_{XOS}}{dt} &= k(H_{XYS}A_Y - H_{XOS}((1-\beta)A_X + A_S)) - d_H H_{XOS} \\
\frac{dH_{XYO}}{dt} &= k(H_{XYS}A_S - H_{XYO}(A_X + A_Y)) - d_h H_{XYO} \\
\frac{dH_{OOS}}{dt} &= k((1-\beta)(H_{OYS}A_Y + H_{XOS}A_X) - H_{OOS}A_S) - d_H H_{OOS} \\
\frac{dH_{OYO}}{dt} &= k(H_{OYS}A_S + H_{XYO}A_X - (1-\beta)H_{OYO}A_Y) - d_H H_{OYO} \\
\frac{dH_{XOO}}{dt} &= k(H_{XOS}A_S + H_{XYO}A_Y - (1-\beta)H_{XOO}A_X) - d_H H_{XOO} \\
\frac{dH_{OOO}}{dt} &= k(H_{OOS}A_S + (1-\beta)(H_{OYO}A_Y + H_{XOO}A_X)) - d_H H_{OOO} \\
\frac{dB_X}{dt} &= \frac{sB_X(H_{XYS} + H_{XYO} + (1-\beta)(H_{XOS} + H_{XOO}))}{\phi + (H_{XYS} + H_{XYO} + (1-\beta)(H_{XOS} + H_{XOO}))} \\
\frac{dB_Y}{dt} &= \frac{sB_Y(H_{XYS} + H_{XYO} + (1-\beta)(H_{OYS} + H_{OYO}))}{\phi + (H_{XYS} + H_{XYO} + (1-\beta)(H_{OYS} + H_{OYO}))} \\
\frac{dB_S}{dt} &= \frac{sB_S(H_{XYS} + H_{OYS} + H_{XOS} + H_{OOS})}{\phi + (H_{XYS} + H_{OYS} + H_{XOS} + H_{OOS})} \\
\frac{dA_X}{dt} &= aB_X - k(H_{XYS} + H_{XYO} + (1-\beta)(H_{XOS} + H_{XOO}))A_X - d_A A_X \\
\frac{dA_Y}{dt} &= aB_Y - k(H_{XYS} + H_{XYO} + (1-\beta)(H_{OYS} + H_{OYO}))A_Y - d_A A_Y \\
\frac{dA_S}{dt} &= aB_S - k(H_{XYS} + H_{OYS} + H_{XOS} + H_{OOS})A_S - d_A A_S
\end{aligned}
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Figure 2: Schematic and equations for the three-epitope model for HA antigen from influenza virus. X, Y are the epitopes on the head of HA and S is an epitope on the stem of HA.

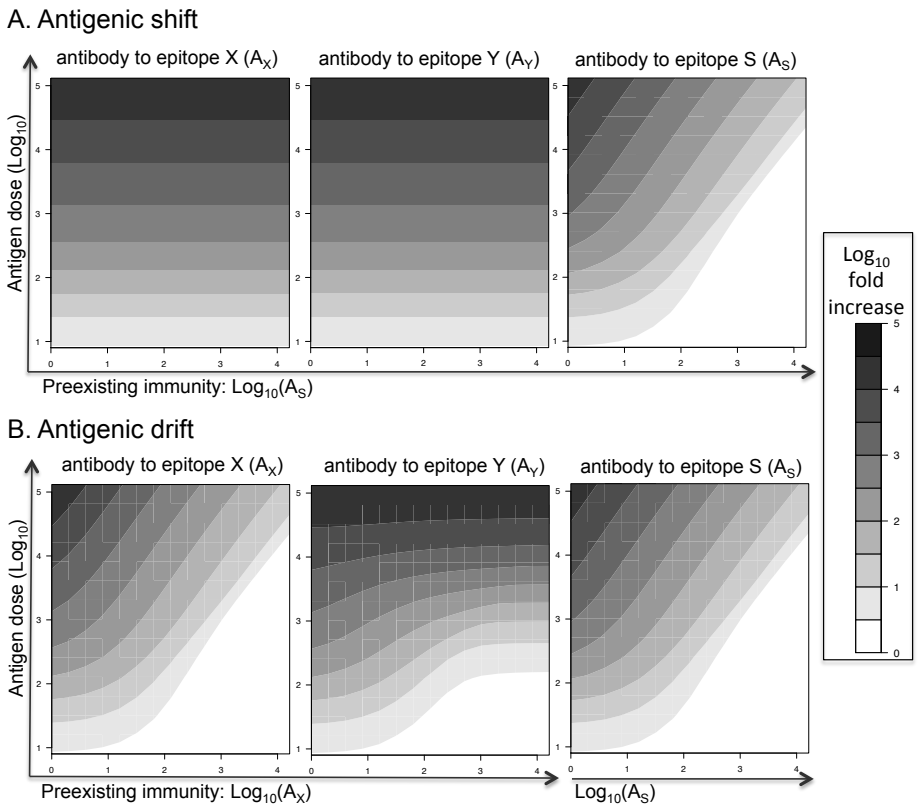

Figure 3: Fold boosting of antibody responses in the three-epitope influenza model. Contour plots showing how the fold boosting of the antibody responses A_X, A_Y to the head epitopes X and Y, respectively, and A_S to the stem epitope S depends on preexisting immunity to indicated epitope (x-axis) as well as antigen dose (y-axis). Top and bottom rows describe responses during immunization with HA from the virus strain resulted from antigenic shift and drift, respectively. Steric interference parameter β was set equal to 0.95. Other parameters as in Figure 1 of the main text.

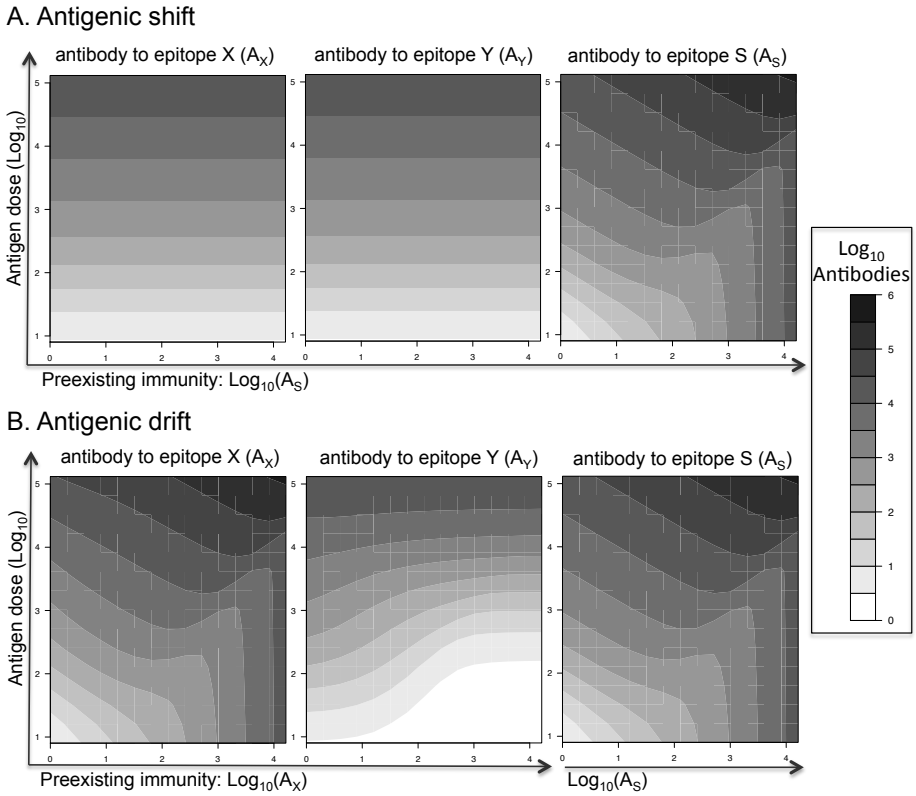

Figure 4: The magnitude of antibody responses to epitopes X, Y and S at the end of the response to vaccination with HA from either shifted (top row) or drifted (bottom row) strain of influenza. This figure complements SI Figure 3 showing the final amount of antibodies for each fold boost of antibody. All parameters are the same as in SI Figure 3.

4 Model predictions

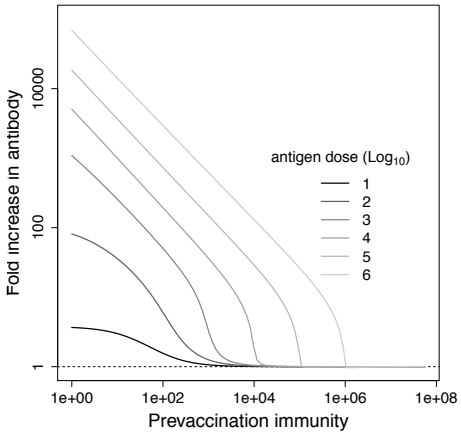

Figure 5: We plot how fold increase in antibody following immunization depends on the level of pre-vaccination immunity (B cells and antibodies). Different lines correspond to different antigen doses shown on the right.

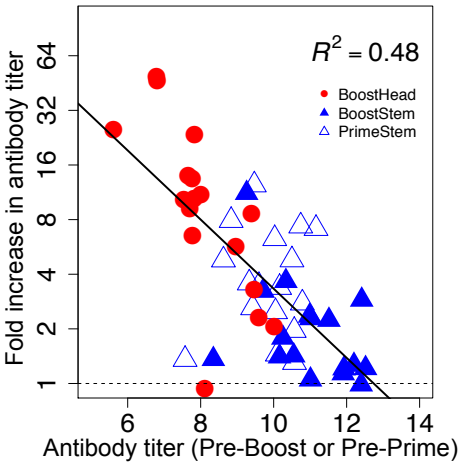

Figure 6: The relationship between the pre-vaccination antibody titer and fold increase in antibody titer for responses to both head (red) and stem (blue) epitopes following H5N1 boost vaccination is shown as in Figure 6C. The corresponding data for stem epitope following prime H5N1 vaccination (open blue triangles) is added.