# Supplementary Text S1: Estimating the life course of influenza A(H3N2) antibody responses from cross-sectional data

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## Likelihood function

For an individual $i$ who was infected with strains in the set $X$, we assumed the true titre against strain $j$ titre was Poisson distributed with mean $\lambda_{ij}$. Let $k$ denote this true log titre, where $0 \leq k \leq 8$. Hence the probability of having true titre $k$ was as follows (we denote $\lambda_{ij} = \lambda$ for brevity):

$$f(k \mid \theta, X) = \begin{cases} \frac{\lambda^k e^{-\lambda}}{k!} & \text{if } k \neq 8; \\ \sum_{k=8}^{\infty} \frac{\lambda^k e^{-\lambda}}{k!} & \text{else.} \end{cases} \quad (1)$$

We accounted for potential observation error by assuming that there was a uniform probability of observing a titre different to the true one. Hence the likelihood of observing titre $c_j$ against test strain $j$ was equal to the sum over all possible true titres:

$$L(c_j) = \sum_k \mathbb{P}(\text{true titre is } k) \times \mathbb{P}(\text{observe } c_j \mid \text{true titre is } k). \quad (2)$$

We also assumed the following uniform observation model:

$$\mathbb{P}(\text{observe } c_j \mid \text{true titre is } k) = \begin{cases} 1-\varepsilon & \text{if } k = c_j; \\ \varepsilon/8 & \text{else.} \end{cases} \tag{3}$$

The likelihood of observing titre $c_j$ could therefore be calculated by combining Equations 1 and 3:

$$\begin{aligned} L(c_j \mid \theta, X) &= \sum_{k=0}^{8} \mathbb{P}(\text{true titre is } k).\mathbb{P}(\text{observe } c_j \mid \text{true titre is } k) && (4) \\ &= \sum_{k \neq c_j} \frac{\varepsilon}{8} \mathbb{P}(\text{true titre is } k) + (1-\varepsilon)\mathbb{P}(\text{true titre is } c_j) && (5) \\ &= \sum_{k \neq c_j} \frac{\varepsilon}{8} f(k; \theta, X) + (1-\varepsilon) f(c_j; \theta, X) && (6) \\ &= \frac{\varepsilon}{8}[1 - f(c_j; \theta, X)] + (1-\varepsilon) f(c_j; \theta, X) && (7) \\ &= (1 - \frac{9\varepsilon}{8}) f(c_j; \theta, X) + \frac{\varepsilon}{8} && (8) \end{aligned}$$

Without loss of generality we set $\varepsilon = 8\nu/9$ to get:

$$L(c_j \mid \theta, X) = (1-\nu) f(c_j; \theta, X) + \frac{\nu}{9}\,. \tag{9}$$

## Parameter estimation

We fit our model to serological data using Markov chain Monte Carlo [1]. Using the likelihood function in Equation 9, we jointly estimated $\theta$ and $X$ for each individual via a Metropolis-Hastings algorithm using 20 million iterations (including a 5 million burn in period). On alternate iterations, we resampled infection histories for each individual (which were independent across individuals), and model parameters (which were shared across all individuals).

To obtain the parameter estimates in Table 1, we calculated the median of the posterior distribution for each parameter, as well as the 95% credible interval. The illustrative plots in Figures 2 and 3 used the maximum likelihood parameter estimates and infection histories. The measured uncertainty in our parameter estimates is shown in Table 1; the variability in estimated infection histories is shown in Figure 4.

## Model of specific and broadly cross-reactive responses

To examine whether broadly cross-reactive antibodies might contribute to observed titres, as has previously been observed during influenza infection [2, 3, 4], we extended our model to incorporate a fixed amount of broad cross-reaction between distant strains. In our original formulation, cross-reactivity declined with the time between strains. The level of cross-reaction between a test strain $j$ and infecting strain $m$ was therefore given by $d(j,m) = e^{-\sigma|t_m - t_j|}$, where $|t_m - t_j|$ was the number of years between strains $j$ and $m$, and $\sigma$ was a parameter to be fitted. If $\sigma$ was large, it was equivalent to having no cross-reactivity between strains.

We extended the model to incorporate broad cross-reactivity by assuming that distant strains would still have a degree of cross-reactivity, controlled by a parameter $\alpha$: $d(j,m) = \alpha + (1-\alpha)e^{-\sigma|t_m - t_j|}$. As before, $\sigma$ represented the degree of strain-specific cross-reactivity. After infection with any strain, individuals would therefore have a contribute of $\alpha$ to their titre against any other strain. When $\alpha = 0$, we recovered the original model presented in the main text.

# References


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