Antigenic distance has a nonlinear negative impact on the humoral response to seasonal influenza vaccination in elderly individuals even after controlling for preexisting antibody titers

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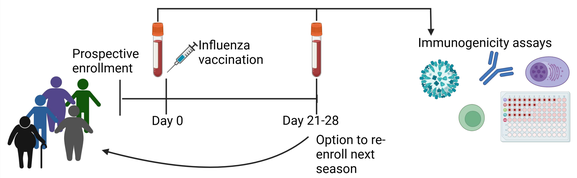
Abstract

The UGAFluVac study is a cohort study which recruits individuals aged 18 and older, provides Fluzone (Sanofi) split-inactivated seasonal influenza vaccination, and collects pre- and post-vaccination serum samples. Individuals aged 65 and older may elect to receive Fluzone High Dose (HD, as opposed to SD, standard dose) vaccination. Serum samples were used for a panel of HAI assays to many historical strains of influenza.

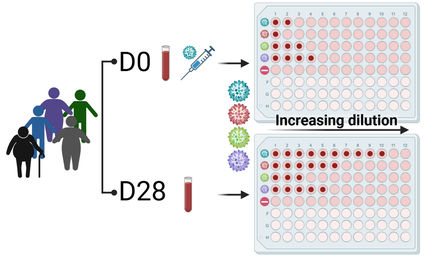
We estimated the antigenic distance between each of the historical strains and the strain included in the vaccine formulation an individual received (all of our analyses were stratified by subtype since the vaccine includes three or four different influenza lineages). Using generalized additive mixed models, we estimated the effect of antigenic distance on post-vaccination titer, while controlling for pre-vaccination titer and vaccine dose to find a nonlinear effect which was not dose-dependent.

Introduction

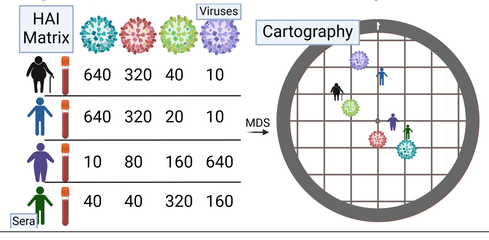
- **UGAFluVac** is a prospective cohort study run by Ted Ross.



- We used data from the 2013/14 influenza season through 2017/18 for individuals who received Fluzone SD or HD (HD was offered to individuals aged 65 or older).
- In these seasons, pre-vaccination and post-vaccination serum samples from each participation were used for a **panel of heterologous hemagglutination inhibition (HAI) assays to historical strains.**



- We calculated the **antigenic distance** from the vaccine strain for each of these historical strains three ways.
- Temporal distance is the difference in isolation years.
- Dominant *p*-epitope distance is the maximum proportion of different amino acids across the 5 HA head epitopes.
- Cartography uses multidimensional scaling of titer data.



Results

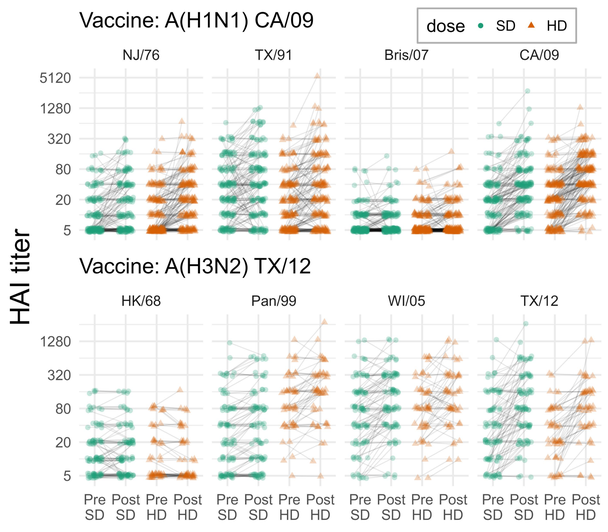


Fig 1. Raw data for HAI assays to selected historical strains, using serum samples from individuals who received a vaccine containing CA/09 or TX/12-like inactivated virus. This is a subset of the data used to shown that sample sizes, average change in titer, and effect of dose varied by historical strain for both H1N1 and H3N2 vaccines.

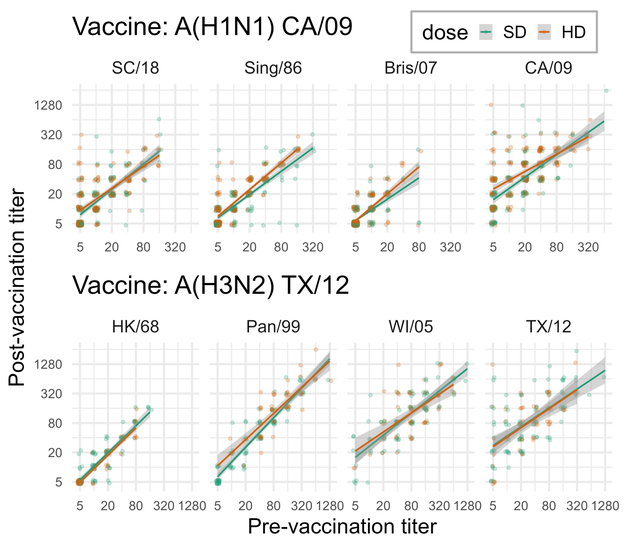


Fig 2. Post-vaccination titer vs. pre-vaccination titer, shown for two vaccine components and selected historical strains for each. Pre-vaccination titer is the most influential factor for predicting an individual's post-vaccination titer. While the relationship is positive and linear across all strains, the strength and variability of the relationship is different across strains.

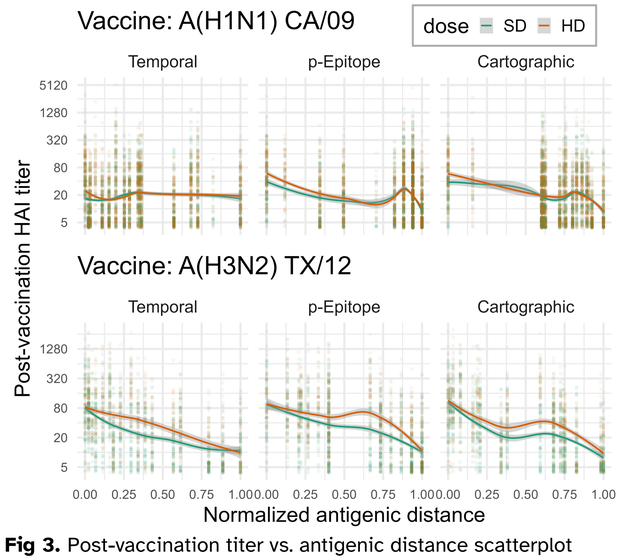


Fig 3. Post-vaccination titer vs. antigenic distance scatterplot for two representative vaccine strains. The curves shown are LOESS local regression smooths. Antigenic distance on the x-axis was normalized by diving by the maximum value within each panel. There are distinct differences in the pattern of responses across distance measures and subtypes.

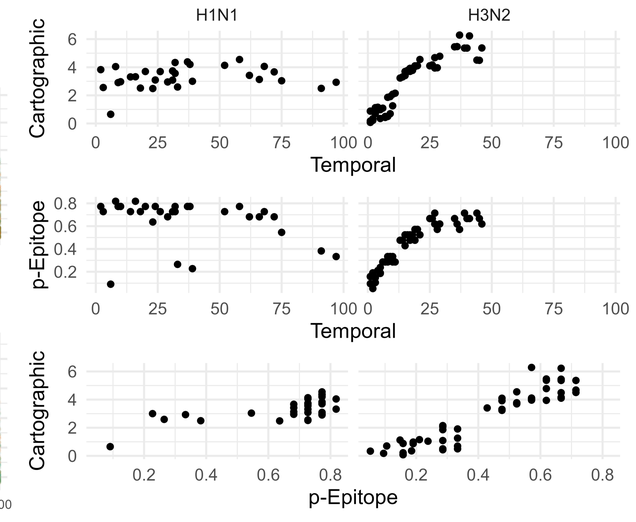


Fig 4. Scatterplots showing correlations between each pairwise combination of antigenic distance metrics. The three metrics are much more correlated for H3N2 strains, although there is a nonlinear relationship between temporal distance and the others. The cartographic and p-epitope distance have a mild relationship for H1N1, but the temporal distance for H1N1 is not correlated with the other two metrics.

Results

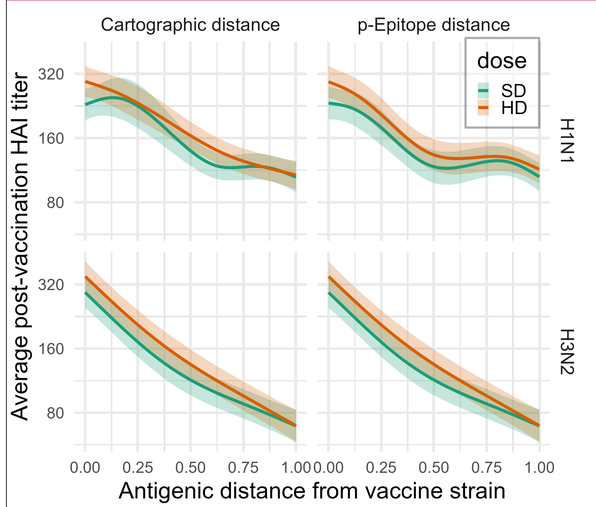


Fig 5. We fit four separate generalized additive mixed models (GAMMs) to a subset of the data including all individuals aged 65 or older (the subcohort eligible to choose to receive HD vaccines). We controlled for dose as a fixed effect and included antigenic distance and pre-vaccination titer using thin plate regression splines, along with random intercepts for individuals. The results are averaged across possible levels of pre-existing titer.

Discussion

Main findings

1. Temporal and p-epitope distances correlate well with cartographic distance for H3N2, not H1N1.
2. After accounting for the effect of pre-vaccination titer, we still saw an effect of antigenic distance.
3. The effect of antigenic distance on post-vaccination titer does not appear to be dose-dependent.

Limitations and Next Steps

- Use a Bayesian approach and adjust for censoring.
- Perform the same analyses on data from other cohorts, or other types of assay panels.
- Address confounding and other effects in the model.

Acknowledgements

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