Sequence-based evaluation of the immune landscape of seasonal influenza A(H3N2) virus

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How does the human T cell epitope landscape of IAV H3N2 change over time? Putative effector T cell epitope conservation with previous strains decreases continuously.

Background

The most effective public health intervention to fight against seasonal influenza infection is through immunization. How well a vaccine works depends on whether it remains effective against circulating strains that evolve during any given influenza season. However, the vaccine effectiveness of each seasonal influenza vaccine is known to vary, and in some cases might be impacted by antigenically mismatched hemagglutinin (HA) surface proteins of circulating viruses. Thus, understanding viral evolution and the impact on host immune selection are crucial. For this study, we aim to use HA sequence data to predict potential T cell epitopes to examine how antigenic drift correlates with the diversity of T cell epitopes presented by the viral population over time.

Objectives

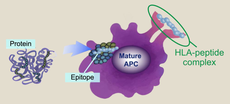
To define the human T cell immune landscape of influenza A(H3N2) virus

- Utilize sequence-based method to characterize diversification of H3 HA
- Relate the evolution of T cell epitope content to hemagglutinin inhibition assay (HI)-defined antigenic clusters

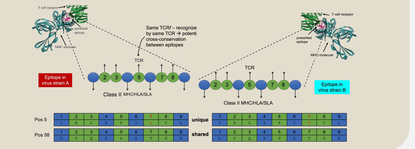
Analysis Workflow

Data acquisition
Seasonal H3N2 IAV HA sequences from 1968-2004 with corresponding HI titer data

T cell epitope prediction



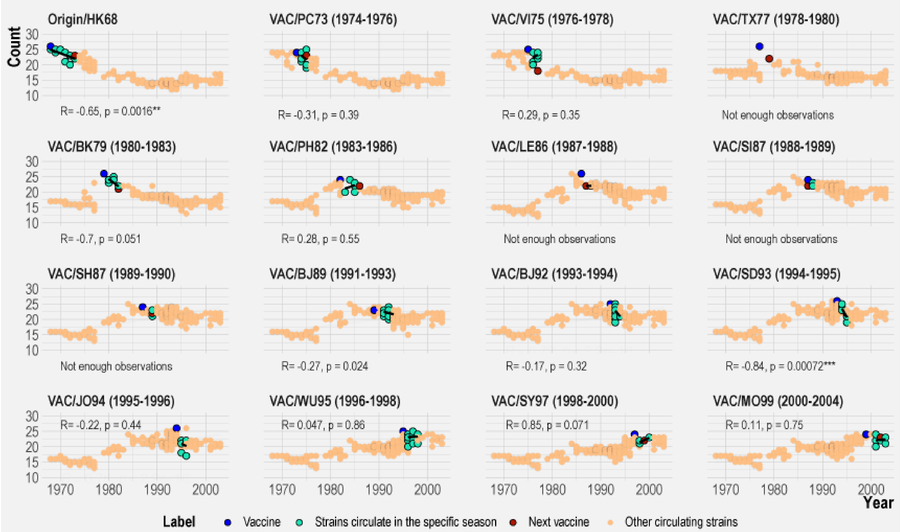
Cross-conservation analysis
Quantification of putative effector CD4+ T cell epitopes ($T_{CD4+eff}$) by pairwise comparison

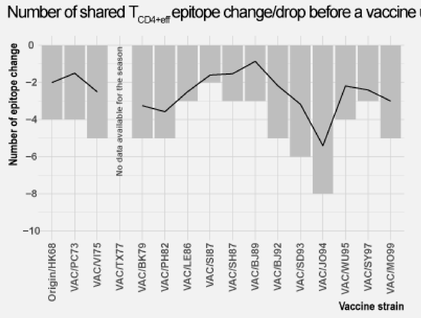


Multidimensional scaling (MDS) and *k*-means clustering analysis

Phylogenetic tree reconstruction using **BEAST v1.10.4**

Results





- Shared $T_{CD4+eff}$ immunogenicity potential increases with introduction of new vaccine strain
- Immediate decline of shared $T_{CD4+eff}$ observed after vaccine introduction. On average, there are 4 shared $T_{CD4+eff}$ drop before a vaccine update, suggesting possible immune escape and changes to T cell imprinting repertoire

Figure 1 | Overview of **shared $T_{CD4+eff}$** over time with reference to H3N2 vaccine strain updates from 1968 to 2004.

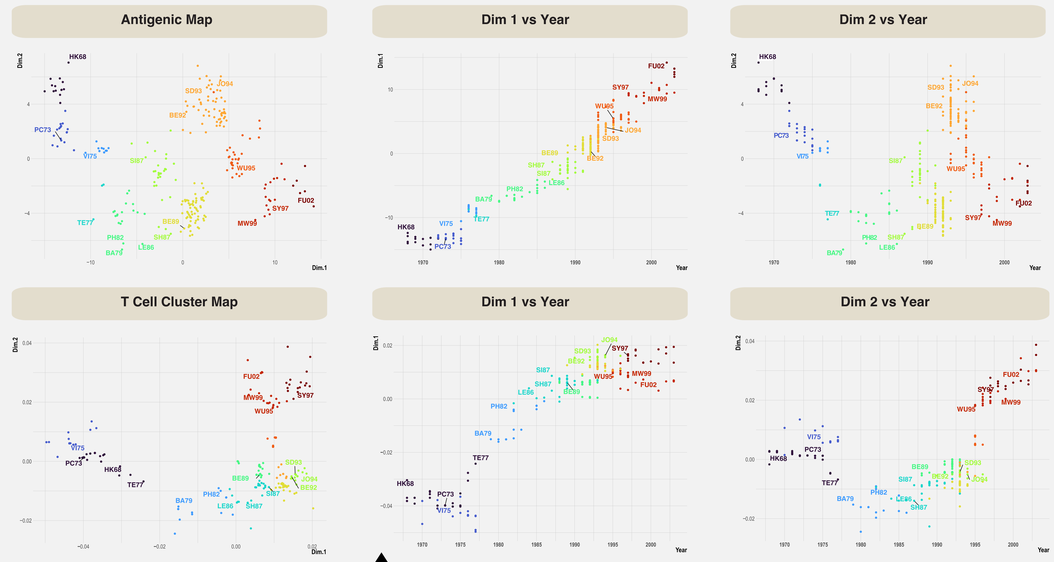


Figure 2 | Comparison between HI measurement (top row) and T cell epitope prediction (bottom row). The 11 antigenic groups are defined as in Smith *et. al* and T cell cluster groups are categorized based on 11 clusters as well. Linear rate of T cell epitope drift corresponds with HA antigenic drift.

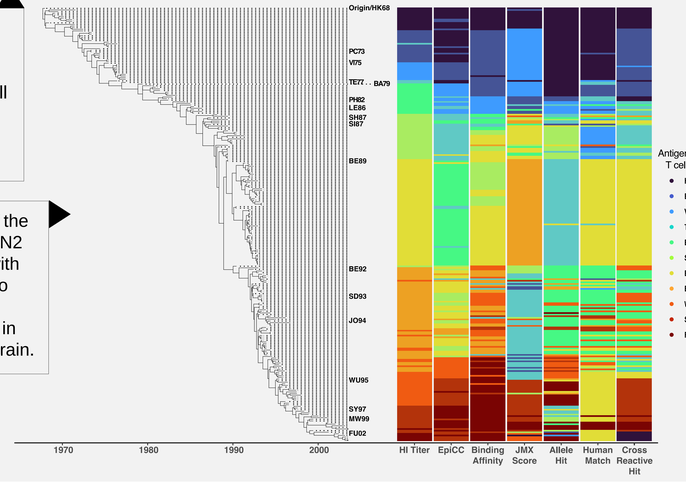


Figure 3 | Phylogenetic tree reconstruction of the 269 HA nucleotide sequences of seasonal H3N2 IAV using BEAST skyride coalescent model with antigenic groups and T cell clusters mapped to the tree tips. The corresponding color-coded antigenic group and T cell clusters are shown in the heatmaps aligned with each associated strain.

Discussion

Preliminary findings show that putative $T_{CD4+eff}$ increase with the introduction of a new A(H3N2) vaccine strain. An immediate decline of shared $T_{CD4+eff}$ is observed after new A(H3N2) vaccine strain introduction, suggesting possible immune escape from the imprinted T cell repertoire. Multidimensional scaling and *k*-means clustering analyses of HI titer data and T cell epitope prediction are based on Smith *et. al* defined cluster groups. Five distinct clusters are found prior to 1990, however, clusters overlap thereafter, indicating greater diversity of T cell epitopes. Our results also show that T cell epitope evolution of H3 HA is linear, which corresponds with HA genetic drift.

T cell epitope population shapes over time due to immune pressure and viral fitness results in the formation of new epitopes. The decrease in T cell epitope content following a vaccine strain change may indicate that the virus is continually mutating. Emerging virus prediction may therefore provide insight for better vaccination strategies.

Reference

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