

Predicting influenza vaccine effectiveness from evolution of the dominant epitope

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Short Abstract — We predict influenza A(H3N2) vaccine effectiveness in humans using a novel measure of antigenic distance, p_{epitope} , between the vaccine and circulating virus strains. p_{epitope} is based on the evolution of the hemagglutinin protein’s dominant epitope, which is the viral site to which an antibody binds. This measure originates as an order parameter from our statistical mechanics model of the antibody-mediated response to infection following vaccination. During 2016-2017, our model predicts 19% effectiveness compared to 20% observed. This robust tool aids vaccine selection by rapidly predicting human protection against all circulating strains.

Keywords — influenza, vaccine effectiveness, pEpitope, antigenic distance

I. BACKGROUND

SEASONAL influenza constitutes a significant disease burden worldwide, with three to five million cases of severe illness and an estimated annual death toll of 290,000 to 650,000; however, vaccination can provide protection [1]. For the 2016-2017 influenza season, the World Health Organization chose an A(H3N2) vaccine reference strain that was well-matched to the dominant infecting viruses. Results from conventional ferret models however did not explain why effectiveness of the manufactured vaccine was unusually low, at only $20 \pm 8\%$ for adults aged 18-64 [2].

Influenza type A viruses are primarily recognized by the immune system via two proteins on their surface, hemagglutinin (HA) and neuraminidase [3]. These viruses constantly evolve to evade human antibody binding, most notably by introducing amino acid substitutions into the HA binding sites. In addition to increased antigenic distance due to virus evolution, the vaccine strain may also diverge from circulating strains due to substitutions acquired during egg passaging [4]. Egg adaptations have posed an issue when manufacturing vaccines for A(H3N2) viruses in particular.

Here we develop a comprehensive model that utilizes the primary protein structure of the antibody binding sites to quantify the vaccine’s antigenic drift [5]. We define an antigenic distance between influenza A(H3N2) viruses and vaccines based on amino acid substitutions in the dominant epitope to predict vaccine effectiveness.

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II. SUMMARY OF RESULTS

We have derived a statistical mechanics model that captures the dynamics of human antibody-mediated response to viral infection following vaccination [6]. We generalize the model to data both from the 1971-1972 to 2015-2016 influenza seasons and from laboratory-confirmed studies over the past decade, and p_{epitope} has $r^2 = 0.77$ in both cases.

We employ this theoretical method to predict how well the administered A(H3N2) vaccine protects humans. We identify $p_{\text{epitope}} = 0.111$ and $19 \pm 4\%$ average effectiveness for the vaccine against all circulating A(H3N2) strains during the 2016-2017 and early 2017-2018 seasons. We establish that this low vaccine performance was largely caused by the substitutions that occurred in the dominant HA epitope B during egg passaging of the vaccine strain.

We compare this method with the typical measure of antigenic distance d_1 , defined in ferret animal models as the \log_2 difference between vaccine antiserum titer against itself and the vaccine antiserum titer against a strain representative of the dominant circulating viruses [7]. The conventional ferret antisera d_1 has $r^2 = 0.42$ on data since 1971, and over the past 10 years this has dropped to $r^2 = 0.23$

III. CONCLUSION

Our model can rapidly calculate p_{epitope} for a vaccine paired with an individual strain or averaged over many circulating viruses, whereas ferret models are time consuming and restricted to a few analysis pairs. While other factors influence vaccine effectiveness in humans, the p_{epitope} theory has accounted for most of the variance over the past 10 and 45 years ($r^2 = 0.77$). This work showcases a robust tool for ensuring optimal reference strain selection and predicting manufactured vaccine effectiveness.

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