Genetic Analysis of A(H3N2) influenza viruses and associations with host characteristics among Kaiser Permanente Northern California adults during the 2018/2019 season

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INTRODUCTION

Influenza A(H3N2) viruses exhibit significant genetic diversity, and mutations may escape acquired host immunity, potentially triggering infections among vaccinees.

OBJECTIVE

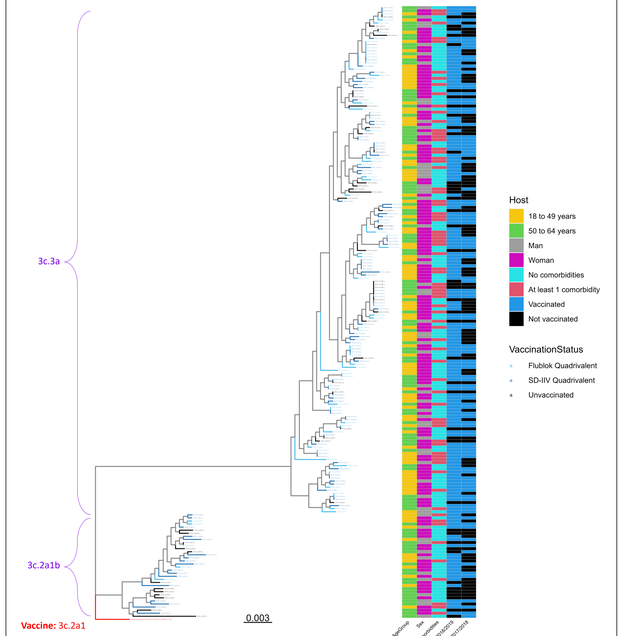
- Explore associations between genetic changes in A(H3N2) viruses and vaccinal status of their adult hosts vaccinated with quadrivalent standard dose inactivated influenza vaccine (SD-IIV4) , with quadrivalent recombinant influenza vaccine (RIV4) vaccine, or not vaccinated.
- Explore associations with other host demographics.

METHODS

- We conducted whole genome sequencing of 192 A(H3N2) viruses collected during the 2018/2019 season from Kaiser Permanente Northern California outpatient members aged 18-64 years[1]. 89 were vaccinated with SD-IIV4, 62 with RIV4, and 41 were unvaccinated. Age, sex, selected underlying medical conditions, and previous season's (2017/2018) influenza vaccination status were known. Selection was done in several steps including random selection ones in order to have 1) most of vaccinated cases and 2) a balance of age groups.
- Phylogenetic analyses were performed at the nucleotide and amino acid levels. Associations between specific mutations of hemagglutinin (HA) and neuraminidase (NA) and vaccine status were assessed by a) known antigenic drift mutations and b) agnostically, considering all mutations. Various analyses were performed, including Multiple Component Analysis, Discriminant Analysis of Principal Components, and machine learning like K-means.

RESULTS

Figure 1: Overview of viruses and associated hosts characteristics

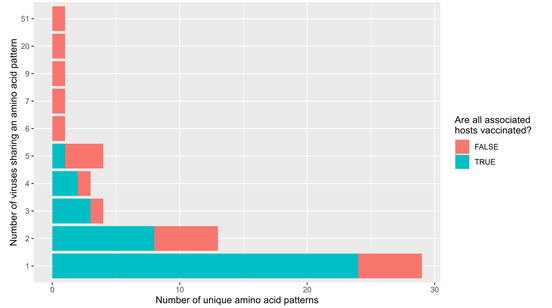


On the left part is shown the phylogenetic tree based on HA nucleotide sequences, rooted with the vaccine strain (in red, last line). On the right is displayed the clinical characteristics of the associated host population: from left to right, the columns represent age, sex, any comorbidities (asthma, diabetes, COPD, CHD), vaccination status in 2018/2019 season and vaccination status in the season just before, 2017/2018 season

CHD: chronic heart disease; COPD: chronic obstructive pulmonary disease; HA: hemagglutinin; SD-IIV4: quadrivalent standard-dose inactivated influenza vaccine

In 2018/2019, there was a documented mismatch between the vaccine strain and the circulating A(H3N2) viruses. Here, we observed two different sub-clades (**Figure 1**): 83% of viruses were 3C.3a and others were 3C.2a1b; the vaccine strain was 3C.2a1.

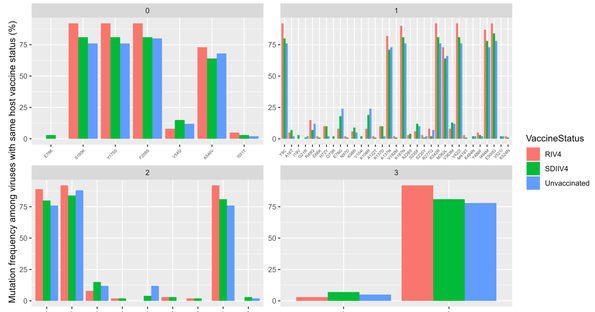
Figure 2: Observed number of amino acid distinct patterns by the vaccination status



Each distinct amino acid pattern (n = 58) - a unique set of HA and NA amino acids - is classified as being exclusively sampled from vaccinated individuals (TRUE, blue, n = 38) or not (FALSE, red, n = 20), in which case the pattern was found for viruses sampled from both vaccinated and unvaccinated individuals (n= 14) or only unvaccinated individuals (n=6)

HA: hemagglutinin; NA: neuraminidase

Figure 3: Relative frequencies of HA amino acid substitutions per vaccine status of their associated host and per known risk of antigenic drift – from 0, no knowledge to 3, high known risk



Risk of antigenic drift were obtained from FluSurver[2]. T151K is highlighted in red (x-axis label) as the only mutation with a significantly different frequency in vaccinated and in unvaccinated sub-populations (p-value=0.023). T151K (immature HA numbering) is also known as T135K (mature HA numbering)

HA: hemagglutinin; SD-IIV4: quadrivalent standard-dose inactivated influenza vaccine; RIV4: quadrivalent recombinant influenza vaccine

- No pattern was observed between the host characteristics and the A(H3N2) virus HA genetic material that triggered its disease (**Figure 1**).
- High viral genetic diversity among vaccinated individuals: 37 (66%) of the 58 observed unique amino acid signatures were found solely in those vaccinated (**Figure 2**).
- HA amino acid mutations frequencies rarely (1 of 44) differed per vaccine status: T151K frequency was observed higher in unvaccinated individuals (**Figure 3**).

CONCLUSIONS

Holistic characterization of influenza viruses can help contextualize the effectiveness of influenza vaccines, especially in a season of substantial mismatch.

These preliminary results revealed most heterogeneous mutations in the HA and NA genes of vaccinated cases compared to non-vaccinated cases, and one mutation, T135K, less present in vaccinated than in non-vaccinated.

Further analysis are on-going to confirm this association, using advance analytics to expand the search for meaningful mutations in the whole virus genome. Repeating these analytical approaches using larger sample size could yield more robust results to support next generation vaccine initiatives.

REFERENCES
1. Hsiao A, et al. *NEJM*. 2023 Dec 14;389:2245-55.
2. FluSurver, A*STAR Bioinformatics Institute, Singapore, accessed through GISAID portal https://gisaid.org/, on April 24th 2024

CONFLICTS OF INTEREST
OJ, SSC, CC, KN and CEG are Sanofi employees, a vaccine manufacturer of influenza vaccines, and may hold shares and/or stock options in the company

AUTHORS
RI, CYP, HG, DAW, NPK, AH designed the data collection, CYP, HG, DAW, NPK, AH performed the virus sequencing, OJ, SSC, CC, KN, WTH and LJ conceptualized this study, OJ performed the analysis and wrote the abstract and all co-authors critically reviewed the results and the final content of the poster

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