Mucosal Correlates of Protection after Influenza Viral Challenge of Vaccinated and Unvaccinated Healthy Volunteers: A Preliminary Report

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Nothing to disclose.

BACKGROUND: Influenza poses a significant threat to health worldwide.[1-3] The cornerstone of prophylaxis is vaccination, with current influenza vaccines stimulating antibodies targeting the major surface protein, hemagglutinin (HA).[4] Limited vaccine effectiveness has led to interest in developing new improved vaccines.[5] Rational vaccine design will benefit from understanding the correlates of protection from influenza illness beyond systemic anti-HA antibodies, which are an imperfect reflection of an individual's immunity to influenza.[6,7] Because the nose is the primary site of influenza exposure and infection, the nasal mucosal correlates of protection are of particular interest.[8] Prior human studies show an inverse correlation between IgA in the nasal mucosa and clinical outcomes including symptoms and duration of viral shedding.[6,9]

METHODS: We enrolled 82 healthy adults aged 18-55 years who had not received recent influenza vaccination, regardless of baseline serum HA inhibition (HAI) titers, at the NIH Clinical Center. Half of participants received licensed seasonal quadrivalent inactivated influenza vaccination (Flucelvax, Seqirus) at least 30 days prior to viral challenge, while the other half received no vaccination. All participants received 10^7 $TCID_{50}$ intranasal dose of the challenge virus, A/Bethesda/MM2/H1N1. Participants remained isolated in the hospital for a minimum of 9 days with repeated phlebotomy and nasal sampling collections as well as daily evaluation for symptoms and viral shedding. After discharge, participants were followed for 2 months. Laboratory evaluation of participants' serologic and nasal mucosal samples followed; mucosal assays have been delayed by the SARS-CoV-2 pandemic response.

RESULTS:

Table 1. Clinical outcomes of participants receiving influenza challenge by group.

Outcome	Vaccinated (N=37)	Unvaccinated (N=37)	p value
MMID	18 (49%)	30 (81%)	**0.007**
Symptoms	27 (73%)	35 (95%)	**0.024**
Shedding	23 (62%)	30 (81%)	0.121

Notes: Mild to moderate influenza disease (MMID) is defined as positive molecular testing AND at least 1 symptom. Data are presented as No. (%).

In a healthy volunteer challenge with influenza A/H1N1 virus, **vaccination did not prevent infection** as measured by viral shedding, but did **reduce the incidence and duration of symptoms.**

Study Design and Sample Collection

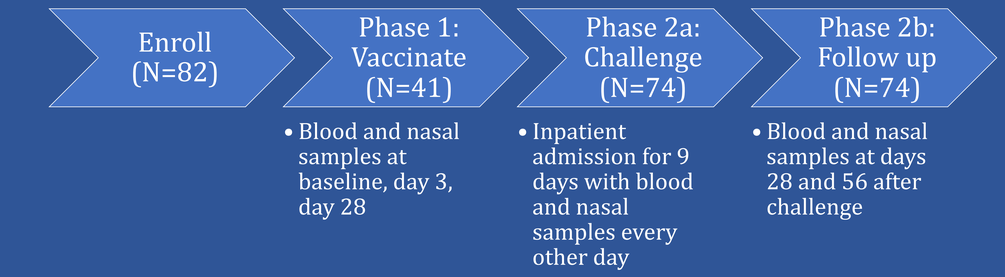

Table 2. Participant demographics.

Demographics	Vaccinated, N (%)	Unvaccinated, N (%)
Gender		
Female	23 (56%)	22 (54%)
Male	18 (44%)	19 (46%)
Race		
White	20 (49%)	21 (51%)
Black	16 (39%)	15 (37%)
Asian	2 (5%)	0
Multiple	1 (2%)	4 (10%)
Unknown	2 (5%)	1 (2%)
Ethnicity		
Hispanic	8 (20%)	5 (12%)
Not Hispanic	33 (80%)	34 (83%)
Unknown	0	1 (2%)

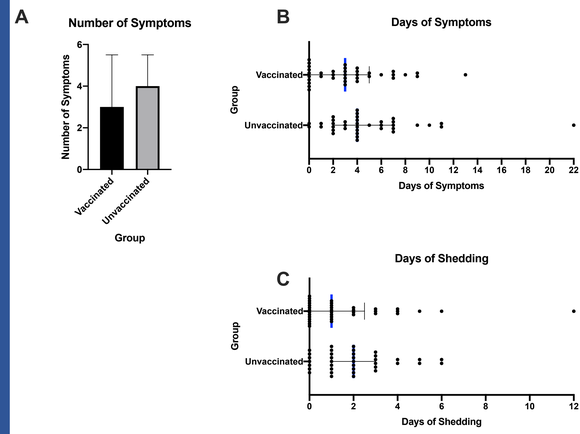

Figure 1. Disease severity measures by number of symptoms, and days of symptoms and shedding. A) Unvaccinated participants experienced more symptoms over the study period than vaccinated participants (p=0.048). B) Unvaccinated participants experienced more days of symptoms than vaccinated participants (p=0.046). C) There was no significant difference between the groups in days of shedding (p=0.095). Blue lines represent medians with error bars representing interquartile ranges.

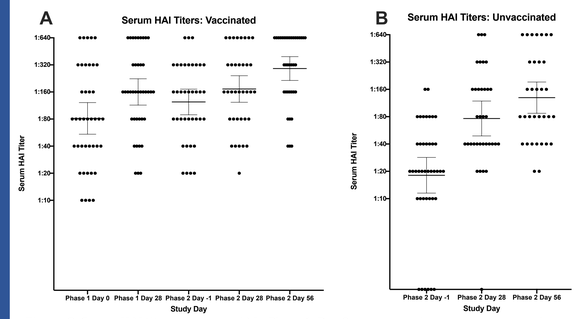

Figure 2. Serum HAI titers of groups. A) In Phase 1, Day 0 serum was drawn prior to same-day vaccination; Day 28 was 4 weeks post-vaccination. In Phase 2, Day -1 was 1 day prior to viral challenge; Days 28 and 56 were 4 and 8 weeks later. B) Unvaccinated group did not complete Phase 1 (vaccination and follow-up), only Phase 2 (challenge and follow-up). Lines represent geometric means with error bars representing 95% confidence interval.

CONCLUSIONS:

- Vaccination was associated with reductions in incidence of symptoms, days of symptoms and total number of symptoms, without significant effect on viral shedding.
- Viral challenge induced MMID in 49% of vaccinated and 81% of unvaccinated participants; these are high rates in the setting of vaccination and inclusion of research participants with baseline serum HAI titers of 1:40 and greater, which are typically considered to be protective from influenza infection.
- This clinical and systemic immune data will be correlated with mucosal immune results once SARS-CoV-2 related restrictions allow our laboratory research to resume.

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