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Factors associated with Humoral Immune Response in Older Adults who Received Egg-free Influenza Vaccine

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Abstract

Background: Immune responses to influenza vaccination tend to be lower among older, frequently vaccinated adults. Use of egg-free influenza vaccines is increasing, but limited data exist on factors associated with their immunogenicity in older adults.

Methods: Community-dwelling older adults ≥56 years of age were enrolled in a prospective, observational study of immunogenicity of 2018–2019 influenza vaccine. Hemagglutination inhibition (HAI) antibody titers were measured pre-vaccination (Day 0) and four weeks after vaccination (Day 28) to calculate geometric mean titers, seropositivity (HAI titers ≥1:40), seroconversion (four-fold rise in HAI titer with post-vaccination titer ≥1:40) and geometric mean fold rise (GMFR). Linear regression models assessed the association of predictors of GMFR for each vaccine antigen.

Results: Among 91 participants who received egg-free influenza vaccines, 84 (92.3%) received quadrivalent recombinant influenza vaccine (RIV4, Flublok, Sanofi Pasteur), and 7 (7.7%) received quadrivalent cell culture-based influenza vaccine (ccIIV4, Flucelvax, Seqirus). Pre-vaccination seropositivity was 52.8% for A(H1N1), 94.5% for A(H3N2), 61.5% for B/Colorado and 48.4% for B/Phuket. Seroconversion by antigen ranged from 16.5% for A(H1N1) and

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B/Colorado to 37.4% for A(H3N2); 40 participants failed to seroconvert to any antigen. Factors independently associated with higher GMFR in multivariable models included lower pre-vaccination HAI antibody titer for A(H1N1), B/Colorado and B/Phuket, and younger age for A(H1N1).

Conclusion: Overall pre-vaccination seropositivity was high and just over half of the cohort seroconverted to ≥1 vaccine antigen. Antibody responses were highest among participants with lower pre-vaccination titers. Among older adults with high pre-existing antibody titers, approaches to improve immune responses are needed.

Keywords

influenza; egg-free influenza vaccine; hemagglutination inhibition assay; adults; humoral response

Introduction

Influenza is a highly contagious, infectious, respiratory disease that causes substantial morbidity and mortality.[1–4] Between 2010 and 2020, influenza is estimated to have caused between 9 million and 41 million illnesses, 140,000–710,00 hospitalizations, and 12,000–52,000 deaths, annually within the United States.[5] Older adults bear the brunt of influenza-attributable morbidity and mortality. Estimates report between 50% and 70% of influenza-related hospitalizations and 70%–85% of annual influenza deaths occur in people ≥65 years of age.[6]

The best protection against risk of influenza-related complications is vaccination.[6] Unfortunately, older individuals tend to have an attenuated immune response (antibody titers, B cells, T cells) to influenza vaccine.[7–9] A number of factors have been associated with the diminished immune response to influenza vaccine including age-related immunosenescence,[7–12] inflammaging (chronic, low levels of inflammation associated with aging),[13] and prior vaccination.[14,15] However, associations between antibody responses and frailty,[16–22] sex,[23–25] obesity,[26–28] and diabetes[29–32] have been inconsistent in community-dwelling older adults.

To address lowered immune response to influenza vaccine among older adults, enhanced influenza vaccines (high-dose, adjuvanted, recombinant) as well as cell culture-based are now available. Two of these vaccines, cell culture-based and recombinant influenza vaccines, are egg-free influenza vaccines, which were designed to overcome the stereochemical changes caused by glycosylation and other mutations resulting from egg-grown vaccines. Glycosylation mutations have been shown to reduce the immunogenicity and effectiveness of egg-based influenza vaccines, particularly against the more virulent strains of A(H3N2) viruses.[33–35]

As non-egg-based influenza vaccines become increasingly available, it is important to assess the immune responses to these newer vaccines among older adults and the factors associated with immune response given inconsistent associations with egg-based influenza vaccines. Limited data exist comparing the immunogenicity of enhanced and cell culture-based influenza vaccine types. One recent randomized controlled trial (RCT) conducted in Hong

Kong, compared the three enhanced influenza vaccines to standard dose vaccine using the 2017–2018 formulation.[36] However, the matching process for the four groups precluded assessment of the effects of demographic and medical factors. We examined characteristics associated with HAI antibody titers in a cohort of older adults who received egg-free (RIV4 or ccIIV4) influenza vaccine in 2018–2019, the first season in which these newer vaccine technologies were available in our health system.

Methods

Study Design and Participants

This was an observational prospective study of antibody response to the 2018–2019 influenza vaccine. Adults ≥56 years of age who had not yet received 2018–2019 influenza vaccination were part of an existing cohort of older adults recruited using nonprobability convenience sampling from three family-medicine practices, 6 long-term care facilities (independent and assisted-living), and the community via recruitment flyers, provider/facility recommendations and word-of-mouth; adults who had participated in a similar study in 2017–2018 were invited to re-enroll. Exclusion criteria were: allergies to the influenza vaccine or its components, having an immunosuppressing health condition (with the exception of localized skin cancer) or taking immunosuppressant medications, a history of an allograft, on dialysis, or a history of Guillain Barre syndrome. The University of Pittsburgh's Human Research Protection Office and Centers for Disease Control and Prevention's Institutional Review Board approved this study. Written informed consent was provided by all participants prior to study initiation.

Baseline data collection

Recruitment, consent, and enrollment occurred from August-November 2018, prior to regional circulation of influenza virus. Personal data were collected by self-report and included: date of birth, sex, race, smoking status, 2017–2018 influenza vaccine type (e.g., standard dose, high-dose; vaccine type was EMR verified), diabetes (yes/no; type), presence of cardiopulmonary chronic diseases (e.g., heart/lung/liver disease), and subjective social economic status (SSES) (scored 0=low to 9=high). Baseline data were directly entered into an online, secure database management system, REDCap™. The level of functional disability was measured using the activities of daily living (ADL) and instrumental activities of daily living (IADL) questionnaires (scores range from 0=low functionality to 14=high functionality). Body mass index (BMI) in kg/m^2 was calculated from self-report or EMR-collected height and weight, calculated as [weight (lb.) ÷ height $(in.)^2$] X 703; obesity was defined as BMI ≥ 30 kg/m^2. Physical frailty as defined by Fried et al.'s Physical Frailty Phenotype,[37] was assessed, adjusted for sex, and scores summed to determine an ordinal frailty score (range=0–5).

Biological samples

Non-fasting whole blood samples were obtained pre-vaccination (Day 0) and post-vaccination (Day 28; range 19–35 days) into BD Vacutainer™ serum separator tubes with polymer gel/silica activator additive (BD 367985). Tubes were kept at room temperature

and delivered to the processing laboratory within 4 hours of being drawn. Aliquoted serum samples were frozen at −80° C until assayed.

Influenza vaccination

After the baseline blood draw, all participants received an intramuscular injection of the 2018–19 seasonal influenza vaccine at a place and from a provider of their convenience. Participants were not restricted by type or valence of the influenza vaccine and therefore vaccine type varied. Participants provided their influenza vaccine documentation, or it was derived from the EMR and included the lot number, dose, vaccine manufacturer and type (e.g., cell cultured-based, recombinant) received.

In 2018–19 all participants received quadrivalent influenza vaccine which contained: A/Michigan/45/2015(H1N1)pdm09-like virus, A/Singapore/INFIMH-16–0019/2016(H3N2)-like virus (clade 3C.2a.1b), B/Colorado/06/2017-like virus (Victoria-lineage) and B/Phuket/3073/2013-like virus (Yamagata-lineage).

HAI processing

HAI assays were conducted on all egg-propagated influenza vaccine reference antigens according to standard protocols.[38] Sera were heat inactivated, tested for nonspecific agglutinins, and adsorbed as needed. Sera were serially diluted 2-fold and incubated with 4 hemagglutination units per 25 μL of virus with erythrocytes for quantification of HAI titers. Turkey erythrocytes were used for the testing of A(H1N1) and B influenza viruses, Guinea pig erythrocytes with 20 mM oseltamivir were used for the testing of A(H3N2) virus. HAI titer was defined as the reciprocal of the last dilution of serum that completely inhibited hemagglutination. Antibody titers <10 (initial sera dilution) were reported as 5 for analysis.

Statistics

Seroconversion was defined as a four-fold rise in HAI titer with Day 28 post-vaccination titer ≥40. Seropositivity was defined as a HAI titer ≥1:40. Post vaccination geometric mean titers (GMT) and geometric mean fold-rise (GMFR, the ratio of HAI titer at Day 28 to the HAI titer at Day 0 (GMT D28/GMT D0)) were also calculated. GMTs and GMFR values were $\log_2$ transformed for linear regression. Reported GMTs, GMFR and their respective 95% confidence intervals (CIs) reflect the anti-log of the respective $\log_2$ values.

The primary outcome measure was seroconversion to ≥1 vaccine antigen versus non-response to all four vaccine antigens. For examining each antigen separately, participants with ≥4-fold rise versus those with <4-fold rise in HAI antibody titer were compared. Characteristics of the two groups were assessed using Chi-square/Fisher's exact tests for categorical variables to report proportions and Wilcoxon/t-tests for continuous variables to report means and 95% confidence intervals or median and quartiles 1 and 3.

The association of characteristics with HAI antibody response to influenza vaccine was conducted using linear regression for $\log_2$ GMFR. For each vaccine antigen, we examined *a priori* in univariable models, the effect of age, sex, race, BMI (examined as a continuous variable and categorical using a BMI of ≥30 to define obesity), frailty, diabetes, baseline

titer, and prior year vaccine type on $\log_2$ GMFR. Final multivariable models included adjustment for $\log_2$ baseline titers, age, and BMI (continuous); prior year vaccine was not included in models due to its correlation with age. Therefore, we separately examined HAI antibody titer outcomes stratified by type of vaccine received in the prior season (HD vs. SD) as well as the association of prior year influenza vaccine type (HD vs. SD) and BMI on $\log_2$ GMFR adjusting for $\log_2$ baseline titers. Multivariable models were run separately for each vaccine antigen.

All analytical procedures were performed using SAS® 9.4 (Cary, NC). Statistical significance of two-sided tests was set at type I error (alpha)=0.05.

Results

Analytic cohort and influenza vaccine type received

Ninety-one of the 114 adults enrolled in the 2018–19 influenza vaccine immunogenicity study received egg-free vaccines and were included in this analysis; 89 of these participants had enrolled in the prior season's (2017–2018) study. Of the 91 participants, 84 (92.3%) received recombinant RIV4 and 7 (7.7%) received ccIIV4 (Table 1); there was no difference in seroconversion by type of egg-free influenza vaccine received (p=0.23), therefore all egg-free vaccine recipients were combined in subsequent analyses.

Demographics

Fifty-one participants seroconverted to ≥1 vaccine antigen while 40 participants did not seroconvert to any vaccine antigen (e.g., non-responders). Table 1 reports demographics overall and by seroconversion status. The majority of this cohort was White (72.5%), female (70.3%), reporting a median SSES of 6 (Q1-Q3: 5–7). Median age was 68.8 years (Q1-Q3: 63.3–78.1); the majority was over 65 years old (70.3%). Mean BMI was 29.5 (95% CI: 20.4–40.1); 40.7% of the cohort were persons with obesity (BMI ≥30) and one third of participants had diabetes (33.0%). Less than one-third of participants reported a major cardiopulmonary condition (29.7%) or being a current smoker (13.2%). The majority of the cohort was high functioning with an average ADL of 14 (Q1-Q3: 14–14) and IADL of 14 (Q1-Q3: 13–14) and was not frail (score =1; Q1-Q3: 0–2).

Seroconverters to ≥1 vaccine antigen did not differ from non-responders by sex (p=0.60), race (p=0.63), obesity (p=0.07), frailty (p=0.93), or diabetes (p=0.33). However, compared to seroconverters to ≥1 vaccine antigen, non-responders were significantly older (72.0 vs. 67.3 years; p=0.01), had lower BMI (28.0 vs. 30.7; p=04) and were more likely to have received high dose versus standard dose, egg-based influenza vaccines in the prior season (76.9% vs. 54.0%; p=0.03).

HAI results

Pre- and post-vaccination HAI antibody titers for the entire cohort and by responder status are reported in Table 2. Nearly or over half of the cohort was seropositive at baseline for all vaccine antigens: 52.8% for A(H1N1), 94.5% for A(H3N2), 61.5% for B/Colorado and

48.4% for B/Phuket. Seropositivity at Day 28 was high with the majority (76%–100%) of participants reaching a HAI antibody titer ≥40.

In the entire cohort, Day 28 GMFRs ranged from 1.7 to 2.6 across the four antigens with the highest response to the A(H1N1) antigen. Seroconversion rates were low in this cohort: 16.5% (n=15) with overall GMFR of 2.6 (2.1–3.2) for A(H1N1), 37.4% (n=34) with overall GMFR of 1.8 (1.5–2.0) for A(H3N2), 16.5% (n=15) with overall GMFR of 1.7 (1.4–2.1) for B/Colorado, and 31.9% (n=29) with overall GMFR of 2.1 (1.7–2.4) for B/Phuket. The majority of participants had a fold-rise of <4 to each vaccine antigen strain (range 62.6% to 83.5%).

Participants with a fold-rise of ≥4 had lower baseline antibody GMTs than those with <4 fold-rise (e.g., non-responders) to A(H1N1) (23 vs. 50, p=0.002) and B/Phuket (22 vs. 38, p=0.01) but not to A(H3N2) or B/Colorado. However, baseline seropositivity rates differed only for A(H1N1) with lower proportions of baseline seropositivity rates (35.3% vs. 63.2%, p=0.01) for participants with a fold-rise of ≥4 vs. non-responders.

Postvaccination seropositivity rates were higher for those with a vaccine antigen fold-rise of ≥4 vs. non-responders to three of the four strains: A(H1N1) (94.1% vs. 73.7%, p=0.02), B/Colorado (100% vs. 73.9%, p=0.04) and B/Phuket (96.6% vs. 66.1%, p=0.002. However, the majority of non-responders had postvaccination titers ≥1:40. Correspondingly, GMFR was significantly higher for participants with a fold-rise of ≥4 compared to non-responders for all four vaccine antigens: A(H1N1) (7.2 vs. 1.4, p<0.001), A(H3N2) (5.9 vs. 1.4, p<0.001), B/Colorado (6.8 vs. 1.3, p<0.001), B/Phuket (5.5 vs. 1.3, p<0.001).

Linear regression: Univariable results

Results of the associations of individual characteristics on $\log_2$ GMFR assessed in univariable linear regression models are reported in Table 3. Associations of characteristics varied by vaccine antigen strain. Age was a significant negative predictor of GMFR only for A(H1N1) (Beta: −0.05; p<0.001). BMI (continuous) was a significant positive predictor of GMFR only for A(H1N1) (Beta: 0.05; p<0.03). Prior year vaccine type was a significant predictor of GMFR for A(H1N1) and A(H3N2) with receipt of HD as compared to SD egg-based influenza vaccine in 2017–18 associated with lower 2018–19 GMFR for A(H1N1) (Beta: −5.02; p=0.03) and A(H3N2) (Beta: −0.90; p=0.04). Baseline $\log_2$ titer was a significant negative predictor of GMFR for all four vaccine antigens with higher baseline titers associated with lower GMFR for A(H1N1) (Beta: −0.30; p<0.001) and A(H3N2) (Beta: −0.20; p=0.04), B/Colorado (Beta: −0.31; p<0.001), and B/Phuket (Beta: −0.22; p<0.001). Race, sex, obesity, diabetes, and frailty were not significant predictors of GMFR (p≥0.05).

Linear regression: Multivariable results

Based on the findings from the univariable analyses, multivariable linear regressions models were run separately for each vaccine antigen and included age, BMI, and baseline $\log_2$ HAI titer with GMFR as the outcome variable (Table 4). Significant predictors of higher GMFR for A(H1N1)/Michigan were younger age (Beta: −0.04; p=0.003) and lower baseline $\log_2$ HAI titer (Beta: −0.25; p<0.001); and for B/Colorado and B/Phuket, lower baseline

log_2 HAI titer (Beta: −0.33; p<0.001 and −0.24; p=0.005, respectively). Because age and prior year vaccine type were highly related, we conducted a separate sensitivity analysis examining the effect of prior year vaccine type in multivariable linear regressions.

As shown in Table 1, 97.8% of this cohort received an influenza vaccine the previous season (2017–18); a higher proportion of non-responders in 2018–19 received HD influenza vaccine the prior season (76.9% vs. seroconverters to ≥1 vaccine antigen 54.0%). The influenza vaccine strain for A(H1N1) (A/Michigan/45/2015(H1N1)pdm09-like virus)) and the Yamagata lineage (B/Phuket/3073–2013-like virus; QIV only) were the same for both years' vaccines (see Table 5).

Supplemental Table 1 reports HAI antibody titer response stratified by prior year vaccine type (2017–18 HD vs. SD vaccine recipients). Though there were no significant differences between percent of participants seropositive at Day 0 or Day 28, significantly more recipients of SD vaccine seroconverted against A(H1N1) (50% vs. 22.9%; p=0.009) and A(H3N2) (28.1% vs 10.5%; p=0.03) strains and they had significantly higher GMFRs than HD recipients (Supplemental Table 1).

Supplemental Table 2 reports the association of prior year vaccine type (2017–18 HD vs. SD vaccine recipients) and BMI upon log_2 GMFR in the multivariable linear regression model adjusting for baseline log_2 titers. Higher GMFR for A(H1N1)/Michigan were related to prior year receipt of SD vaccine (Beta: −0.90; p=0.002), higher BMI (Beta: 0.05; p=0.03) and lower baseline log_2 HAI titer (Beta: −0.26; p=0.001). For A(H3N2)/Singapore, receipt of SD prior year vaccine was associated with higher GMFR (Beta: −0.48; p=0.03); and, for B/Colorado and B/Phuket higher GMFR was associated with lower baseline log_2 HAI titer (B/Colorado: Beta: −0.29; p=0.001) and (B/Phuket: Beta: −0.24; p=0.005).

Discussion

Despite protective levels of HAI titers elicited by influenza vaccine, vaccine effectiveness (VE) has been lower for egg-based influenza vaccines particularly against more virulent A(H3N2) strains due in part to antigenic mutations and their resultant stereochemical changes caused by the manufacturing process.[33,34,39] Due to this reduced VE, advocacy efforts within the UPMC Health Plan have resulted in egg-free and enhanced influenza vaccines becoming standard of care for both outpatient and inpatient settings according to their age-indicated licensure approvals. This analysis examined the humoral immune response to egg-free influenza vaccines, the majority of which was enhanced RIV4 (92.3%), in a cohort receiving these newer vaccine technologies in the first season they were widely available within our healthcare system.

Using seroconversion as a measure of vaccine response, we compared participants who seroconverted to at least one vaccine antigen with those who did not. The few demographic differences between groups included age, BMI, and prior year vaccine type. Non-responders were, on average, ~5 years older, had a slightly lower BMI level, and had higher proportion receiving HD influenza vaccine the prior season compared with those who seroconverted to ≥1 vaccine antigen.

High proportions of participants had HAI titers ≥1:40 pre- and post-vaccination. Correspondingly, while greater than half of participants seroconverted to at least one vaccine antigen, fold-rise of ≥4 varied across vaccine antigens ranging from a low of 16.5% (A(H1N1) and B/Colorado) to a high of 37.4% (A(H3N2)). However, in the cohort overall, the rise in antibody titers was low with GMFR levels >2 noted for only two vaccine antigen strains: A(H1N1) and B/Phuket.

The relationships between humoral immune response to egg-based influenza vaccine and demographic and medical characteristics such as age, frailty, sex, obesity, diabetes, and race have been inconsistent.[16–32] We found in univariable models that antibody titer response to non-egg-based influenza vaccine did not differ by race, sex, obesity, frailty and diabetes. It should be noted that there was little heterogeneity in the study sample as the majority of participants were White, female, non-obese, not frail (median frailty score indicated participants were primarily pre-frail), and non-diabetic. Only age and BMI for A(H1N1) and prior year vaccine type for A(H1N1) and A(H3N2) were associated with GMFR. Indeed, the most consistent association with GMFR was participants' baseline $\log_2$ titer with higher titers associated with reduced GMFR.

In multivariable models adjusted for baseline $\log_2$ HAI titer examining age and BMI, age was a significant negative predictor of GMFR for A(H1N1), a relationship not observed with the other vaccine antigens. BMI was not associated with GMFR in adjusted models for any vaccine antigen.

Older adults tend to have a decreased immune system response to influenza vaccine[7–9] and bear a disproportionate burden of seasonal influenza-attributable morbidity and mortality.[6] While few studies exist which compare the immunogenicity of enhanced and cell culture-based influenza vaccines to one another, particularly among older adults, existing studies indicate that enhanced influenza vaccines have been shown to offer increased immunogenicity over standard-dose influenza vaccines, including among older adults.[36,40] One comparative study (N=48) among adults ≥60 years of age, found HAI antibody responses to RIV were slightly higher or similar to egg-based HD influenza vaccine; and lower antibody responses to ccIIV were noted compared with RIV and egg-based HD vaccine.[41] These differences may be explained by the fact that RIV4 at 45 μg of HA per antigen strain has a higher HA content than ccIIV4 which contains 15 μg of HA per antigen strain the same as standard-dose IIV4 vaccine[40]

A recent study among older adults compared three enhanced 2017–2018 influenza vaccines (RIV4, HD-TIV, and MF59-adjuvanted TIV) with SD. Two of the vaccine stains were the same as those included in our study (A/Michigan/45/2015 (H1N1) and B/Phuket/3073/2013 (Yamagata lineage).[36] Post-vaccination GMTs to A(H1N1) were significantly higher for two of the enhanced vaccines: HD-TIV (125 vs. 69) and MF59-adjuvanted TIV (94 vs. 69) compared with SD. MFR was significantly higher among all three enhanced vaccines compared to SD. For A(H1N1) the percent of persons who seroconverted was significantly higher for all three enhanced vaccines compared to SD: 60% for RIV4 and MF59-adjuvanted TIV and 59% for HD compared to 42% for SD.[36] However, for B(Phuket), SD outperformed HD-TIV and MF59-adjuvanted in post-vaccination GMTs,

MFR and seroconversion.[36] Though RIV4 post-vaccination GMTs were higher than SD (131 vs 121), neither they nor MFR and seroconversion were statistically significantly higher. Thus, RIV has been shown in randomized studies to elicit higher titers than egg-based SD against some vaccine strains,[36,40] RIV4 failed to elicit four-fold increases in antibody titer levels against any vaccine antigen in our study.

To further understand the role of HD and SD egg-based influenza vaccine the prior season on egg-free influenza vaccine antibody response the next season, we examined HAI antibody response. We found that pre- and post-vaccination seropositivity to the 2018–19 influenza vaccine was not different between participants who received HD vs. SD vaccine the prior season. Close to or more than 50% of participants met the definition for protection by seropositivity (e.g., ≥1:40 level) at baseline for the four vaccine antigens. However, in adjusted models, participants who received HD influenza vaccine in 2017–18 had lower GMFR to the 2018–19 A(H1N1) (A(H1N1) was the same vaccine antigen in both seasons) and A(H3N2) vaccine antigens compared to 2017–18 SD recipients.

Our results differ from others who have studied the effect of repeated vaccination of egg-based influenza vaccine on egg- and cell-propagated vaccine response. Liu et al. (2021) studied the response of 3 years of repeat annual vaccination with SD influenza vaccine to egg- and cell-grown A(H3N2) vaccine and circulating viruses across a cohort of children and adults.[15] They found that among patients ≥65 years, repeated vaccination with egg-adapted epitopes resulted in a significantly reduced antibody response to wild type cell-grown A(H3N2) viruses,[15] whereas we found that receipt of any (HD or SD) egg-based vaccination in the prior season did not impede some older adults from having a significant GMFR response to 2018–19 egg-free vaccine with GMFR's ≥5.5 for all vaccine antigens for those with a fold-rise ≥4. Therefore, the response may be dictated by the amount of antigen received as opposed to the formulation of the vaccine.

Strengths and limitations

To date, the majority of the literature published on older adults' HAI response to influenza vaccination have been conducted with egg-based influenza vaccines. Limited reports of immunogenicity measured by HAI of non-egg-based influenza vaccines in older adults exist, likely due to their relative recent addition to the influenza vaccine repertoire and lower frequency of use and this is particularly so for comparative studies across seasons.

We examined antibody response to two types of non-egg-based influenza vaccines, the majority of which was RIV4, in a relatively large cohort of older adults. This cohort was racially diverse, high functioning, but with substantial levels of comorbidities (e.g., diabetes, obesity, cardiopulmonary disease). Moreover, we were able to evaluate response to non-egg-based influenza vaccine technologies in their first year of use in our cohort and we were able to confirm type of vaccine received in the prior year on 98% of participants.

The study is limited by the nature of the observational design using a convenience sample. While we examined antibody response to each vaccine antigen, for a deeper understanding of seroconversion while accounting for baseline antibody levels, an RCT study design is needed to compare immunogenicity of vaccine types. Another limitation is that though our

sample consisted primarily of RIV4 recipients, 8% received ccIIV4; the small sample size of ccIIV4 recipients limited our ability to do further individual comparisons by vaccine type. A third limitation is the use of egg-propagated influenza vaccine reference antigens rather than cell-culture derived antigens in HAI assays. While antibody responses to RIV4 measured against egg-based and cell-based antigens are highly correlated, magnitude of responses may be lower against cell-propagated antigens.[40] Finally, this study is constrained by its analysis of only one season of egg-free influenza vaccine.

Conclusions

Two non-egg-based influenza vaccines, RIV4 and ccIIV4, elicited significant seroconversion antibody responses in 51% of participants one-month post vaccination among previously vaccinated older, non-frail, adults despite high pre-vaccination titers. Demographic and medical factors other than age and baseline titer were not related to GMFR. The most consistent predictor of increased GMFR in recipients of non-egg-based influenza vaccines, was lower baseline titers. For influenza vaccine strains, these associations were strengthened when accounting for the antigen level in the previous year's vaccine (HD vs. SD). As uptake of newer influenza vaccine technologies continues to increase, future research should include maximizing post-vaccination immune response among older adults with high levels of pre-existing antibody titers in order to enhance protection. Identification of the ideal sequence of vaccine formulations across influenza seasons will help guide policy and practice recommendations. Additionally, identification of older adults who are considered non-responsive or who have low responses to all vaccine antigens would be an important population to study further by cellular immunity analyses. Given the non-significant demographic and medical factors associations seen in this study due possibly to our largely homogenous cohort, future studies should maximize sample size in enhanced and egg-free influenza vaccine studies for assessment of the impact of demographic and medical factors with variable associations noted for egg-based influenza vaccines on humoral immune response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Age and baseline HAI titers were associated with immune response to egg-free influenza vaccine
- HAI response differed by antigen level contained in prior season's influenza vaccine
- The ideal sequence of vaccine formulations across influenza seasons remains unknown

Table 1.

Demographics overall and by 2018–19 influenza vaccine responder status[a]

Variables	Entire cohort (N=91)	Non-response to vaccine antigens (n=40)	Seroconverted to ≥1 vaccine antigen (n=51)	p-value*
Age, yr, Median (Q1, Q3)	68.8 (63.3–78.1)	72.0 (66.7–83.2)	67.3 (62.3–73.7)	**0.01**
Age, N (%)				**0.02**
Under 65 years	27 (29.7)	7 (7.7)	20 (22.0)	
65 and older	64 (70.3)	33 (36.3)	31 (34.1)	
Non-white race, N (%)[1]	25 (27.5)	12 (30.0)	13 (25.5)	0.63
Female sex, N (%)	64 (70.3)	27 (67.5)	37 (72.6)	0.60
SES, Median (Q1, Q3)[2]	6 (5,7)	5 (5,7)	6 (5,7)	0.92
BMI, kg/m^2, Mean (95% CI)	29.5 (20.4–40.1)	28.0 (19.4–39.7)	30.7 (20.4–40.1)	**0.04**
BMI ≥ 30 (Obese), N (%)	37 (40.7)	12 (30.0)	25 (49.0)	0.07
Diabetes, N (%)	30 (33.0)	11 (27.5)	19 (37.3)	0.33
Current Smoker, N (%)	12 (13.2)	4 (10.0)	8 (15.7)	0.43
Cardiopulmonary disease, N (%)[3]	27 (29.7)	12 (30.0)	15 (29.4)	0.95
Fried Frailty score, Median (Q1, Q3)	1 (0,2)	1 (0,2)	1 (0,2)	0.93
ADL Score, Median (Q1, Q3)[4]	14 (14,14)	14 (14,14)	14 (14,14)	0.60
IADL score, Median (Q1, Q3)[4]	14 (13,14)	14 (12,14)	14 (13,14)	0.10
2017–18 influenza vaccine (n=89), N (%)				**0.03**
Standard dose (QIV)	32 (36.0)	9 (23.1)	23 (46.0)	
High dose (TIV)	57 (64.0)	30 (76.9)	27 (54.0)	
2018–2019 influenza vaccine, N (%)				0.23
Flublock QIV (RIV4)	84 (92.3)	35 (87.5)	49 (96.0)	
Flucelvax QIV (ccIIV4)	7 (7.7)	5 (12.5)	2 (4.0)	

[a]Non-responders are those who did not seroconvert to any vaccine antigen, responders are those who converted to ≥1 vaccine antigen.

*Chi-square/Fisher's Exact test for categorical variables; Wilcoxon ranked sum for continuous variables.

[1]Nonwhite race: Includes self-identified categories of AIAN, Asian, Black, NHPI and multi-race.

[2]SES, score ranges from 0–9, higher scores indicate greater SES status.

[3]Includes self-reported comorbidities of: heart disease, chronic lung disease, or asthma.

[4]ADL and IADL, scores range from 0–14, higher scores indicate greater functionality.

Table 2.

Pre- and post-vaccination 2018–19 HAI antibody responses overall and by responder status for all vaccine antigens*

HAI response to	Entire Cohort	Fold-rise <4	Fold-rise ≥4	p-value
A/H1NI/Michigan	**(N=91)**	**(n=76)**	**(n=15)**	
Day 0 GMT	37 (29–48)	50 (36–70)	23 (16–32)	**0.002**
Day 28 GMT	97 (75–125)	71 (52–98)	163 (110–244)	**0.002**
Day 0 seropositivity rate, N (%)	48 (52.8)	36 (63.2)	12 (35.3)	**0.01**
Day 28 seropositivity rate, N (%)	74 (81.3)	42 (73.7)	32 (94.1)	**0.02**
Day 28 GMFR	2.6 (2.1–3.2)	1.4 (1.2–1.6)	7.2 (5.6–9.3)	**<0.001**
A(H3N2)/Singapore	**(N=91)**	**(n=57)**	**(n=34)**	
Day 0 GMT	87 (75–101)	89 (75–105)	78 (55–112)	0.54
Day 28 GMT	154 (129–186)	124 (105–148)	465 (326–657)	**<0.001**
Day 0 seropositivity rate, N (%)	86 (94.5)	72 (94.7)	14 (93.3)	1.00
Day 28 seropositivity rate, N (%)	91 (100)	76 (100)	15 (100)	--
Day 28 GMFR	1.8 (1.5–2.0)	1.4 (1.3–1.5)	5.9 (5.0–7.1)	**<0.001**
B/Colorado-Victoria lineage	**(N=91)**	**(n=76)**	**(n=15)**	
Day 0 GMT	46 (37–58)	48 (38–58)	36 (22–59)	0.31
Day 28 GMT	78 (62–98)	78 (62–79)	242 (139–425)	**<0.001**
Day 0 seropositivity rate, N (%)	56 (61.5)	47 (61.8)	9 (60.0)	0.89
Day 28 seropositivity rate, N (%)	71 (78.0)	56 (73.9)	15 (100)	**0.04**
Day 28 GMFR	1.7 (1.4–2.1))	1.3 (1.1–1.5)	6.8 (4.0–11.6)	**<0.001**
B/Phuket-Yamagata lineage	**(N=91)**	**(n=62)**	**(n=29)**	
Day 0 GMT	32 (26–39)	38 (30–48)	22 (15–32)	**0.01**
Day 28 GMT	65 (52–82)	50 (38–64)	117 (77–177))	**<0.001**
Day 0 seropositivity rate, N (%)	44 (48.4)	33 (53.2)	11 (37.9)	0.18
Day 28 seropositivity rate, N (%)	69 (75.8)	41 (66.1)	28 (96.6)	**0.002**
Day 28 GMFR	2.1 (1.7–2.4)	1.3 (1.2–1.5)	5.5 (4.7–6.4)	**<0.001**

*Data are reported as mean (95% confidence interval) or number (percent). P-value for tests: Chi-square/Fisher's Exact for categorial variables

T-test for continuous variables.

GMT = Geometric mean titer. Seropositivity = HAI titer ≥40. GMFR is GMTD28/GMTD0 HAI titer.

Table 3.

Univariable linear regressions of the relationship of individual characteristics on 2018–19 GMFR vaccine response

Variables	Beta (SE or 95% CI) *	p-value
A(H1N1)/Michigan		
Age	−0.05 (0.01)	**<0.001**
Non-white race (ref=white)	0.25 (−0.42, 0.94)	0.46
Female sex (ref=male)	0.07 (−0.58, 0.72)	0.82
BMI	0.05 (0.02)	**0.03**
Obesity (ref=BMI <30)	−0.33 (−0.93, 0.27)	0.28
Diabetes (ref=non-diabetic)	−0.20 (−0.83, 0.43)	0.54
Fried Frailty Score (ref=0)		
1	−0.33 (−1.02, 0.36)	
2	−0.67 (−1.43, 0.10)	0.06
3	0.98 (−0.24, 2.21)	
2017–18 HD influenza vaccine (ref=SD)	−5.02 (−9.46, −0.55)	**0.03**
Baseline log_2 HAI titer	−0.30 (0.08)	**<0.001**
A(H3N2)/Singapore		
Age	−0.01 (0.01)	0.23
Non-white race (ref=white)	0.07 (−0.41, 0.55)	0.76
Female sex (ref=male)	−0.14 (−0.59, 0.31))	0.55
BMI	−0.01 (−0.53)	0.60
Obesity (ref=BMI <30)	0.19 (−0.23, 0.61)	0.37
Diabetes (ref=non-diabetic)	−0.18 (−0.62, 0.26)	0.42
Fried Frailty Score (ref=0)		
1	−0.32 (−0.81, 0.18)	
2	−0.14 (−0.70, 0.41)	0.65
3	−0.67 (−0.95, 0.81)	
2017–18 HD influenza vaccine (ref=SD)	−0.90 (−1.78, −0.02)	**0.04**
Baseline log_2 HAI titer	−0.20 (0.10)	**0.04**
B/Colorado		
Age	−0.00 (0.01)	0.80
Non-white race (ref=white)	−0.11 (−0.73, 0.50))	0.71
Female sex (ref=male)	0.15 (−0.43, 0.74)	0.60
BMI	0.01 (0.02)	0.58
Obesity (ref=BMI <30)	−0.31 (−0.85, 0.23)	0.26
Diabetes (ref=non-diabetic)	0.04 (−0.53, 0.61)	0.90
Fried Frailty Score (ref=0)		
1	−0.05 (−0.70, 0.60)	

Variables	Beta (SE or 95% CI) *	p-value
2	−0.29 (−1.01, 0.43)	0.70
3	−0.57 (−1.71, 0.58)	
2017–18 HD influenza vaccine (ref=SD)	−4.08 (−10.0, 1.84)	0.17
Baseline log_2 HAI titer	−0.31 (0.08)	**<0.001**
B/Phuket		
Age	0.00 (0.01)	0.95
Non-white race (ref=white)	−0.57 (−1.14, −0.01)	0.05
Female sex (ref=male)	0.27 (−0.26, 0.81)	0.32
BMI	0.03 (0.02)	0.15
Obesity (ref=BMI <30)	−0.34 (−0.83, 0.16)	0.18
Diabetes (ref=non-diabetic)	−0.31 (−0.83, 0.21)	0.24
Fried Frailty Score (ref=0)		
1	−0.05 (−0.64, 0.55)	
2	0.26 (−0.39, 0.41)	0.51
3	−0.67 (−0.95, 0.81)	
2017–18 HD influenza vaccine (ref=SD)	−0.19 (−1.46, 1.08)	0.77
Baseline log_2 HAI titer	−0.22 (0.08)	**0.01**

* Continuous variables include the standard error (SE), categorical variables include the 95% Confidence Interval (CI).

Table 4.

Multivariable linear regression of the relationship of age and BMI on 2018–19 GMFR vaccine response*

Variables	Beta (SE)	p-value
A(H1N1)/Michigan		
Age	−0.04 (0.01)	**0.003**
BMI	0.03 (0.02)	0.20
Baseline log_2 HAI titer	−0.25 (0.08)	**<0.001**
A(H3N2)/Singapore		
Age	−0.01 (0.01)	0.18
BMI	−0.01 (0.02)	0.50
Baseline log_2 HAI titer	−0.19 (0.10)	0.05
B/Colorado		
Age	0.01 (0.01)	0.32
BMI	0.01 (0.02)	0.53
Baseline log_2 HAI titer	−0.33 (0.09)	**<0.001**
B/Phuket		
Age	0.00 (0.01)	0.84
BMI	0.04 (0.02)	0.06
Baseline log_2 HAI titer	−0.24 (0.08)	**0.005**

*Models adjusted for baseline log2 titers

Table 5.

Influenza virus strains included in the 2017–18 and 2018–19 influenza vaccine

2017–2018	2018–2019
A/Michigan/45/2015 (H1N1)pdm09-like virus	A/Michigan/45/2015 (H1N1)pdm09-like virus
A/Hong Kong/4801/2014(H3N2)-like virus	A/Singapore/INFIMN-16-0019/2016 A(A3N2)-like virus
B/Brisbane/60/2008-like virus (Victoria lineage)	B/Colorado/06/2017-like virus (Victoria lineage)
B/Phuket/3073/2013-like * virus (Yamagata lineage)	B/Phuket/3073/2013-like * virus (Yamagata lineage)

* in QIV; 2017–18 Fluzone Standard Dose was QIV and Fluzone High Dose was TIV