

Background: Globally, prevention and control of seasonal influenza has faced many challenges in the selection of a vaccine composition that antigenically matches circulating viruses. A universal influenza vaccine approach that targets small conserved influenza virus epitopes/peptides such as the extracellular domain of Matrix 2 (M2e) and induces broadly reactive antibodies may be helpful for both seasonal influenza outbreaks and pandemics. Here we report the ability of two composite peptide vaccines, individually and in combination, to induce broadly reactive antibodies that have binding and functional activity across several contemporary influenza strains in Group 1 and 2.

Methods: Mice were immunized with peptide composite vaccines against Hemagglutinin (HA), Neuraminidase (NA) and M2e, individually and in combination. Peptide composite vaccines, conjugated to CRM were administered subcutaneously with adjuvant and at least two booster doses. Serum antibody titers were analyzed using an anti-influenza ELISA for binding activity to peptides and live influenza viruses (H3N2 and H1N1) and functional activity was evaluated *in vitro* using Microneutralization, Hemagglutination Inhibition (HAI), and Antibody-Dependent Cellular Cytotoxicity (ADCC) assays.

Results: Mice given the peptide composite conjugate vaccines, individually and in combination, had strong humoral responses producing high serum anti-influenza titers post-booster immunization. Anti-influenza serum antibodies demonstrated functional activity against influenza A (H3N2 and H1N1) contemporary strains showing neutralization, HAI and ADCC activity.

Conclusion: Peptide conjugate vaccines were highly immunogenic in mice. Broadly reactive serum antibodies against the peptides and live influenza viruses were detected. These vaccines individually or in combination, induced antibodies that demonstrated functional activity against contemporary influenza strains in Group 1 and 2 and induced functional anti-influenza monoclonal antibodies. A vaccine that targets one or more HA, NA and M2e influenza epitopes may more closely approach the goal for a true universal influenza vaccine. *In vivo* protection studies are currently being designed.

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2753. Induction of Broadly Cross-Reactive Immune Responses Against A(H3N2) Viruses: Results of a Phase 2 Trial of a Novel Recombinant Hemagglutinin Saponin-Adjuvanted Nanoparticle Seasonal Influenza Vaccine

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Background: We developed a recombinant saponin-adjuvanted (Matrix-M1) quadrivalent hemagglutinin nanoparticle influenza vaccine (qNIV; NanoFlu) for older adults to address two impediments to efficacy of current, predominantly egg-derived, seasonal influenza vaccines: (1) limited protection against antigenic drift variants, particularly H3N2 viruses; and (2) antigenic mismatch between vaccine and circulating strains due to egg-adaptive mutations arising during manufacturing. In a prior Phase 1 trial, we showed that qNIV induced robust, broadly cross-reactive antibody responses against multiple antigenically drifted H3N2 viruses, which were 47–64% better than the egg-derived comparator trivalent high-dose inactivated influenza vaccine (IIV3-HD; Fluzone-High Dose). We undertook a Phase 2 trial to optimize the formulation of qNIV, and to compare qNIV immune responses to those of IIV3-HD and quadrivalent recombinant influenza vaccine (RIV4; FluBlok).

Methods: In this phase 2 dose and formulation finding RCT, we randomized 1,375 subjects aged ≥65 years to be immunized with 1 of 7 test vaccines: 5 different formulations of qNIV, IIV3-HD, or RIV4; and assessed wild-type hemagglutinin-inhibition (wt-HAI) and microneutralization (wt-MN) antibody responses (Day 0/28/56).

Results: Matrix-M1-adjuvanted qNIV induced 15–29% higher wt-HAI titers across 5 vaccine homologous or drifted H3N2 strains at Day 28 relative to unadjuvanted qNIV (statistically significantly superior for 5 of 6 strains tested). At Day 28, several qNIV formulations induced significantly superior wt-HAI titers vs. IIV3-HD (39–45%, 17–22%, and 44–48% greater titers for homologous A/Singapore/INF16H-16-0019/2016—H3N2, historic-drifted A/Switzerland/9715293/2013—H3N2, and forward-drifted A/Wisconsin/19/2017—H3N2, respectively); and comparable HAI titers vs. RIV4. Wt-MN and wt-HAI data showed concordant patterns across treatment groups.

Conclusion: qNIV induced superior wt-HAI antibody responses vs. IIV3-HD against homologous or drifted H3N2 viruses and similar responses to RIV4. qNIV may address several critical challenges confronting current egg-derived influenza vaccines, especially in the older adult population.

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2754. Phase 1 Trial of an mRNA-Based Combination Vaccine Against hMPV and PIV3

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Background: Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) are important causes of upper and lower respiratory tract infections, particularly in young children. Despite their public health impact, no effective therapeutic or preventive options are available. mRNA-1653 is a mRNA-based investigational combination vaccine against hMPV and PIV3, and consists of two distinct mRNA sequences encoding the fusion proteins of hMPV and PIV3, co-formulated in lipid nanoparticles.

Methods: This phase 1, first-in-human, randomized, placebo-controlled, dose-ranging study assesses the safety and immunogenicity of mRNA-1653 in healthy adults aged 18–49. The 124-subject study evaluates four vaccine dose levels (25, 75, 150, and 300 µg) administered intramuscularly in either single-dose or two-dose (Day 1, Month 1) vaccination schedules, with follow-up through 1 year after the last vaccination. Objectives include safety and immunogenicity measured by hMPV- and PIV3-specific neutralizing antibody titers.

Results: An interim analysis demonstrated that the mRNA-1653 vaccine was generally well-tolerated at all dose levels. Neutralizing antibodies against hMPV and PIV3 were present at baseline in all subjects, consistent with prior exposure to both viruses. A single dose of mRNA-1653 boosted serum neutralization titers against both hMPV and PIV3, and the magnitude of boosting was similar at all dose levels. The geometric mean ratio of Month 1 to baseline titers was approximately 6 for hMPV and 3 for PIV3. A second dose of mRNA-1653 at Month 1 was not associated with further increase of hMPV or PIV3 neutralization titers.

Conclusion: mRNA-1653 is well-tolerated and induces a functional immune response, and is therefore a promising vaccine candidate for the prevention of pediatric respiratory tract diseases caused by hMPV and PIV3.

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2755. Phase 1/2, First-in-Human Study of the Safety, Tolerability, and Immunogenicity of an RSV Prefusion F-Based Subunit Vaccine Candidate

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Background: The respiratory syncytial virus (RSV) fusion glycoprotein (F) is a molecule that fuses the viral and host cell membranes during virus entry as it rearranges from a meta-stable prefusion to a stable postfusion conformation. Using structure-guided design, Pfizer engineered a prefusion RSV F subunit vaccine antigen with stable and well-characterized conformational homogeneity.

Methods: We report results of a 1,182 subject, first-in-human, phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, and immunogenicity of the Pfizer RSV vaccine candidate in healthy men and non-pregnant women from 18 to 85 years of age. The study compares three dosages of the vaccine candidate, with and without aluminum hydroxide, and also compares immunization with the RSV vaccine candidate alone or concomitantly with influenza vaccine. The study is ongoing to collect antibody persistence and additional safety data.

Results: The data, which are currently available for the 18- to 49-year-old subgroup, demonstrate an excellent safety and tolerability profile. Immunization with the various formulations of the vaccine candidate elicited RSV 50% neutralization titer geometric mean fold rises (GMFRs) of 10.6–17.2 for subgroup A and 10.4–19.8 for subgroup B, measured one month after immunization, with evidence of a dose–response.

Conclusion: The 10- to 20-fold increases in neutralizing antibody titers elicited by this vaccine with a stable prefusion F antigen represent a step change relative to the historical performance of vaccine candidates, such as Wyeth's PPF, with F antigens that were not stabilized in the prefusion conformation (Simoes et al., Vaccine 20:954–60, 2002). The data strongly support development of this vaccine candidate to prevent RSV disease in infants, by immunizing pregnant women, and to prevent RSV disease in older adults, by direct immunization.

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2756. Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED), Influenza-Like-Illnesses (ILIs) Sub-Study at the Marine Corps Recruit Depot-San Diego, CA (MCRD-SD) During the 2018–2019 Influenza Season

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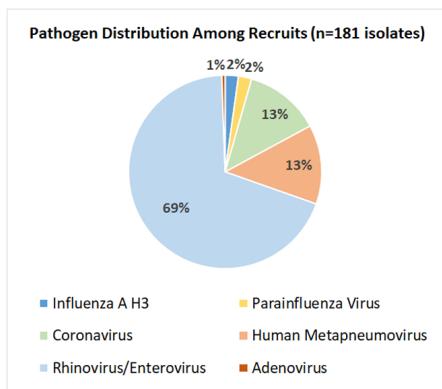
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Background: Military recruits suffer high rates of influenza and influenza-like illness (ILI) during training. ILIs may lead to morbidity, lost training time, and hospitalization. We evaluated the incidence and clinical outcomes of ILI among recruits at Marine Corps Recruit Depot San Diego (MCRD-SD) in a prospective trial of influenza vaccine efficacy.

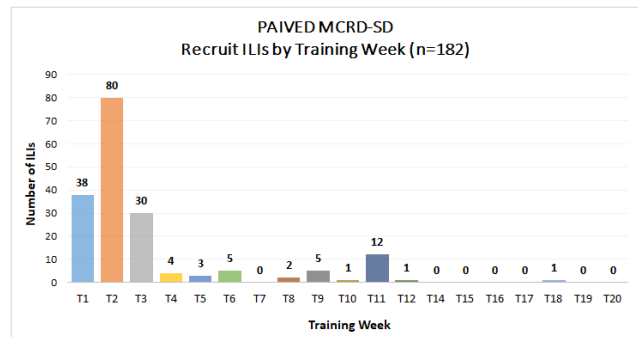
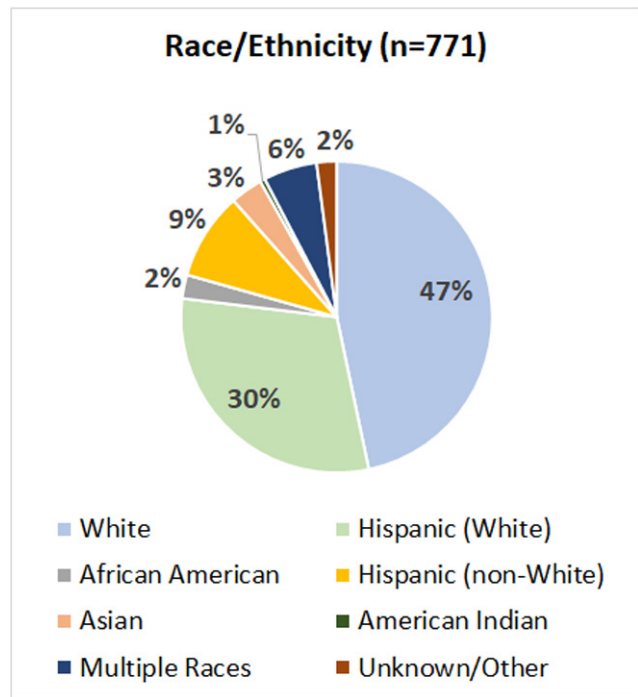
Methods: Recruits at MCRD-SD were enrolled to compare the effectiveness of 3 types of FDA approved influenza vaccine: Afluria[®], an egg-based vaccine; Flucelvax[®], a cell-culture-derived vaccine; and Flublok[®], a recombinant vaccine. Four companies of recruits were enrolled sequentially from 28 November 2018 to 19 December 2018, then randomized in a 1:1:1 ratio. Participants were followed for 18 weeks at MCRD-SD and Camp Pendleton. All participants who presented with ILI symptoms at medical care sites underwent viral diagnostic testing in addition to immunologic studies. Recruits were excluded from participation if <18 years of age, if previously vaccinated in the 2018–2019 season, or if reporting allergy to the vaccines.

Results: Of 1338 recruits approached, 771 (57.6%) participants consented for enrollment. All recruits were men between 18 and 28 years. There were 182 ILIs amongst 177 recruits (23% of 771 recruits). Nasal swabs were obtained in 180/182 cases (99%). Mean duration of ILI symptoms was 7 days. Mean days of fever was 4. Subjects reported a total 168 days of reduced training (range 0–14 days; mean 0.9 days). There were 47 total days of missed training for all subjects (range of 0–4 days; mean 0.3 days/subject). There were no hospitalizations related to ILIs. Approximately 82% (148/182) of ILIs presented within the first 3 weeks of training; 44% (80/182) of ILIs occurred during the second week of training. PCR- nasal swabs results; race/ethnicity data, and frequency of ILI mapped to week of training are illustrated below.

Conclusion: ILIs can negatively impact training effectiveness. Days lost to training from ILIs and hospitalizations can prevent successful completion of training with impact on military readiness. PAIVED may inform the DoD on future strategies to minimize influenza and other respiratory threats in recruit military populations. Influenza vaccine effectiveness will be reported separately.



*Additional pathogens tested for that yielded 0 positives include: Influenza A H1, Influenza B, Respiratory Syncytial Virus, Human Bocavirus, Chlamydia pneumoniae, and Mycoplasma pneumoniae.



Disclaimer

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2757. Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED): Immunogenicity Sub-Study

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