2750. Sequential Influenza A H1N1 and Influenza A H3N2 Challenge Infections in Healthy Volunteers

Alison Han, MD, MS; Luca Giurgea, MD; Adriana Cervantes-Medina, BS; Kristina Edwards, BS; Luz Angela Rosas, MS, MLS(ASCP)CM; Lindsay Czajkowski, MSN, NP-C; Holly Ann Baus, RN, MSN; Rani Athota, PhD; Susan Reed, BA, CRC; Jeffery Taubenberger, MD, PhD; Matthew Memoli, MD, MS; NIH, Rockville, Maryland

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

Background: Seasonal influenza causes significant annual morbidity and mortality. The effects of yearly exposures on immunity are not clear and recent observations have demonstrated that long lasting protection against a matched strain may not naturally occur. The 2018–2019 influenza season consisted of an initial peak of H1N1 infections followed by a wave of H3N2 infections. These consecutive waves raise questions about how influenza immunity is affected by sequential exposure to different influenza strains. Challenge studies provide a unique opportunity to study this phenomenon. Here we describe a subset of participants who were sequentially infected in two separate challenge studies with wild-type H1N1 and H3N2 viruses.

Methods: Healthy volunteers completed two sequential influenza challenge studies at the NIH Clinical Center. Participants were inoculated with reverse genetics, cell-based, GMP wild-type influenza viruses, A(H1N1)pdm09 and A(H3N2) strains. Participants remained isolated in the hospital for a minimum of 9 days and were monitored daily for viral shedding and clinical symptoms. After discharge, participants were followed for 2 months.

Results: Between 2014 and 2017, 14 healthy volunteers were exposed to Influenza A(H1N1) and Influenza A(H3N2). Time between infections ranged from 2 months to 2 years. Thirteen (93%) participants developed confirmed influenza infection after H1N1 challenge and 9 (64%) after H3N2 challenge. Eight (57%) participants developed confirmed infections after both exposures. Variable degrees of symptoms, shedding, and disease severity were observed. Systemic antibody responses to the HA and NA of both H1N1 and H3N2 varied over time during these sequential infections.

Conclusion: More than half of all participants who completed 2 sequential H1N1 and H3N2 challenge studies demonstrated confirmed infection to both viruses. These sequential infections had varying effects on the disease experienced and the immunity that developed after infection. These observations are important in understanding the impact of sequential exposures on influenza immunity.

Disclosures. **All authors:** No reported disclosures.

2751. Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED): Methods

Timothy Burgess, MD, MPH[1,2]; Stephanie Richard, PhD, MHS[3]; Limone Collins, MD[4,5,6]; Rhonda Colombo, MD, MHS[7,8,9,10]; Anuradha Ganesan, MBBS, MPH[11,12]; Casey Geaney, MD[13]; Tahaniyat Lalani, MBBS[14,15,16]; Ana E. Markelz, MD[17]; Ryan Maves, MD[18,19,20]; Katrin Mende, PhD[21,22,23,24]; Christina Schofield, MD[25]; Srihari Seshadri, MBBS, MPH[26]; Christina Spooner, MS[26]; Gregory Utz, MD[27,28,29]; Tyler Warkentien, MD, MPH[30]; Christian L. Coles, PhD[31,32]; [1]Infectious Disease Clinical Research Program, Bethesda, Maryland; [2]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, [3]Henry M. Jackson Foundation, Bethesda, Maryland; [4]Immunization Health Branch, Defense Health Agency, Bethesda, Maryland, [5]Immunization Health Branch, Defense Health Agency, Falls Church, Virginia, [6]Immunization Health Branch, Defense Health Agency, San Diego, California; [7]Madigan Army Medical Center, Tacoma, WA, [8]Infectious Disease Clinical Research Program, Bethesda, MD, [9]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, Maryland, [10]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Tacoma, Washington; [11]Infectious Disease Clinical Research Program and the Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, [12]Walter Reed National Military Medical Center, Bethesda, Maryland; [13]Walter Reed National Military Medical Center, Bethesda, Maryland; [14]Infectious Disease Clinical Research Program, Bethesda, Maryland, [15]The Henry M. Jackson Foundation, Bethesda, Maryland, [16]Naval Medical Center, Portsmouth, Virginia; [17]Brooke Army Medical Center, Fort Sam Houston, Texas; [18]Naval Medical Center San Diego, San Diego, California, [19]Infectious Disease Clinical Research Program, Bethesda, Maryland, [20]Infectious Disease Clinical Research Program, San Diego, California, [21]Infectious Disease Clinical Research Program, Bethesda, Maryland, [22]The Henry M. Jackson Foundation, Bethesda, Maryland, [23]Brooke Army Medical Center, Fort Sam Houston, Texas, [24]Brooke Army Medical Center, San Antonio, Texas, [25]Madigan Army Medical Center, Tacoma, Washington, [26]Immunization Health Branch, Defense Health Agency, Falls Church, Virginia, [27]Naval Medical Center San Diego, Infectious Disease Clinical Research Program, Bethesda, MD, [28]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, Maryland, [29]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., San Diego, California, [30]Naval Medical Center Portsmouth, Portsmouth, Virginia, [31]Infectious Disease Clinical Research Program, Bethesda, MD, [32]The Henry M. Jackson Foundation, Bethesda, Maryland

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

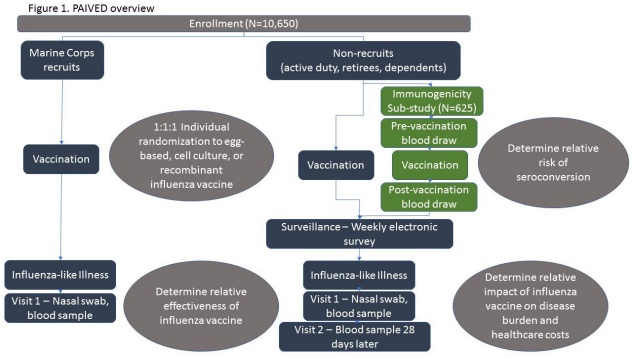
Background: Most influenza vaccines come from inactivated virus grown in egg culture, and studies suggest that egg-adapted virus may have decreased immunogenicity in humans for certain influenza A strains. Cell culture-based and recombinant vaccines may be more immunogenic, but comparative studies are lacking. We are conducting a randomized, controlled trial of 3 FDA-licensed influenza vaccines (cell culture, recombinant, and egg culture) to assess differences in immunogenicity and effectiveness in adults.

Methods: A total of 10,650 eligible adults will be individually randomized 1:1:1 (cell culture, recombinant, or egg-based vaccine) over 2 influenza seasons (2018–2019 and 2019–2020) at military facilities in geographically diverse locations in the US Participants who are not military recruits will report the presence or absence of ILI symptoms on a weekly basis through an automated electronic (text message or email) survey; those who experience ILI symptoms will be scheduled for two in-person visits. Military recruits who experience an ILI report will report directly to clinic and will not receive weekly surveillance reminders (Figure 1).

Results: Enrollment for year 1 of PAIVED occurred November 7 to December 31, 2018 at 5 military bases. During this season, 1,623 participants were enrolled, among whom 34% were randomized to receive cell culture vaccine, 33% to recombinant vaccine, and 33% to egg-based vaccine. The participants were 61% active military, 19% retired military, and 20% military dependents. One quarter of the participants were women, and the participants were 18–88 years old, median 26 years of age. Among the 1,559 participants with complete data, 324 (21%) experienced ILI at least once. Blood and swab samples were successfully collected at visit 1 from 93% of the participants with case-defined ILIs.

Conclusion: The initial phase of PAIVED successfully enrolled and randomized 1,623 participants during the 2018/2019 influenza season. Follow-up of this season's participants is on-going. PAIVED will apply lessons learned during the 2018/2019 influenza season to the next season's study implementation, with the goal of enrolling more than 9,000 additional participants through increasing the number of individuals enrolled at some sites and adding new sites to the trial.

Figure 1. PAIVED overview



Disclaimer
This study IDCRP-120 was conducted by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USUHS) through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been funded in whole, or in part, with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement (12012-001-07000) and the Defense Health Program.

The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views, opinions or policies of Uniformed Services University of the Health Sciences (USUHS), The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense (DoD), or the Departments of the Army, Navy, or Air Force or Brooke Army Medical Center. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

The authors have no conflict of interest to disclose.

The investigators have adhered to the policies for protection of human subjects as prescribed in 45CRF46.

Disclosures. **All authors:** No reported disclosures.

2752. Peptide Vaccines Utilizing Conserved Hemagglutinin, Neuraminidase, and Matrix Ectodomain Influenza Epitopes Demonstrate Functional Activity Against Group 1 and 2 Influenza Strains

Clara J. Sei, MPH[1]; Nimisha Rikhi, PhD[2]; Rachmat Hidajat, PhD[2]; Richard F. Schuman, PhD[2]; Kevin Muema, BSc[2]; Jasmine M. Mutunga, BSc[2]; Luke T. Daum, PhD[2]; Gerald W. Fischer, MD[2]; [1]Longhorn Vaccines and Diagnostics, LLC, Gaithersburg, Maryland; [2]Antibody and Immunoassay Consultants, Rockville, Maryland

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

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.

Disclosures. **All authors:** No reported disclosures.

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

Vivek Shinde, MD, MPH; Rongman Cai, PhD; Joyce S. Plested, PhD;
Bin Zhou, PhD; Haixia Zhou, PhD; Mingzhu Zhu, PhD; Nan Wang;
Shane Cloney-Clark; Sapeck Agrawal, PhD;
Michelle S. Spindler, MS, CCRA; Nita Patel, MS; Michael Massare, PhD;
Gale Smith, PhD; D. Nigel. Thomas, PhD; Iksung Cho, MS;
Louis F. Fries, III, MD; Gregory M. Glenn, MD; Novavax, Inc., Gaithersburg, Maryland

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

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/INFIMH-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.

Disclosures. **All authors:** No reported disclosures.

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

Christine Shaw, PhD; Heather Lee, BS; Conor Knightly, MPH;
Shiva Kalidindi, MBA; Tal Zaks, MD, PhD; Igor Smolenov, MD, PhD;
Lori Panther, MD, MPH; Moderna, Cambridge, Massachusetts

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

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.

Disclosures. **All authors:** No reported disclosures.

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

Beate Schmoele-Thoma, MD[1]; Ann R. Falsey, MD[2]; Edward E. Walsh, MD[3];
Kena Swanson, PhD[4]; Agnieszka Zareba, MD, PhD[4]; David Cooper, PhD[4];
William C. Gruber, MD[5]; Kathrin U. Jansen, PhD[4]; David Radley, MSc[4];
Daniel Scott, MD[4]; Philip R. Dormitzer, MD, PhD[6]; [1]Pfizer Pharma GmbH, Berlin, Germany; [2]University of Rochester, Rochester General Hospital, Rochester, New York; [3]University of Rochester, Rochester, New York; [4]Pfizer, Pearl River, New York; [5]Pfizer Inc., Pearl River, New York; [6]Pfizer Vaccine Research and Development, Pearl River, New York

Session: 278. Vaccines: Influenza
Saturday, October 5, 2019: 12:15 PM

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 PFP, 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.

Disclosures. **All authors:** No reported disclosures.

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

Ryan Maves, MD[1,2,3]; Gregory Utz, MD[4,5,6]; Stephanie Richard, PhD, MHS[7,8];
Melissa Smith, BS[9,10]; Limone Collins, MD[11,12,13]; Christopher Myers, PhD[14];
Paul Graf, PhD[14]; Rhonda Colombo, MD, MHS[15,16,17,18];
Anuradha Ganesan, MBBS, MPH[19,20]; Casey Geaney, MD[21];
Tahaniyat Lalani, MBBS[22,23,24]; Ana E. Markelz, MD[25];
Katrin Mende, PhD[26,27,28,29]; Christina Schofield, MD[30];
Srihari Seshadri, MBBS, MPH[31]; Christina Spooner, MS[31];
Tyler Warkentien, MD, MPH[32]; Christian L. Coles, PhD[33,34];
Timothy Burgess, MD, MPH[35]; [1]Naval Medical Center San Diego, San Diego, California, [2]Infectious Disease Clinical Research Program, Bethesda, Maryland, [3]Infectious Disease Clinical Research Program, San Diego, California; [4]Naval Medical Center San Diego, Infectious Disease Clinical Research Program, Bethesda,