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Background. MenACYW-TT (MenQuadfi®, Sanofi) is a quadrivalent (serogroups A, C, W, and Y) meningococcal tetanus toxoid conjugate vaccine. It was recently approved for use in persons aged ≥ 2 years in the US and persons aged ≥ 1 year in Europe and certain other countries; trials in infants as young as 6 weeks are ongoing. This study evaluated seroresponse after a MenACYW-TT booster given to adults who received either quadrivalent meningococcal polysaccharide vaccine (MSPV4) or MenACYW-TT three years earlier at age ≥ 56 years. Immune persistence up to 7 years after primary vaccination was also evaluated.

Methods. This was a Phase 3 randomized, open-label study (NCT04142242) of adults aged ≥ 59 years who participated in previous studies of MenACYW-TT vs MPSV4 (NCT01732627 and NCT02842866). The study was conducted in the US and Puerto Rico. Immune response and persistence were assessed with a serum bactericidal assay using human complement (hSBA). Sufficiency of the vaccine seroresponse was considered demonstrated if the lower limit of the 1-sided 97.5% CI for the percentage of subjects with an hSBA vaccine seroresponse against serogroups A, C, W and Y was > 40%. Safety data were collected up to 30 days after booster vaccination.

Results. A total of 471 persons were enrolled. Sufficiency of a MenACYW-TT booster was demonstrated for MPSV4- and for MenACYW-TT-primed subjects. hSBA seroresponse rates were higher among MenACYW-TT- vs MPSV4-primed subjects (79.3%–93.1% vs 49.2%–60.8%, respectively). Three to 7 years after primary vaccination, hSBA geometric mean titers (GMTs) and seroprotection rates (SPRs) declined in both MenACYW-TT- and MPSV4-primed subjects, with hSBA GMTs and SPRs for serogroups C, W, and Y generally remaining higher for MenACYW-TT- vs MPSV4-primed subjects; those for serogroup A were similar regardless of priming vaccine. Rates of adverse events following a MenACYW-TT booster were similar between MenACYW-TT- and MPSV4-primed subjects. No safety concerns were identified.

Conclusion. A MenACYW-TT booster was well tolerated and immunogenic when administered to either MPSV4- or MenACYW-primed adults aged ≥ 59 years. Up to 7 years after primary vaccination, immune persistence for serogroups C, W, and Y tended to be greater for MenACYW-TT vs MPSV4.

Disclosures. **Corwin A. Robertson, MD, MPH, FACP**, **Sanofi Pasteur** (Employee, Other Financial or Material Support, Stockholder) **Alexandre Selmani, PhD**, **Sanofi Pasteur** (Employee) **Katherine Galarza, MD**, **Sanofi Pasteur** (Employee) **Philipp Oster, MD**, **Sanofi Pasteur** (Employee, Stockholder)

1047. Development of a Next Generation 30^{+} Valent Pneumococcal Conjugate Vaccine (VAX-XP) Using Site-Specific Carrier Protein Conjugation

Chris Behrens, PhD[1]; Jeff Fairman, PhD[1]; Paresh Agarwal, PhD[1]; Shylaja Arulkumar, MS[1]; Sandrine Barbanel, MS[1]; Leslie Bautista, n/a[1]; Aym Berges, PhD[1]; John Burky, BS[1]; Peter Davey, MS[1]; Chris Grainger, PhD[1]; Sherry Guo, PhD[1]; Sam Iki, MS[1]; Mark Iverson, BS[1]; Neeraj Kapoor, PhD[1]; Olivier Marcq, PhD[1]; Thi-Sau Migone, PhD[1]; Lucy Pill, MS[1]; Mohammed Sardar, n/a[1]; Paul Sauer, MBA[1]; James Wassil, MS MBA[1]; [1]Vaxcyte, Inc, Foster City, California

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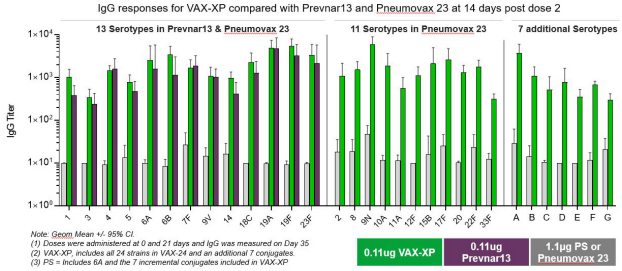
Background. Due to the diversity of serotypes, exacerbated by the phenomenon of serotype replacement, there remains an unmet medical need for a pneumococcal conjugate vaccine (PCV) containing additional serotypes. Using a cell-free protein synthesis (CFPS) platform to produce an enhanced carrier protein (eCRM®) based on the CRM_{197} sequence, Vaxcyte is developing a PCV encompassing over 30 serotypes. The eCRM carrier protein contains multiple insertions of the non-native amino acid para-azidomethyl-L-phenylalanine (pAMF) that facilitates site-specific conjugation of the pneumococcal polysaccharides (PS) to eCRM. Unlike conventional methodologies, site-selective conjugation enhances process consistency and increases capacity for inclusion of additional serotypes in a PCV without promoting carrier suppression. Using this platform, the aim of the current study was to employ CFPS technology to construct a 31-valent PCV and evaluate its immunogenicity in New Zealand White (NZW) rabbits.

Methods. The eCRM carrier protein was individually conjugated to each of 31 selected pneumococcal PSs using copper-free click chemistry to produce 31 Conjugate Drug Substances (DS), which were then mixed with aluminum phosphate to produce the VAX-XP Drug Product. 24 of the DS conjugates in VAX-XP were generated at manufacturing scale. Two doses of VAX-XP were administered to NZW rabbits at 0 and 21 days to assess its ability to elicit anti-capsular IgG antibodies. Additionally, rabbits were also administered either Prevnar13 or a mixture of Pneumovax 23 and 8 incremental PS in isotonic saline, as comparators.

Results. VAX-XP showed conjugate-like immune responses for all 31 serotypes, as demonstrated by superior responses to PS-based vaccines and comparable responses to Prevnar13. IgG responses for VAX-XP compared with Prevnar13 and Pneumovax 23 at 14 days post dose 2



Conclusion. These results demonstrate that increasing the number of pneumococcal serotypes does not result in immunological attenuation in any of the serotypes contained in VAX-XP relative to the current standard of care. Furthermore, the data confirm the scalability and reproducibility of the CFPS platform in the production of VAX-XP conjugates, creating the foundation for a next generation broad-valency PCV.

Disclosures. **Chris Behrens, PhD**, **Vaxcyte, Inc.** (Employee) **Jeff Fairman, PhD**, **Vaxcyte, Inc.** (Employee) **Paresh Agarwal, PhD**, **Vaxcyte, Inc.** (Employee) **Shylaja Arulkumar, MS**, **Vaxcyte, Inc.** (Employee) **Sandrine Barbanel, MS**, **Vaxcyte, Inc.** (Employee) **Leslie Bautista, n/a**, **Vaxcyte, Inc.** (Employee) **Aym Berges, PhD**, **Vaxcyte, Inc.** (Employee) **John Burky, BS**, **Vaxcyte, Inc.** (Employee) **Peter Davey, MS**, **Vaxcyte, Inc.** (Employee) **Chris Grainger, PhD**, **Vaxcyte, Inc.** (Employee) **Sherry Guo, PhD**, **Vaxcyte, Inc.** (Employee) **Sam Iki, MS**, **Vaxcyte, Inc.** (Employee) **Mark Iverson, BS**, **Vaxcyte, Inc.** (Employee) **Neeraj Kapoor, PhD**, **Vaxcyte, Inc.** (Employee) **Olivier Marcq, PhD**, **Vaxcyte, Inc.** (Employee) **Thi-Sau Migone, PhD**, **Vaxcyte, Inc.** (Employee) **Lucy Pill, MS**, **Vaxcyte, Inc.** (Employee) **Mohammed Sardar, n/a**, **Vaxcyte, Inc.** (Employee) **Paul Sauer, MBA**, **Vaxcyte, Inc.** (Employee) **James Wassil, MS MBA**, **Vaxcyte, Inc.** (Employee)

1048. Double-Blind, Randomized, Placebo-Controlled Phase 2b Multicenter Trial of V160, a Replication-Defective Human Cytomegalovirus (CMV) Vaccine

Rituparna Das, MD[1]; Daniel Blazquez-Gamero, MD[2]; David I. Bernstein, MD MA[3]; Soren Gantt, MD[4]; Oliver Bautista, PhD[1]; Karen Beck, RN, BSN[1]; Anthony Conlon, PhD[1]; Daniel Rosenbloom, PhD[1]; Dai Wang, PhD[1]; Michael Ritter, BA[1]; Beth Arnold, MS[1]; Paula Annunziato, MD[1]; Kevin Russell, MD, MTM&H[5]; [1]Merck & Co., Inc., Kenilworth, New Jersey; [2]Pediatric Infectious Diseases Unit, Hospital Universitario; [12] de Octubre and Universidad Complutense, Instituto de Investigación Hospital; [12] de Octubre (imas12) RECLIP, Madrid, Madrid, Spain; [3]Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH; [4]CHU Sainte-Justine Research Centre, Université de Montréal, Montreal, Quebec, Canada; [5]Merck and Co Inc., North Wales, PA

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Background. Preventing congenital cytomegalovirus infection (CMVi) is an important unmet need. Natural maternal immunity to CMV acquired prior to pregnancy appears to reduce fetal transmission. In a Phase 1 trial, V160, a replication-defective CMV vaccine expressing the pentameric complex, induced humoral and cell-mediated immune (CMI) responses comparable to natural immunity.

Methods. Healthy, CMV-seronegative women aged 16–35 years were randomized 1:1:1 to receive double-blind V160 in a 3- or 2-dose regimen or placebo. Primary and secondary endpoints were efficacy in reducing the incidence of CMVi with 3-dose or 2-dose regimens of V160 vs placebo, respectively, using a fixed-event design. Monthly urine and saliva samples were collected to identify CMVi by polymerase chain reaction (PCR) with a single positive sample considered evidence of infection. Immunoglobulin G (IgG) binding to glycoprotein B (gB) and CMV-specific neutralizing antibody (NAb) were measured in all participants, and CMI responses were measured in a subset. Injection-site and systemic adverse events (AEs) were collected for 5 days and 14 days, respectively, after each vaccination and serious AEs were collected for the trial duration.

Results. 2200 women from 7 countries were enrolled (of 7458 screened). Over 80% of participants received all doses, and compliance with saliva and urine samples was > 95%. Vaccine efficacy (VE) of 42.4% (95% CI -13.5, 71.1%) was demonstrated in the 3-dose group vs placebo. In the 2-dose group, VE was -32.0% (95% CI -135.0, 25.0%). Both the quantity and duration of CMV shedding in urine and saliva among cases of CMVi decreased in the 3-dose, but not the 2-dose group vs placebo. Both V160 regimens elicited humoral and CMI responses detected by CMV-specific NAb, gB IgG, and ELISpot, which peaked at Month 7 and continued to be detectable at Month 24. Mild to moderate AEs were more frequently reported in V160 vs placebo recipients, but no vaccine-related serious AEs or deaths were reported.

Conclusion. V160 was well tolerated and immunogenic, but neither the 3-dose nor 2-dose regimen demonstrated significant efficacy against CMVi as defined in this trial. The quantity and duration of CMV shedding was reduced in the 3-dose group, suggesting V160 may improve immune control of viral replication after CMVi.

Disclosures. **Rituparna Das, MD**, **Merck & Co, Inc.** (Employee) **Daniel Blazquez-Gamero, MD**, **MSD** (Other Financial or Material Support, Fees for lectures in educational activities) **Soren Gantt, MD**, **Altona Diagnostics** (Research Grant or Support)**Merck** (Consultant, Grant/Research Support)**Meridian Biosciences** (Research Grant or Support)**Moderna** (Consultant, Research Grant or Support)**VBI Vaccines Inc** (Research Grant or Support) **Oliver Bautista, PhD**, **Merck & Co, Inc.** (Employee) **Karen Beck, RN, BSN**, **Merck & Co, Inc.** (Employee) **Anthony Conlon, PhD**, **Merck & Co, Inc.** (Employee) **Daniel Rosenbloom, PhD**, **Merck & Co, Inc.** (Employee) **Dai Wang, PhD**, **Merck & Co, Inc.** (Employee) **Michael Ritter, BA**, **Merck & Co, Inc.** (Employee) **Beth Arnold, MS**, **Merck & Co, Inc.** (Employee, Shareholder) **Paula Annunziato, MD**, **Merck & Co, Inc.** (Employee) **Kevin Russell, MD, MTM&H**, **Merck & Co., Inc.** (Employee, Shareholder)

1049. Minimal Transient HIV-1 Viremia Following Vaccination Regimens Containing AD26. ZEBOV and MVA-BN-Filo in ART-Suppressed People Living with HIV

Benjamin L. Custer, M.D.[1]; Betty Mwesigwa, MBchB, MSc Clinical Trials[2]; Fredrick Sawe, MBCHB, MMED[3]; Janet Oyieko, MD[4]; Nyanda Ntinginya, MD, MSc, PhD[5]; Ilesh Jani, MD PhD[6]; Michael Iroezindu, MB, BS[7]; Jack Hutter, MD[8]; Linda Jagodzinski, Ph.D.[9]; Georgi Shukarev, MD[10]; Leigh Anne Eller, PhD[11];

Lucy Ward, DMV, Ph.D.[12]; Rachel Overman, MD[12]; Janice M. Rusnak, M.D.[13]; Callie Bounds, Ph.D.[14]; Christopher Badorrek, Ph.D.[15]; Christina Polyak, MD MPH[16]; Allahna L. Esber, PhD[16]; Amber D. Moodley, MPH[17]; Chi Tran, BSN[18]; Auguste Gaddah, PhD[19]; Kerstin Luhn, PhD[20]; Macaya Douoguih, MD, MPH[10]; Cynthia Robinson, MD[20]; Julie A. Ake, MD[21]; [1]Walter Reed National Military Medical Center, Rockville, Maryland; [2]Makerere university Walter Reed Project, Kampala, Kampala, Uganda; [3]Henry M. Jackson Foundation Medical Research International, Kenya; U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA, Kericho, Rift Valley, Kenya; [4]Henry M. Jackson Foundation Medical Research International, Kenya; Kenya Medical Research Institute/U.S. Army Medical Research Directorate-Africa/Kenya, Kisumu, Nyanza, Kenya; [5]National Institute for Medical Research-Mbeya Medical Research Center, Mbeya, Tanzania, Mbeya, Mbeya, Tanzania; [6]Instituto Nacional de Saúde, Maputo, Maputo, Mozambique; [7]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA, Silver Spring, Maryland; [8]Clinical Trials Center, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA, Silver Spring, Maryland; [9]Walter Reed Army Institute of Research, Silver Spring, Maryland; [10]Janssen Vaccines and Prevention, Leiden, Netherlands, Leiden, Zuid-Holland, Netherlands; [11]US Military HIV Research Program/HJF, Bethesda, Maryland; [12]U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical), Fort Detrick, Maryland, USA, Fort Detrick, Maryland; [13]Contract Support for U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical),, Fort Detrick, Maryland; [14]Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical, Fort Detrick, Maryland; [15]Contract Support for U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical), Fort Detrick, Maryland, USA, Fort Detrick, Maryland; [16]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD and Walter Reed Army Institute of Research, Silver Spring, MD, Bethesda, Maryland; [17]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland; Henry M. Jackson Foundation for the Advancement of Military Medicine. Bethesda, Maryland, USA, Rockville, Maryland; [18]HJF/MHRP, Silver Spring, Maryland; [19]Janssen Research and Development, Beerse, Antwerpen, Belgium; [20]Janssen Vaccines and Prevention, Leiden, Zuid-Holland, Netherlands; [21]Walter Reed Army Institute of Research, Silver Spring, MD, Silver Spring, Maryland

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Background. Ebola Virus Disease (EVD) outbreaks primarily occur in the HIV endemic setting of Sub-Saharan Africa. Transient increases in HIV viral load (VL), or blips, have been described following routine vaccinations. We characterized VL blips among PLWH enrolled in a phase 2 trial of a heterologous two-dose EVD vaccine.

Methods. In EBL2003, adult participants with and without HIV were randomized 1:4 to receive placebo or vaccine. Part A in the US studied MVA-BN-Filo followed by Ad26.ZEBOV 14 days later. Part B in Africa evaluated this MVA/Ad26 regimen and also a schedule of Ad26.ZEBOV followed by MVA-BN-Filo 29 days later. VL was assessed at screening, pre-vaccination, and 21, 42, 180, and 365 days post dose 2. Participants with VL < 20 copies/mL at the first 2 visits who received both doses and had complete VL data through 42 days post dose 2 were evaluated. Blips were defined as a post-injection VL ≥ 20 copies/mL no later than 42 days post dose 2, with subsequent return to VL < 20 copies/mL.

Results. A total of 277 PLWH on antiretroviral therapy (ART) were assessed; 73.3% (203) had baseline virologic suppression, and 89.2% (181) of those received both doses with complete VL data for inclusion in the analysis. Overall, 19.9% (36) experienced blips: 20.0% (29) of vaccinees vs 19.4% (7) of placebo recipients (p=1.0). All baseline suppressed participants with post-injection viremia subsequently regained suppression. Among vaccinees, the mean blip VL was 192 copies/mL, and the mean blip duration was 56 days, which was not significantly different from placebo. Of all blips, only 2 were > 1,000 copies/mL. Blips occurred in 24.0% (25) of Ad26/MVA recipients, and 9.7% (4) of MVA/Ad26 recipients (p=0.07). A dose of Ad26 was associated with a blip in 6.9% (10) of recipients vs 13.1% (19) for MVA recipients (p=0.12). Regardless of regimen, dose 1 was associated with a blip in 8.3% (12) of vaccinees, compared to 11.7% (17) of vaccinees for dose 2 (p=0.43).

Conclusion. Among successfully treated PLWH, we observed low magnitude post-dose HIV blips that were not more common in vaccine vs. placebo recipients and did not result in loss of virologic suppression. This data is favorable for the deployment of the EVD vaccines in this trial in areas of high HIV endemicity.

Disclosures. **Benjamin L. Custer, M.D.**, **Alexion Pharmaceuticals** (Shareholder)**Armata Pharmaceuticals** (Shareholder)**Biomarin Pharmaceutical** (Shareholder)**Crispr Therapeutics** (Shareholder)**CVS Health Corp** (Shareholder)**Editas Medicine** (Shareholder)**Gilead** (Shareholder)**Glaxo Smith Kline** (Shareholder)**Hologic Inc** (Shareholder)**Merck** (Shareholder)**Mesoblast LTD** (Shareholder)**Pfizer** (Shareholder)**Sanofi** (Shareholder)**Unitedhealth Group** (Shareholder)**Vertex Pharmaceuticals** (Shareholder) **Georgi Shukarev, MD**, **Janssen** (Employee) **Auguste Gaddah, PhD**, **Janssen Pharmaceutica N.V** (Employee) **Kerstin Luhn, PhD**, **Janssen Vaccines and Prevention** (Employee, Shareholder) **Macaya Douoguih, MD, MPH**, **Janssen** (Employee) **Cynthia Robinson, MD**, **Janssen Vaccines** (Employee)

1050. Phase 3 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by 23valent Pneumococcal Polysaccharide Vaccine 6 Months Later in At-risk Adults Aged 18–49 Years (PNEU-DAY): A Subgroup Analysis by Baseline Risk Factors

Laura Hammitt, MD[1]; Dean Quinn, BSc(Hons), MBChB[2]; Ewa Janczewska, MD, PhD, DSc[3]; Francisco J. Pasquel, MD, MPH[4]; Richard Tytus, BSc Phm, MD[5]; K. Rajender Reddy, MD[6]; Katia Abarca, MD[7]; Ilsiyar M. Khaertynova, MD[8]; Ron Dagan, MD[9]; Rachel Dawson, D.O. MPH[10]; Jennifer McCauley, BSc[10]; Kyeongmi Cheon, Ph.D.[10]; Alison Pedley, PhD[10]; Tina Sterling, BS[10]; Gretchen Tamms, B.S.[10]; Luwy Musey, MD[10]; Ulrike K. Buchwald, MD, MS[10]; [1]Johns Hopkins, Baltimore, MD; [2]P3 Research, Wellington Clinical Trial Research Unit, Wellington, Wellington, New Zealand; [3]The School of Health Sciences in Bytom, Medical University of Silesia, Bytom, Slaskie, Poland; [4]Emory, University School of Medicine, Atlanta, Georgia; [5]McMaster University, Hamilton, Ontario, Canada; [6]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [7]Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Region Metropolitana, Chile; [8]Department of Infectious Diseases, Kazan State Medical Academy, Kazan, Tatarstan, Russia; [9]Ben-Gurion University of the Negev, Beer Sheva, HaDarom, Israel; [10]Merck & Co., Inc., Kenilworth, New Jersey

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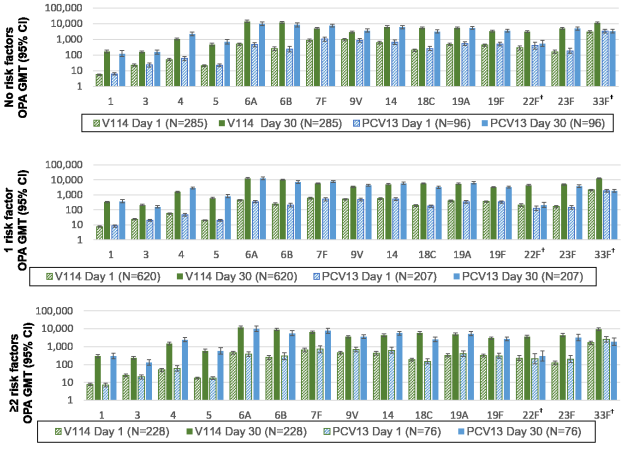
Background. Risk factors (RFs) for pneumococcal disease (PD) in immunocompetent individuals include comorbidities, behavioral habits, or living in a community with increased risk of PD transmission. RF stacking of comorbidities is associated with a higher incidence of PD, approaching that of immunocompromised individuals. Pneumococcal vaccination of certain adults is recommended with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) alone/sequentially with pneumococcal conjugate vaccine (PCV). V114, an investigational 15-valent PCV, contains 2 epidemiologically important serotypes (STs), 22F and 33F, in addition to the 13 STs in 13-valent PCV (PCV13).

Methods. PNEU-DAY was a Phase 3 study evaluating V114 or PCV13 administered on Day 1, and PPSV23 given 6 months later, in adults aged 18–49 years with or without RFs. This subgroup analysis assessed safety, tolerability, and immunogenicity of V114 and PCV13 based on the number of baseline PD RFs, which included chronic liver, lung, and heart disease, diabetes mellitus, tobacco use, and alcohol consumption. Adverse events (AEs; overall and solicited) were collected after each vaccination. Immunogenicity assessment was based on ST-specific opsonophagocytic activity (OPA) at 30 days after each vaccination. Subgroup analyses were conducted by RF group (0, 1, or ≥2 RFs for PD).

Results. Among the 1515 participants randomized to V114 (n=1135) or PCV13 (n=380), 25.2% had no RFs, 54.7% had 1 RF and 20.1% had ≥2 RFs for PD at baseline. The proportions of participants with solicited AEs following V114/PCV13 and PPSV23 were comparable across the 3 subgroups, with injection-site pain, myalgia, and fatigue being the most common. V114 and PCV13 were immunogenic in all subgroups based on OPA geometric mean titers (GMTs) at 30 days post-vaccination for the 13 shared STs (**Figure**); in addition, V114 induced a robust immune response to the 2 unique STs (22F, 33F) in all subgroups. PPSV23 following PCV was immunogenic for all 15 STs contained in V114 across all subgroups.

Figure. Serotype-specific OPA GMTs at baseline and 30 days post-vaccination with V114 and PCV13 by number of baseline risk factors (per-protocol population)



†Serotypes not included in PCV13.

The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. Per protocol, Day 1 is pre-vaccination with PCV, Day 30 is 30 days following vaccination with PCV. Risk factors include chronic lung disease, tobacco use, diabetes mellitus, chronic liver disease, chronic heart disease, or alcohol consumption. N is the number of participants randomized and vaccinated with PCV.

CI, confidence interval; GMT, geometric mean titer (1/dilution); OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.