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RESEARCH PAPER

Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, administered concomitantly with influenza vaccine in healthy adults aged ≥50 years: a randomized phase 3 trial (PNEU-FLU)

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ABSTRACT

Streptococcus pneumoniae and influenza viruses are associated with significant morbidity and mortality in older adults. Concomitant vaccination against these agents reduces hospitalization and mortality rates. This phase 3 trial evaluated safety, tolerability, and immunogenicity of concomitant and non-concomitant administration of V114, a 15-valent pneumococcal conjugate vaccine containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, 33F, and quadrivalent inactivated influenza vaccine (QIV), in healthy adults aged ≥50 years. Participants (N = 1,200) were randomized 1:1 to receive either V114 administered concomitantly with QIV (concomitant group) or QIV plus placebo (non-concomitant group) on Day 1, followed by placebo (concomitant group) or V114 (non-concomitant group) 30 days later. Randomization was stratified by age and history of pneumococcal polysaccharide vaccine receipt. Overall, 426 (71.0%) and 438 (73.5%) participants in the concomitant and non-concomitant groups experienced solicited injection-site adverse events (AEs); 278 (46.3%) and 300 (50.3%) reported solicited systemic AEs. Most solicited AEs were mild or moderate in severity and of short duration. Non-inferiority for pneumococcal- and influenza-specific antibody responses (lower bound 95% confidence interval of opsonophagocytic activity [OPA] and hemagglutination inhibition geometric mean titers [GMTs] ratios ≥0.5) was demonstrated for concomitant versus non-concomitant administration for all 15 pneumococcal serotypes and all four influenza strains. Consistent with previous studies, a trend was observed toward lower pneumococcal OPA GMTs in the concomitant versus the non-concomitant group. V114 administered concomitantly with QIV is generally well tolerated and immunologically non-inferior to non-concomitant administration, supporting coadministration of both vaccines.

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Introduction

Streptococcus pneumoniae and influenza virus cause significant burden of disease worldwide in both adult and pediatric populations.[1–4] In adults ≥50 years of age, there is an increased risk for pneumococcal disease and influenza-associated morbidity and mortality compared with younger adults.[5–7] In addition, pneumococcal pneumonia is a frequent complication of influenza in adults,[8,9] leading to more severe clinical outcomes and placing a significant burden on health systems during the influenza season.[9,10] Vaccination against both influenza viruses and *S. pneumoniae* in older adults has been shown to reduce rates of hospitalization and mortality.[10–13]

Pneumococcal vaccine recommendations for adults vary by country; while some countries recommend vaccination of older adults with the 23-valent pneumococcal polysaccharide vaccine (PPSV23), others recommend administration of a pneumococcal conjugate vaccine (PCV), or a sequential PCV/PPSV23 regimen.[14–17] Owing to the emergence of non-PCV serotypes and persistence of some vaccine serotypes included in currently licensed PCVs, such as serotypes 3 and 19A,[2,18] there is a need for the development of new PCVs with broader serotype coverage and improved effectiveness against disease caused by serotypes in licensed PCVs. V114 is a recently approved 15-valent PCV that contains serotypes 22F and 33F, in addition to the 13 serotypes included in the 13-valent PCV (PCV13; 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).[19] In 2017, serotypes 22F and 33F were responsible for 9% and 4% of all invasive pneumococcal disease (IPD) cases, respectively, across age groups in the United States, and serotype 22F was associated with 7–8% of IPD cases in adults aged ≥45 years in Europe.[2,18] Both serotypes have been associated with invasive disease,[20] and serotype 33F is associated with multidrug resistance.[21] V114 has been shown to be well tolerated and immunogenic in infants, young adults, and older adults in phase 2 trials.[19,22,23]

Annual influenza vaccination for older adults is included in routine national vaccination programs in many countries.[16] As coverage of both influenza and pneumococcal vaccines in adults is low (45% in adults aged ≥19 years for influenza vaccine in 2016–2017 and 69% in adults aged

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≥65 years for pneumococcal vaccine in 2017 in the United States),[24] concomitant administration is a desirable strategy to increase vaccine uptake.[25] Coadministration of PCV13 or PPSV23 with inactivated influenza vaccines has been shown previously to be well tolerated without adversely affecting immunogenicity (albeit with slightly reduced opsonophagocytic activity [OPA] responses in some studies), when compared with separate administration.[25–31] This study was designed to evaluate the safety, tolerability, and immunogenicity of a single dose of V114 when administered either concomitantly (on the same day) or non-concomitantly (30 days later) with quadrivalent inactivated influenza vaccine (QIV).

Methods

Study design

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and immunogenicity of V114 administered concomitantly or non-concomitantly with QIV in healthy adults 50 years of age or older. The study is registered with ClinicalTrials.gov as NCT03615482. The trial was conducted from September 24, 2018, to June 24, 2019, at 45 sites across the United States.

Investigators and site staff enrolled participants using central randomization and assignment to vaccination group via an interactive response technology system. The randomization and vaccine identification schedules were created by an unblinded representative of the sponsor. As V114 and placebo differed in appearance, they were prepared, dispensed, and administered by unblinded study personnel who were not involved in any subsequent participant assessments. The participant and the investigator who was involved in the clinical evaluation of the participant remained blinded. QIV was administered open label.

The study was conducted in accordance with the principles of Good Clinical Practice and the ethical principles originating from the Declaration of Helsinki, and was approved by the appropriate institutional review boards, regulatory agencies, and independent ethics committees at participating sites. An external Data Monitoring Committee conducted periodic reviews of safety and tolerability data. Written informed consent was obtained from each participant prior to any study procedure.

The study was designed to enroll approximately 1,200 participants randomized in a 1:1 ratio to receive either V114 with concomitant QIV (concomitant group) or QIV and placebo (non-concomitant group) on Day 1. Approximately 30 days later, participants in the non-concomitant group received V114 and those in the concomitant group received placebo. Randomization was stratified by participant age at enrollment (50–64 years, 65–74 years, and ≥75 years), with at least 50% of participants being ≥65 years of age, and by history of PPSV23 receipt versus non-receipt, with at least 50% of participants being PPSV23-naïve. For participants who had prior vaccination with PPSV23, vaccination was required to have occurred >12 months prior to the first study visit. Blood samples were obtained for immunogenicity assays on Day 1, Day 30, and Day 60. Telephone contacts for safety review occurred on Day 15, Day 45, and Month 7.

Participants

Male or female participants ≥50 years of age in generally good health and/or with stable underlying medical conditions were eligible for the study. Key exclusion criteria included: history of IPD or other culture-positive pneumococcal disease within the previous 3 years, known hypersensitivity to a vaccine component, known or suspected impairment of immunological function, prior administration of any PCV, or prior administration of influenza vaccine during the 2018/2019 influenza season.

Vaccines and administration

V114 (VAXNEUVANCE™; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) is a 15-valent pneumococcal conjugate vaccine. Each 0.5 mL dose contains 2 µg of pneumococcal capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F, and 4 µg of serotype 6B all conjugated to CRM_{197} carrier protein, adjuvanted with 125 µg of aluminum phosphate.

The Northern Hemisphere 2018–2019 season formulation of QIV (Fluarix® Quadrivalent; GlaxoSmithKline, Research Triangle Park, NC, USA) was used in this study, which included the following influenza strains: A/Michigan/45/2015 (H1N1) pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage), and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

V114 was provided as a sterile suspension and QIV was provided as a sterile solution. V114 and QIV were supplied in a prefilled syringe and stored at 2–8°C; placebo (sterile saline) was provided in an ampule and taken up into a syringe by unblinded study personnel who were not involved in any subsequent participant assessments. All vaccines and the placebo were provided in 0.5 mL doses and were administered intramuscularly in separate arms (V114 or placebo in the left arm and QIV in the right arm). Needle gauge size was determined per institutional guidelines for the study site and may have varied based on participant characteristics, such as body habitus.

Safety assessments

Adverse events (AEs) experienced following receipt of study vaccines were recorded by participants using an electronic Vaccination Report Card and subsequently assessed and reported by the investigator. Injection-site reactions (injection-site pain, injection-site swelling, and injection-site erythema) occurring from Days 1–5 after vaccination and systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, and fatigue) occurring from Days 1–14 after vaccination were solicited.

Daily body temperature was measured on Days 1–5 after vaccination. In addition, participants were followed for non-solicited injection-site and systemic AEs from Days 1–14 after vaccination. Information for serious adverse events (SAEs) and deaths, regardless of whether the events were considered to be vaccine related by the investigator, were collected from the time of signed consent through to the end of study (approximately 7 months after the first vaccination).

All solicited and non-solicited events were assessed for severity by the investigator. The severity of AEs was categorized as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life-threatening (Grade 4), adapted from FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007.[32] For solicited injection-site erythema and injection-site swelling, mild events were those measuring >0 to ≤5 cm, moderate events measured >5 to ≤10 cm, and severe events measured >10 cm. For injection-site pain and systemic AEs, the severity was defined by the degree to which the event affected daily activities and the use of medications for pain relief.[32]

All injection-site AEs were considered to be vaccine related. For systemic AEs, relatedness to study vaccine was assessed by the investigator.

Immunogenicity assessments

Immunogenicity analyses were conducted separately for each of the 15 pneumococcal serotypes in V114 and each of the four influenza strains in QIV. Serum samples were drawn pre-vaccination on Day 1 (baseline) and at 30 and 60 days post-vaccination (Day 30 and Day 60) to assess immune responses. Functional antibodies were measured using serotype-specific opsonophagocytic killing activity using a validated microcolony multiplexed opsonophagocytic assay (MOPA).[33] Serotype-specific pneumococcal capsular polysaccharide immunoglobulin G (IgG) antibodies were evaluated using a validated multiplexed electrochemiluminescence assay.[34] Both assays were developed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The validated hemagglutination inhibition (HAI) test was performed by Q^2 Solutions (San Juan Capistrano, CA, USA) for the four strains included in the vaccine.

Study endpoints and statistical analysis

Determination of sample size

The planned study sample size of 1,200 participants (600 per intervention group) provided nearly 90% power to demonstrate non-inferiority of V114 administered concomitantly with QIV to V114 administered non-concomitantly with QIV with respect to the serotype-specific OPA geometric mean titers (GMTs) for the 15 serotypes included in V114 and the strain-specific HAI GMT ratios for the four influenza strains in QIV at an overall 1-sided 2.5% alpha level. Assumptions for the sample size calculations were based on an underlying OPA GMT ratio of 0.80 (based on previous studies evaluating concomitant administration of PCV13 with influenza vaccines).[26,28]

Analysis populations

Safety analyses were conducted on the All Participants as Treated (APaT) population, which consisted of all randomized participants who received at least one dose of study vaccine.

The Per-Protocol (PP) population served as the primary population for the analysis of immunogenicity data. The PP population consisted of all randomized participants without deviations from the protocol that could have substantially affected the results of the immunogenicity endpoints.

Primary safety endpoints and statistical methods

The safety endpoints following any vaccination received on Day 1 or Day 30 included: i) the proportions of participants with solicited injection-site AEs from Day 1 through Day 5 post-vaccination, ii) the proportions of participants with solicited systemic AEs from Day 1 through Day 14 post-vaccination, and iii) the proportions of participants within the broad AE categories of any AE or SAE including vaccine-related SAEs. Point estimates were provided for all safety endpoints and 95% confidence intervals (CIs) were provided for between-treatment differences in the proportions of participants with solicited AEs and the aforementioned broad categories of AEs using the unstratified Miettinen and Nurminen method.[35] *P*-values were also provided for the differences in the proportions of participants with solicited AEs. No multiplicity adjustments were made for the safety comparisons.

Solicited injection-site AEs were also assessed following each individual study vaccine; data are reported for events following V114 only. Systemic AEs could not be assessed following individual vaccines in the concomitant group as events occurring following the vaccinations on Day 1 could not be attributed to a specific vaccine. Systemic AEs following vaccination with V114 in the non-concomitant group are reported.

Subgroup analyses of safety endpoints by age, sex, race, ethnicity, and history of PPSV23 receipt were performed.

Primary immunogenicity endpoints and statistical methods

The primary immunogenicity objectives were to compare V114 administered concomitantly with QIV to V114 administered non-concomitantly with QIV to assess: i) non-inferiority of serotype-specific OPA GMTs at 30 days post-vaccination with V114 for all 15 serotypes included in V114 and ii) non-inferiority of strain-specific HAI GMTs at 30 days post-vaccination with QIV for all four influenza strains included in QIV. The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for the OPA GMT ratio or HAI GMT ratio (concomitant/non-concomitant) to be greater than 0.5.

OPA GMTs and OPA GMT ratios (with corresponding 95% CIs) were estimated using serotype-specific constrained longitudinal data analysis (cLDA) models utilizing data from both vaccination groups.[36] The serotype-specific repeated measures models included vaccination group, time, the interaction of time-by vaccination group (with a restriction of the same baseline mean across groups), age stratum, age stratum-by-time interaction, history of PPSV23 receipt stratum, and history of PPSV23 receipt stratum-by-time interaction as fixed effects.

Similarly, strain-specific cLDA models were used to calculate the HAI GMTs and HAI GMT ratios (with corresponding 95% CIs).

All hypotheses were tested individually for each pneumococcal serotype and each influenza strain at a 1-sided 0.025 alpha-level. Study success was predicated upon meeting all primary immunogenicity objectives and, thus, no multiplicity adjustments were required to control the 1-sided type-I error rate at 0.025.

To determine whether the intervention effect was consistent across the age strata (50–64 years, 65–74 years, and ≥75 years) and by history of PPSV23 receipt versus non-receipt strata, the estimate of the between-group treatment effect (with a nominal 95% CI) was summarized for the primary immunogenicity endpoints. Subgroup analyses were also performed by sex, race, and ethnicity.

Secondary immunogenicity endpoints and statistical methods

A secondary immunogenicity objective was to compare the serotype-specific IgG geometric mean concentrations (GMCs) for the 15 serotypes included in V114 at 30 days post-vaccination with V114 between vaccination groups. IgG GMCs and IgG GMC ratios (with corresponding 95% CIs) at 30 days post-vaccination with V114 were calculated using serotype-specific cLDA models similar to those described for the primary immunogenicity endpoints.

Additional secondary pneumococcal immunogenicity endpoints included observed serotype-specific geometric mean fold rises (GMFRs) and the proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination with V114 for both OPA and IgG responses. Reverse cumulative distribution curves for OPA titers were generated per serotype.

Secondary influenza immunogenicity endpoints included strain-specific GMFRs from pre-vaccination to 30 days post-vaccination with QIV, the proportions of participants with an HAI titer of ≥1:40 at 30 days post-vaccination with QIV, and the proportions of participants who seroconverted at 30 days post-vaccination with QIV. Seroconversion for HAI responses was defined as either achievement of a 4-fold rise in HAI titer from pre-vaccination to 30 days post-vaccination with QIV among participants who were seropositive (HAI titer ≥1:10) at baseline or achievement of an HAI titer of ≥1:40 at 30 days post-vaccination with QIV among participants who were seronegative (HAI titer <1:10) at baseline.

Descriptive statistics with point estimates and within-group 95% CIs are provided for these endpoints. For the continuous endpoints, the within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs were based on the exact binomial method proposed by Clopper and Pearson.[37]

Analysis software

All the analyses were performed using SAS© software, version 9.4. of the SAS System for Unix. Copyright© 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Results

Study population

Overall, 1,200 participants were randomized, with 600 in each group (Figure 1). In the concomitant group, 599 (99.8%) participants were vaccinated with V114 and QIV on Day 1, and 583 (97.2%) received placebo on Day 30 and completed the study. In the non-concomitant group, 598 (99.7%) were vaccinated with QIV and 596 (99.3%) were vaccinated with placebo on Day 1 (two participants received V114 instead of placebo), 586 (97.7%) were vaccinated with V114 on Day 30 (one participant who mistakenly received V114 on Day 1 was given

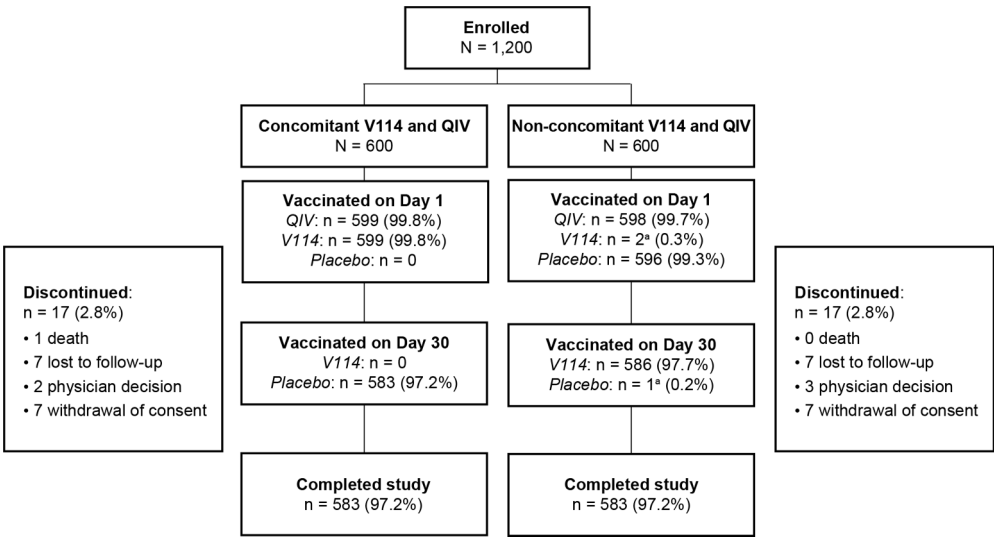

Figure 1. Participant disposition. [a]Two participants were dispensed study intervention other than that assigned in the allocation schedule. In the non-concomitant group, 2 participants received V114 on Day 1, and 1 of these 2 participants received placebo on Day 30. QIV, quadrivalent influenza vaccine; V114, 15-valent pneumococcal conjugate vaccine.

placebo on Day 30), and 583 (97.2%) completed the study. The participant who received two doses of V114 was excluded from the APaT population. The most common reasons for discontinuation were voluntary withdrawal of consent and loss to follow-up (both 1.2% in each group).

Both groups were generally balanced for baseline characteristics such as age, sex, race, ethnicity, and underlying medical conditions, as well as history of PPSV23 receipt (Table 1). The mean age of study participants was 64.2 years (range 50–98 years); 672 (56.1%) were female and 250 (20.9%) had a history of PPSV23 receipt. The most common conditions in the medical history of the participants were hypertension, osteoarthritis, hyperlipidemia, gastroesophageal reflux disease, and seasonal allergy. These and other reported medical conditions were comparable across the two vaccine groups (Supplementary Table 1).

Safety

Overall, 482 (80.3%) participants in the concomitant group and 488 (81.9%) in the non-concomitant group experienced at least one AE. The most frequently reported AEs were the solicited events of injection-site pain, injection-site swelling, injection-site erythema, fatigue, myalgia, headache, and arthralgia. In total, 430 (71.7%) and 440 (73.8%) of participants in the concomitant and non-concomitant groups, respectively, experienced any injection-site AE following any vaccination (Table 2); of these, 426 (71.0%) participants in the concomitant group and 438 (73.5%) in the non-concomitant group experienced solicited injection-site AEs, of which injection-site pain was the most common (Table 2 and Figure 2; observed differences between the concomitant and non-concomitant group were not statistically significant; injection-site erythema is not shown as the interpretability of results is limited by missing data). Three hundred and forty-one (56.8%) and 345 (57.9%) participants in the concomitant and non-concomitant groups experienced any systemic AE (Table 2); of these, 278 (46.3%) and 300 (50.3%) experienced solicited systemic AEs, of which fatigue was the most common (Table 2 and Figure 2). The majority of participants with solicited AEs had events that were mild or moderate in maximum severity (Figure 2), and of short duration (≤3 days) (data not shown). The proportion of participants with elevated body temperature (≥100.4°F [38.0°C]) was low (≤1.5% in both groups) (data not shown).

Following V114 vaccination only, the proportions of participants in each group experiencing solicited injection-site AEs were similar (403 [67.2%] in the concomitant group and 408 [69.7%] in the non-concomitant group) (Supplementary Table 2). Solicited systemic AEs after V114 occurred in 202 (34.5%) participants in the non-concomitant group (data not shown).

The proportion of participants experiencing SAEs was low (<4%) across both groups, and no SAEs were considered by the investigator to be related to study vaccine (Table 2). One participant in the concomitant group died of myocardial infarction on Day 42. Three participants discontinued study intervention due to AEs; of these, two experienced events considered to be related to study vaccine by the investigator. One participant in the concomitant group experienced sinusitis on Day 4 (lasting for 1.6 months), and one participant in the non-concomitant group experienced upper abdominal pain, fatigue, and nausea on Day 1 (lasting for 4 days, 2 weeks, and 3 days, respectively), rhinorrhea and arthralgia on Day 2 (lasting for 2 days and 3 days, respectively), and myalgia on Day 5 (lasting for 3 days).

Table 1. Baseline participant characteristics.

Characteristic[a]	Concomitant (N = 599)	Non-concomitant (N = 598)
Sex		
Female	330 (55.1)	342 (57.2)
Male	269 (44.9)	256 (42.8)
Age (years)		
50 to 64	299 (49.9)	298 (49.8)
65 to 74	236 (39.4)	236 (39.5)
≥75	64 (10.7)	64 (10.7)
Mean age (range)	64.2 (50–98)	64.2 (50–88)
Race		
White	493 (82.3)	495 (82.8)
Black or African American	73 (12.2)	63 (10.5)
Asian	25 (4.2)	30 (5.0)
Multiple	5 (0.8)	3 (0.5)
American Indian or Alaska Native	1 (0.2)	3 (0.5)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.2)
Missing	0	3 (0.5)
Ethnicity		
Not Hispanic or Latino	471 (78.6)	472 (78.9)
Hispanic or Latino	120 (20.0)	119 (19.9)
Not reported	6 (1.0)	5 (0.8)
Unknown	2 (0.3)	2 (0.3)
History of PPVS23 receipt		
No receipt of PPSV23	475 (79.3)	472 (78.9)
Receipt of PPSV23	124 (20.7)	126 (21.1)

PPSV23, 23-valent pneumococcal polysaccharide vaccine.
[a]Values are n (%) unless otherwise stated. Table includes all vaccinated participants.

Table 2. Adverse events after any vaccination.

N (%)	Concomitant (N = 600)	Non-concomitant (N = 596)	Difference in percent versus non-concomitant (95% CI)	P-value
Any AE	482 (80.3)	488 (81.9)	−1.5 (−6.0, 2.9)	
Injection site	430 (71.7)	440 (73.8)		
Systemic	341 (56.8)	345 (57.9)		
Any vaccine-related AE	452 (75.3)	460 (77.2)	−1.8 (−6.7, 3.0)	
Injection site	430 (71.7)	440 (73.8)		
Systemic	222 (37.0)	227 (38.1)		
Any SAE	22 (3.7)	14 (2.3)	1.3 (−0.7, 3.4)	
Any vaccine-related SAE	0	0	0.0 (−0.6, 0.6)	
Death	1 (0.2)[a]	0	0.2 (−0.5, 0.9)	
Solicited injection-site AEs (Day 1 to Day 5)	426 (71.0)	438 (73.5)		
Injection-site pain	411 (68.5)	424 (71.1)	−2.6 (−7.8, 2.6)	0.320
Injection-site swelling	85 (14.2)	97 (16.3)	−2.1 (−6.2, 2.0)	0.310
Injection-site erythema	64 (10.7)	69 (11.6)	−0.9 (−4.5, 2.7)	0.617
Solicited systemic AEs (Day 1 to Day 14)	278 (46.3)	300 (50.3)		
Fatigue	163 (27.2)	179 (30.0)	−2.9 (−8.0, 2.3)	0.273
Myalgia	142 (23.7)	127 (21.3)	2.4 (−2.4, 7.1)	0.329
Headache	129 (21.5)	141 (23.7)	−2.2 (−6.9, 2.6)	0.372
Arthralgia	56 (9.3)	69 (11.6)	−2.2 (−5.8, 1.2)	0.205

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
[a]Myocardial infarction 10 days following Visit 2 (placebo) resulting in death 2 days later; assessed as not related to study vaccine by the investigator.

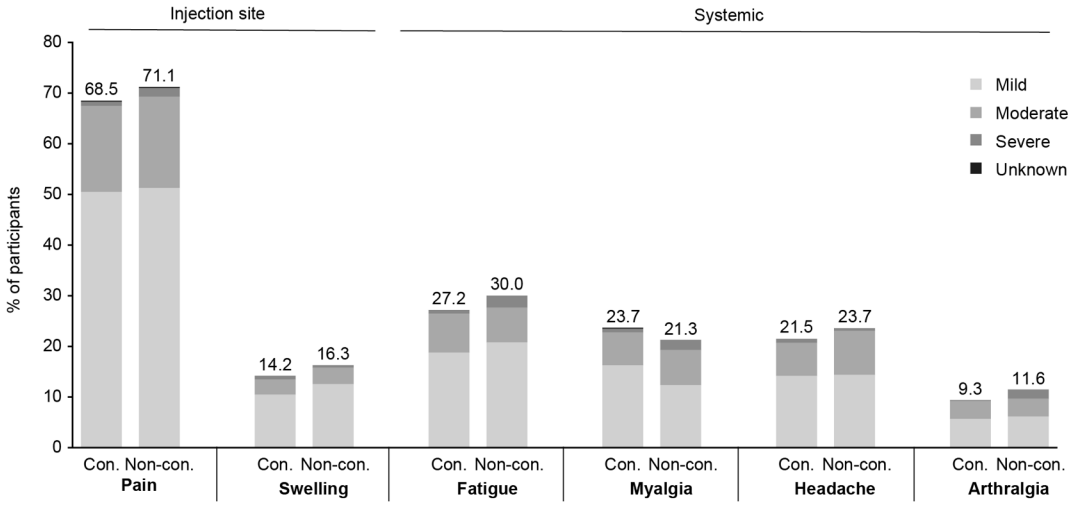

Figure 2. Proportion of participants with solicited adverse events after any vaccination by severity. Solicited adverse events collected post-vaccination (Days 1–5 for injection-site events and Days 1–14 for systemic events) (concomitant [N = 600], non-concomitant [N = 596]) are shown with severity grades. The height of the stacked bar represents the total percentage of participants reporting the adverse event. The severity grades (mild, moderate or severe) within the bar indicate the proportion of the total attributed to each respective category. Injection-site erythema is not shown as the impact of missing data limits the interpretability of results. Con, concomitant group; non-con, non-concomitant group.

Based on subgroup analyses, safety profiles across the two vaccine groups were generally comparable by sex, race, and history of PPSV23 administration (data not shown). Trends were observed toward a lower proportion of participants aged ≥65 years compared with those aged 50–64 years experiencing AEs, and toward lower proportions of Hispanic or Latino participants versus non-Hispanic or non-Latino participants experiencing solicited AEs (Supplementary Tables 3 and 4).

Immunogenicity

V114 administered concomitantly with QIV was non-inferior to V114 administered non-concomitantly with QIV as assessed by OPA GMTs at 30 days post-vaccination with V114 for all 15 serotypes in the vaccine. The lower bound of the 2-sided 95% CI of the OPA GMT ratio was >0.50 for all serotypes (Figure 3). A trend toward lower OPA GMTs in the concomitant group compared with the non-concomitant group was observed (Figure 4). QIV administered concomitantly with V114 was non-inferior to QIV administered non-concomitantly with V114 as assessed by HAI GMTs at 30 days post-vaccination with QIV. The lower bound of the 2-sided 95% CI of the HAI GMT ratio was >0.50 for all strains (Figure 5).

IgG GMCs at 30 days post-vaccination with V114 were generally consistent with OPA GMTs (Figure 6). OPA GMFRs and proportions of participants with a ≥4-fold rise in OPA GMTs and IgG GMCs from baseline to 30 days post-vaccination with V114 were generally comparable between the concomitant and non-concomitant groups; there was a trend toward lower IgG GMFRs in the concomitant group compared with the non-concomitant group (Tables 3 and 4).

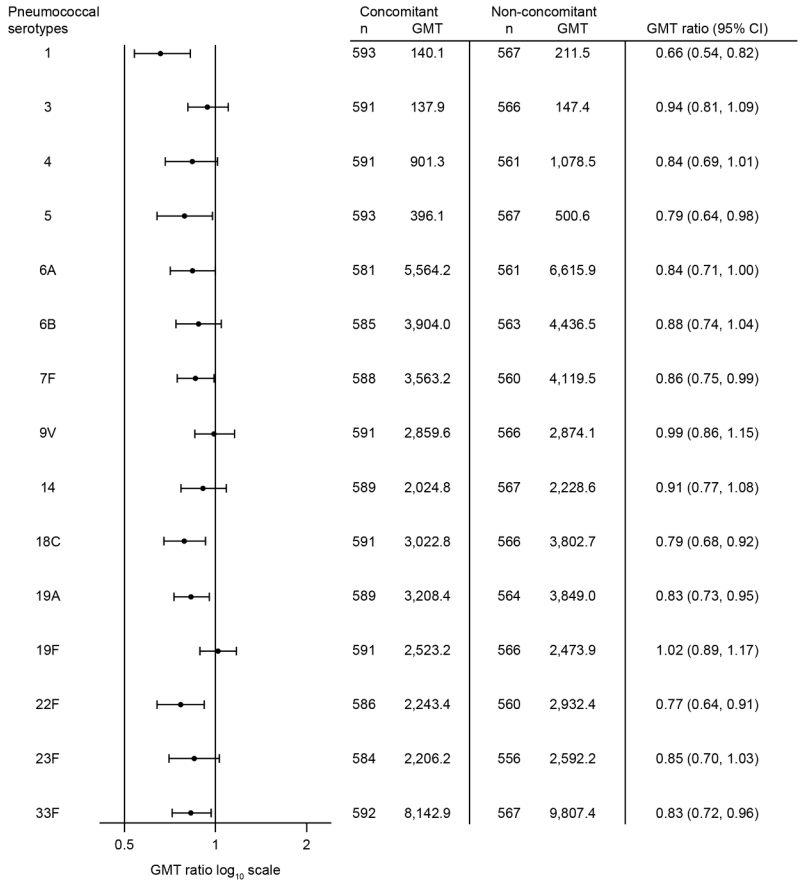

Figure 3. Estimated serotype-specific OPA GMTs 30 days after vaccination with V114. The forest plot depicts serotype-specific GMT ratios with the corresponding 95% CIs. GMTs, GMT ratios, and 95% CIs were estimated from a constrained longitudinal data analysis model. CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity; V114, 15-valent pneumococcal conjugate vaccine.

HAI GMFRs, proportions of participants with HAI titer ≥1:40, and proportions of participants who seroconverted at 30 days post-vaccination with QIV were generally comparable between the concomitant and non-concomitant groups (Table 5).

Subgroup analyses of OPA GMT ratios by age, sex, ethnicity, race, and history of PPSV23 administration were generally consistent with results observed in the overall population. Within both the concomitant and non-concomitant groups, there was a trend toward lower serotype-specific OPA GMTs in older (≥65 years) versus younger (50–64 years) participants (Figure 7).

Discussion

This study of adults ≥50 years of age who were in generally good health and/or with stable underlying medical conditions demonstrated that concomitant administration of V114 and QIV on the same day is generally well tolerated, with a safety profile similar to that of non-concomitant administration of QIV and V114 given 30 days apart. The proportions of participants experiencing injection-site and systemic AEs when administered V114 concomitantly or non-concomitantly with QIV are generally comparable with those seen in previous studies of V114 in older adults.[22,38] Vaccine-induced immune responses in the concomitant group are non-inferior to the non-concomitant group for the 15 pneumococcal serotypes in V114 and the four influenza strains in QIV, as measured by OPA and HAI GMTs at 30 days post-vaccination. These findings demonstrate that V114 and QIV can be administered concomitantly in healthy older adults without significantly affecting the safety or immunogenicity of these vaccines when given separately.

Consistent with a number of previous studies evaluating the coadministration of PCV13 with trivalent inactivated influenza vaccine or QIV,[25–29] there was a trend toward lower pneumococcal serotype-specific OPA GMTs and IgG GMCs 30 days following V114 vaccination in the concomitant group, which resulted in the point estimates of the GMT ratios and GMC ratios being <1.0 for most serotypes. A trend toward lower GMFRs from baseline to 30 days post-vaccination with concomitant administration of V114 and QIV compared with V114 alone was also observed for serotype-specific IgG GMCs. OPA GMFRs and the proportion of participants with a ≥4-fold rise of OPA and IgG responses from baseline to post-vaccination were generally comparable between groups, suggesting that between-group differences in serotype-specific OPA GMTs and IgG GMCs may have limited clinical impact. Notably, in a previous study, small differences in serotype-specific OPA and IgG responses 30 days after concomitant administration of PCV and trivalent influenza vaccine compared with non-concomitant administration were not maintained over

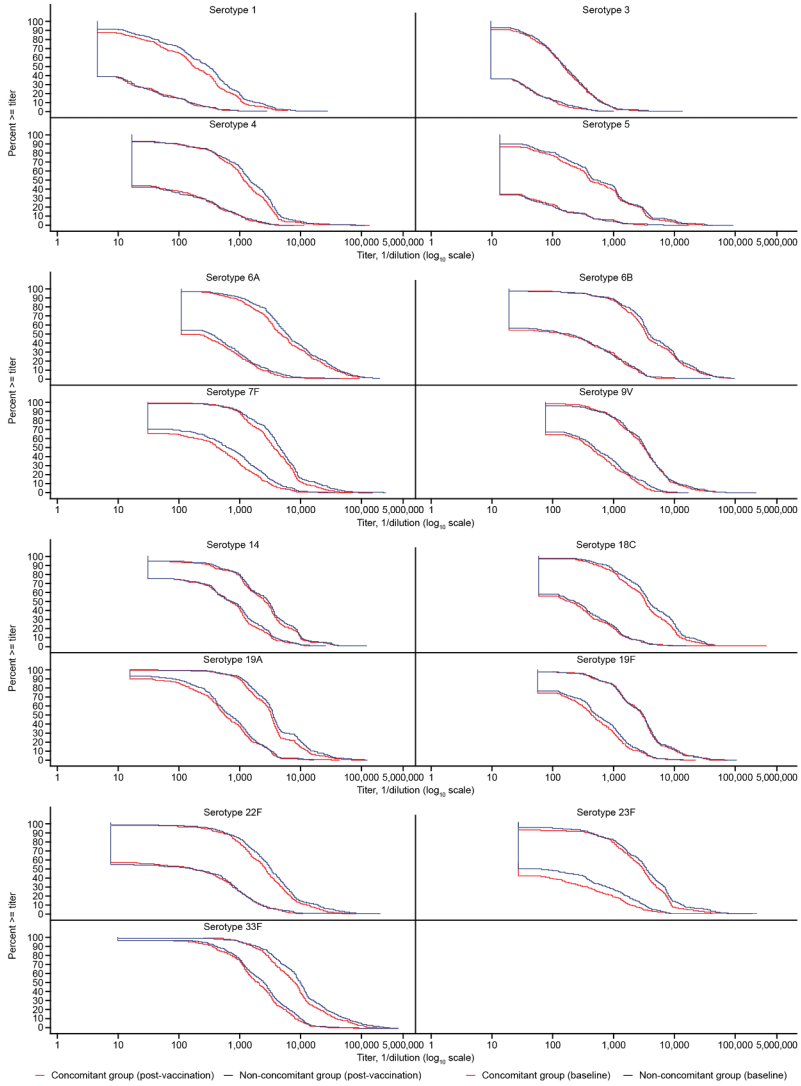

Figure 4. Reverse cumulative distribution curves for OPA GMTs by serotype. Reverse cumulative distribution curves for OPA titers by serotype at baseline (Day 1) and 30 days after vaccination with V114. GMT, geometric mean titer; OPA, opsonophagocytic activity; V114, 15-valent pneumococcal conjugate vaccine.

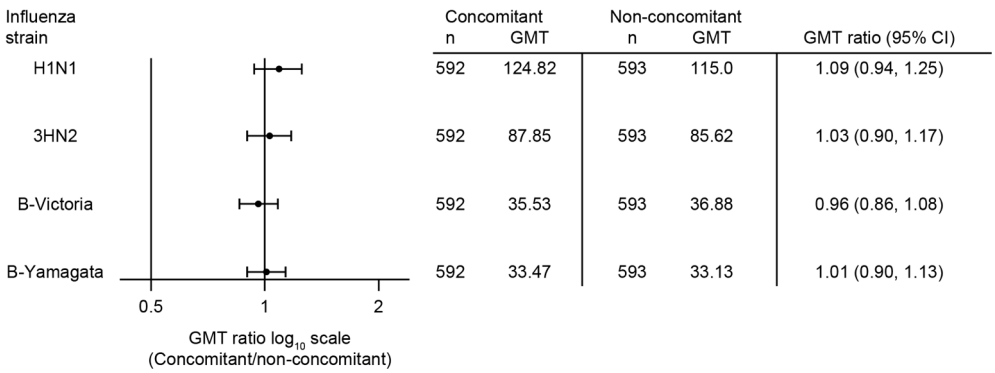

Figure 5. Estimated strain-specific HAI GMTs at 30 days after vaccination with QIV. The forest plot depicts strain-specific HAI GMT ratios with the corresponding 95% CIs. GMTs, GMT ratios, and 95% CIs were estimated from a constrained longitudinal data analysis model. CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutination inhibition; QIV, quadrivalent influenza vaccine.

time,[39] suggesting that the between-group differences observed may be transient. No effectiveness studies are available for the concomitant administration of a PCV and influenza vaccine in adults; however, effectiveness studies of the concomitant use of PPSV23 and trivalent influenza vaccine support the coadministration of both vaccines to prevent pneumonia, influenza hospitalizations, and death.[11–13]

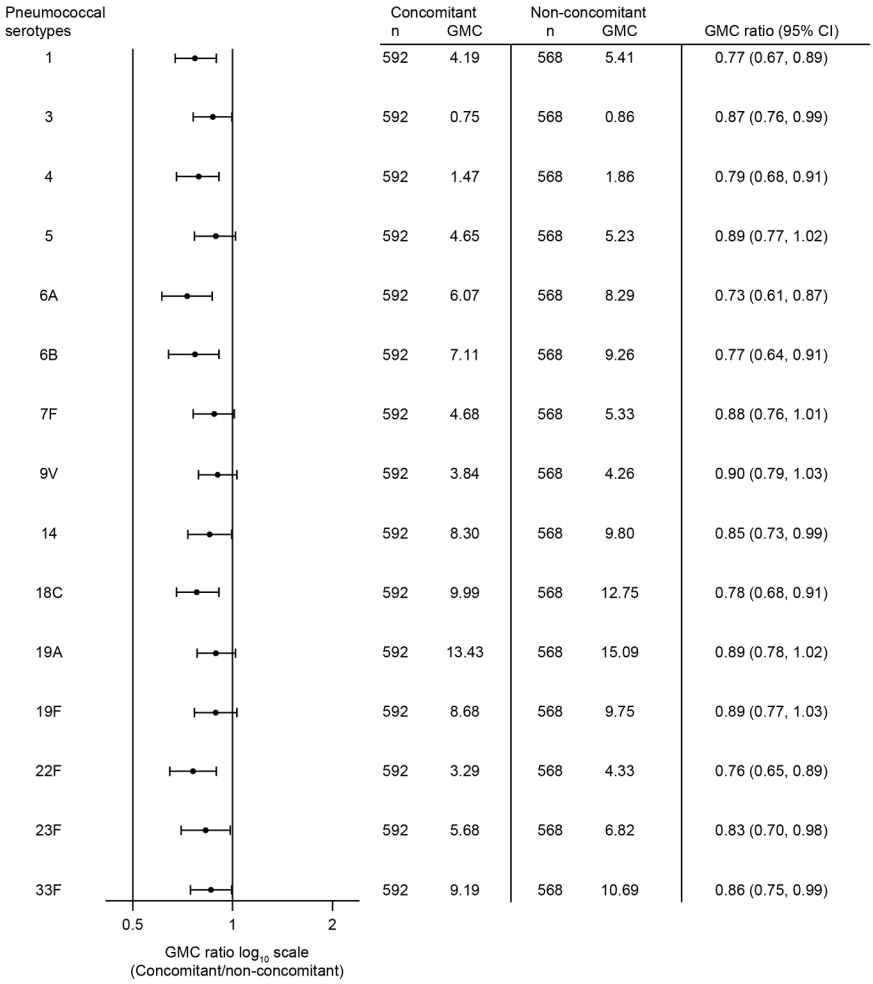

Figure 6. Estimated serotype-specific IgG GMCs 30 days after vaccination with V114. The forest plot depicts serotype-specific IgG GMC ratios with the corresponding 95% CIs. GMCs, GMC ratios, and 95% CIs were estimated from a constrained longitudinal data analysis model. CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; V114, 15-valent pneumococcal conjugate vaccine.

The coadministration of V114 and QIV did not impact strain-specific influenza responses when compared with non-concomitant administration. These findings are consistent with studies that have evaluated the coadministration of PCV13 and influenza vaccines.[25–27,29]

Subgroup analyses showed a trend toward lower pneumococcal immune responses in older adults (65–74 years and ≥75 years) compared with younger adults (50–64 years) in both the concomitant and non-concomitant groups. This is consistent with PCV administration in older adults,[40] as well as a previous study of PPSV23 and influenza vaccine coadministration in older adults,[30] and is likely attributable to immunosenescence.[41,42] Within the subgroup of participants with history of PPSV23 receipt, pneumococcal and influenza immune responses were comparable between the concomitant and non-concomitant groups. Similar results were observed in a clinical trial that evaluated concomitant administration of PCV13 and QIV in participants ≥50 years of age who had received PPSV23 at least 1 year prior to enrollment.[29]

Limitations of this study include the lack of follow-up for immunogenicity beyond 30 days following each vaccination. In addition, the study did not evaluate the efficacy of concomitant versus non-concomitant administration of QIV and V114, given the lack of a well-accepted serotype-specific threshold level of antibody titers or concentrations needed to protect against pneumococcal disease in adults.

In conclusion, in adults ≥50 years of age who are generally in good health, concomitant administration of V114 and QIV is generally well tolerated and is immunologically non-inferior to non-concomitant administration for all 15 pneumococcal serotypes in V114 and all four influenza strains in QIV, supporting coadministration of these two vaccines.

Table 3. GMTs, GMFR, and proportion of participants with ≥4-fold rise in serotype-specific OPA antibodies from pre-vaccination to 30 days after vaccination with V114.

		Concomitant (N = 599)			Non-concomitant (N = 598)		
Serotype	Outcome	n	Response	95% CI	n	Response	95% CI
1	GMT (Day 1)	559	12.4	11.0–14.1	549	12.3	10.9–14.0
	GMT (Day 30)	551	141.5	120.9–165.5	523	209.1	178.1–245.5
	GMFR	517	8.0	6.8–9.3	505	11.8	10.1–13.9
	≥4-fold rise, % (n)	517	57.8 (299)	53.4–62.1	505	66.3 (335)	62.0–70.5
3	GMT (Day 1)	546	19.9	18.2–21.9	538	20.3	18.4–22.4
	GMT (Day 30)	540	137.3	123.0–153.2	521	148.2	132.7–165.4
	GMFR	495	4.7	4.3–5.3	493	4.8	4.3–5.4
	≥4-fold rise, % (n)	495	54.7 (271)	50.2–59.2	493	54.8 (270)	50.3–59.2
4	GMT (Day 1)	519	67.5	58.0–78.4	524	66.2	56.8–77.0
	GMT (Day 30)	543	910.3	796.1–1,040.9	513	1,074.4	926.7–1,245.5
	GMFR	471	9.4	8.0–11.0	476	11.5	9.7–13.6
	≥4-fold rise, % (n)	471	63.1 (297)	58.5–67.4	476	66.4 (316)	61.9–70.6
5	GMT (Day 1)	560	33.6	29.8–38.0	547	33.0	29.1–37.4
	GMT (Day 30)	549	402.1	342.0–472.7	523	494.4	419.2–583.0
	GMFR	516	8.1	7.0–9.4	503	10.2	8.7–12.0
	≥4-fold rise, % (n)	516	60.5 (312)	56.1–64.7	503	63.4 (319)	59.0–67.6
6A	GMT (Day 1)	498	366.4	325.4–412.6	499	426.1	376.5–482.2
	GMT (Day 30)	526	5,419.5	4,759.9–6,170.5	513	6,812.6	5,998.4–7,737.3
	GMFR	443	10.5	9.1–12.1	451	12.1	10.5–14.0
	≥4-fold rise, % (n)	443	71.1 (315)	66.6–75.3	451	75.6 (341)	71.4–79.5
6B	GMT (Day 1)	512	157.5	131.7–188.3	524	166.9	139.7–199.5
	GMT (Day 30)	539	3,912.9	3,456.6–4,429.5	520	4,408.7	3,870.5–5,021.7
	GMFR	466	17.6	14.8–20.9	481	20.5	17.3–24.4
	≥4-fold rise, % (n)	466	72.5 (338)	68.2–76.5	481	76.1 (366)	72.0–79.8
7F	GMT (Day 1)	535	301.4	256.6–354.1	520	418.9	353.6–496.3
	GMT (Day 30)	545	3,469.7	3,148.8–3,823.2	524	4,244.0	3,799.0–4,741.1
	GMFR	492	9.2	7.9–10.8	484	8.0	6.9–9.4
	≥4-fold rise, % (n)	492	63.0 (310)	58.6–67.3	484	59.7 (289)	55.2–64.1
9V	GMT (Day 1)	540	384.8	341.2–434.0	528	450.8	396.6–512.3
	GMT (Day 30)	534	2,831.9	2,560.8–3,131.7	521	2,900.8	2,592.6–3,245.8
	GMFR	483	5.8	5.1–6.6	483	5.3	4.6–6.1
	≥4-fold rise, % (n)	483	54.9 (265)	50.3–59.4	483	53.4 (258)	48.9–57.9
14	GMT (Day 1)	542	440.3	379.2–511.3	540	475.5	407.3–555.2
	GMT (Day 30)	545	2,021.1	1,777.9–2,297.6	518	2,258.4	1,982.4–2,572.9
	GMFR	498	3.9	3.3–4.4	491	4.1	3.5–4.7
	≥4-fold rise, % (n)	498	38.6 (192)	34.3–43.0	491	40.9 (201)	36.6–45.4
18C	GMT (Day 1)	545	226.9	200.7–256.4	535	246.3	217.8–278.5
	GMT (Day 30)	549	3,000.9	2,686.1–3,352.6	522	3,807.1	3,402.5–4,259.8
	GMFR	503	9.8	8.6–11.2	491	11.6	10.0–13.4
	≥4-fold rise, % (n)	503	67.4 (339)	63.1–71.5	491	70.3 (345)	66.0–74.3
19A	GMT (Day 1)	533	480.2	418.5–550.9	522	580.1	509.8–660.2
	GMT (Day 30)	538	3,158.2	2,872.4–3,472.3	518	3,884.3	3,516.1–4,291.1
	GMFR	482	6.2	5.4–7.2	476	6.6	5.7–7.6
	≥4-fold rise, % (n)	482	53.7 (259)	49.2–58.3	476	57.1 (272)	52.6–61.6
19F	GMT (Day 1)	534	394.9	349.6–446.1	536	463.7	409.9–524.5
	GMT (Day 30)	547	2,462.4	2,222.2–2,728.7	522	2,518.7	2,261.9–2,804.6
	GMFR	490	5.2	4.6–5.9	492	4.7	4.2–5.4
	≥4-fold rise, % (n)	490	53.7 (263)	49.1–58.2	492	48.8 (240)	44.3–53.3
22F	GMT (Day 1)	481	101.5	81.2–126.8	490	100.4	80.0–125.8
	GMT (Day 30)	543	2,250.0	1,974.7–2,563.8	516	2,900.1	2,535.5–3,317.3
	GMFR	438	15.9	12.8–19.8	446	20.6	16.4–25.9
	≥4-fold rise, % (n)	438	64.2 (281)	59.5–68.7	446	67.5 (301)	62.9–71.8
23F	GMT (Day 1)	471	110.2	93.3–130.1	473	165.7	138.3–198.6
	GMT (Day 30)	540	2,130.1	1,853.1–2,448.4	519	2,714.1	2,360.1–3,121.2
	GMFR	427	13.9	11.7–16.6	436	11.9	9.9–14.3
	≥4-fold rise, % (n)	427	73.1 (312)	68.6–77.2	436	67.2 (293)	62.6–71.6
33F	GMT (Day 1)	555	1,791.9	1,581.0–2,030.9	537	2,131.4	1,880.8–2,415.4
	GMT (Day 30)	547	7,879.3	7,041.9–8,816.4	518	10,077.9	8,946.7–11,352.2
	GMFR	510	4.3	3.8–4.9	488	4.6	4.0–5.3
	≥4-fold rise, % (n)	510	44.1 (225)	39.8–48.5	488	44.9 (219)	40.4–49.4

CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; OPA, opsonophagocytic activity; V114, 15-valent pneumococcal conjugate vaccine. Within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution for continuous endpoints and using the exact binomial method proposed by Clopper and Pearson for dichotomous endpoints.

Table 4. GMCs, GMFR, and proportion of participants with ≥4-fold rise in serotype-specific IgG antibodies from pre-vaccination to 30 days after vaccination with V114.

		Concomitant (N = 599)			Non-concomitant (N = 598)		
Serotype	Outcome	n	Response	95% CI	n	Response	95% CI
1	GMC (Day 1)	586	0.67	0.60–0.75	566	0.73	0.65–0.82
	GMC (Day 30)	574	4.12	3.69–4.59	551	5.49	4.92–6.12
	GMFR	568	6.1	5.5–6.9	549	7.5	6.6–8.5
	≥4-fold rise, % (n)	568	54.8 (311)	50.6–58.9	549	60.8 (334)	56.6–64.9
3	GMC (Day 1)	586	0.16	0.15–0.18	566	0.15	0.14–0.17
	GMC (Day 30)	574	0.75	0.68–0.83	551	0.85	0.77–0.95
	GMFR	568	4.4	4.0–4.8	549	5.1	4.6–5.7
	≥4-fold rise, % (n)	568	46.8 (266)	42.7–51.0	549	50.6 (278)	46.4–54.9
4	GMC (Day 1)	586	0.26	0.24–0.29	566	0.28	0.25–0.31
	GMC (Day 30)	574	1.44	1.28–1.62	551	1.88	1.67–2.13
	GMFR	568	5.3	4.8–5.9	549	6.5	5.8–7.4
	≥4-fold rise, % (n)	568	53.7 (305)	49.5–57.9	549	57.2 (314)	52.9–61.4
5	GMC (Day 1)	586	1.31	1.19–1.45	566	1.32	1.20–1.44
	GMC (Day 30)	574	4.68	4.16–5.27	552	5.20	4.59–5.89
	GMFR	568	3.5	3.2–3.9	550	4.0	3.5–4.5
	≥4-fold rise, % (n)	568	38.0 (216)	34.0–42.2	550	40.4 (222)	36.2–44.6
6A	GMC (Day 1)	586	0.35	0.31–0.39	566	0.42	0.36–0.48
	GMC (Day 30)	574	5.71	4.89–6.67	551	8.87	7.64–10.30
	GMFR	568	15.6	13.7–17.8	549	19.9	17.3–22.9
	≥4-fold rise, % (n)	568	77.3 (439)	73.6–80.7	549	79.2 (435)	75.6–82.6
6B	GMC (Day 1)	586	0.48	0.43–0.55	566	0.51	0.45–0.59
	GMC (Day 30)	572	6.99	6.01–8.13	551	9.47	8.20–10.93
	GMFR	566	14.0	12.2–15.9	549	17.8	15.5–20.5
	≥4-fold rise, % (n)	566	74.9 (424)	71.1–78.4	549	79.1 (434)	75.4–82.4
7F	GMC (Day 1)	586	0.66	0.58–0.75	566	0.76	0.67–0.86
	GMC (Day 30)	574	4.51	4.03–5.04	552	5.52	4.89–6.24
	GMFR	568	6.7	6.0–7.5	550	7.2	6.4–8.2
	≥4-fold rise, % (n)	568	60.2 (342)	56.1–64.3	550	59.6 (328)	55.4–63.8
9V	GMC (Day 1)	586	0.65	0.58–0.73	565	0.63	0.56–0.70
	GMC (Day 30)	574	3.88	3.47–4.34	550	4.20	3.76–4.69
	GMFR	568	5.9	5.3–6.6	547	6.6	5.8–7.4
	≥4-fold rise, % (n)	568	54.4 (309)	50.2–58.6	547	55.4 (303)	51.1–59.6
14	GMC (Day 1)	586	2.17	1.89–2.48	566	2.23	1.94–2.55
	GMC (Day 30)	574	8.25	7.22–9.43	511	9.81	8.58–11.23
	GMFR	568	3.8	3.4–4.3	549	4.4	3.9–5.0
	≥4-fold rise, % (n)	568	39.8 (226)	35.7–43.9	549	43.0 (236)	38.8–47.2
18C	GMC (Day 1)	586	0.86	0.77–0.97	566	1.00	0.89–1.13
	GMC (Day 30)	573	9.72	8.67–10.91	551	13.03	11.63–14.61
	GMFR	567	11.2	9.8–12.8	549	12.9	11.2–14.9
	≥4-fold rise, % (n)	567	67.5 (383)	63.5–71.4	549	68.9 (378)	64.8–72.7
19A	GMC (Day 1)	585	2.09	1.89–2.32	566	2.24	2.03–2.48
	GMC (Day 30)	574	13.14	11.79–14.64	551	15.35	13.77–17.11
	GMFR	567	6.4	5.7–7.1	549	6.8	6.1–7.7
	≥4-fold rise, % (n)	567	59.3 (336)	55.1–63.3	549	60.1 (330)	55.9–64.2
19F	GMC (Day 1)	586	1.07	0.94–1.21	566	1.09	0.97–1.23
	GMC (Day 30)	573	8.61	7.58–9.76	551	9.79	8.66–11.08
	GMFR	567	8.1	7.2–9.2	549	8.9	7.9–10.1
	≥4-fold rise, % (n)	567	63.7 (361)	59.6–67.6	549	66.7 (366)	62.6–70.6
22F	GMC (Day 1)	586	0.43	0.38–0.48	566	0.42	0.37–0.47
	GMC (Day 30)	574	3.31	2.94–3.72	552	4.29	3.79–4.85
	GMFR	568	7.6	6.6–8.6	550	10.1	8.8–11.6
	≥4-fold rise, % (n)	568	56.5 (321)	52.3–60.6	550	64.9 (357)	60.8–68.9
23F	GMC (Day 1)	586	0.51	0.45–0.57	566	0.58	0.52–0.66
	GMC (Day 30)	574	5.49	4.80–6.27	550	7.02	6.17–8.00
	GMFR	568	10.7	9.4–12.2	548	11.9	10.3–13.7
	≥4-fold rise, % (n)	568	67.4 (383)	63.4–71.3	548	69.7 (382)	65.7–73.5
33F	GMC (Day 1)	586	1.67	1.48–1.89	566	1.80	1.61–2.02
	GMC (Day 30)	574	8.99	8.01–10.08	551	10.87	9.66–12.23
	GMFR	568	5.5	4.8–6.1	549	6.0	5.3–6.8
	≥4-fold rise, % (n)	568	50.4 (286)	46.2–54.5	549	53.9 (296)	49.6–58.1

CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold rise; IgG, immunoglobulin G; V114, 15-valent pneumococcal conjugate vaccine. Within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution for continuous endpoints and using the exact binomial method proposed by Clopper and Pearson for dichotomous endpoints.

Table 5. GMT, GMFR, and proportion of participants with seroconversion or HAI titer ≥1:40 from pre-vaccination to 30 days or at 30 days after vaccination with QIV.

		Concomitant (N = 599)			Non-concomitant (N = 598)		
Strain	Outcome	n	Response	95% CI	n	Response	95% CI
H1N1	GMT (Day 1)	585	25.84	23.39–28.55	587	23.32	21.09–25.79
	GMT (Day 30)	576	127.35	114.55–141.58	567	112.60	100.96–125.57
	GMFR	569	4.2	3.8–4.7	561	4.2	3.8–4.8
	Seroconversion, % (n)	569	48.5 (276)	44.3–52.7	561	48.3 (271)	44.1–52.5
	≥1:40, % (n)	576	85.9 (495)	82.8–88.7	567	84.7 (480)	81.4–87.5
H3N2	GMT (Day 1)	585	37.04	33.02–41.54	587	34.23	30.58–38.31
	GMT (Day 30)	576	90.11	80.29–101.13	567	83.63	74.88–93.40
	GMFR	569	2.2	2.0–2.4	561	2.2	2.0–2.4
	Seroconversion, % (n)	569	27.8 (158)	24.1–31.6	561	25.3 (142)	21.8–29.1
	≥1:40, % (n)	576	77.4 (446)	73.8–80.8	567	79.2 (449)	75.6–82.5
B/Victoria	GMT (Day 1)	585	13.77	12.66–14.96	587	14.01	12.91–15.21
	GMT (Day 30)	576	35.58	32.35–39.12	567	37.13	33.72–40.88
	GMFR	569	2.1	2.0–2.3	561	2.2	2.0–2.4
	Seroconversion, % (n)	569	29.2 (166)	25.5–33.1	561	28.7 (161)	25.0–32.6
	≥1:40, % (n)	576	55.0 (317)	50.9–59.1	567	54.9 (311)	50.6–59.0
B/Yamagata	GMT (Day 1)	585	11.78	10.93–12.70	587	11.48	10.67–12.36
	GMT (Day 30)	576	33.82	30.95–36.94	567	33.03	30.06–36.29
	GMFR	569	2.3	2.1–2.5	561	2.3	2.1–2.4
	Seroconversion, % (n)	569	31.1 (177)	27.3–35.1	561	30.5 (171)	26.7–34.5
	≥1:40, % (n)	576	52.4 (302)	48.3–56.6	567	50.8 (288)	46.6–55.0

CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; HAI, hemagglutination inhibition; QIV, quadrivalent influenza vaccine.
Within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution for continuous endpoints and using the exact binomial method proposed by Clopper and Pearson for dichotomous endpoints.

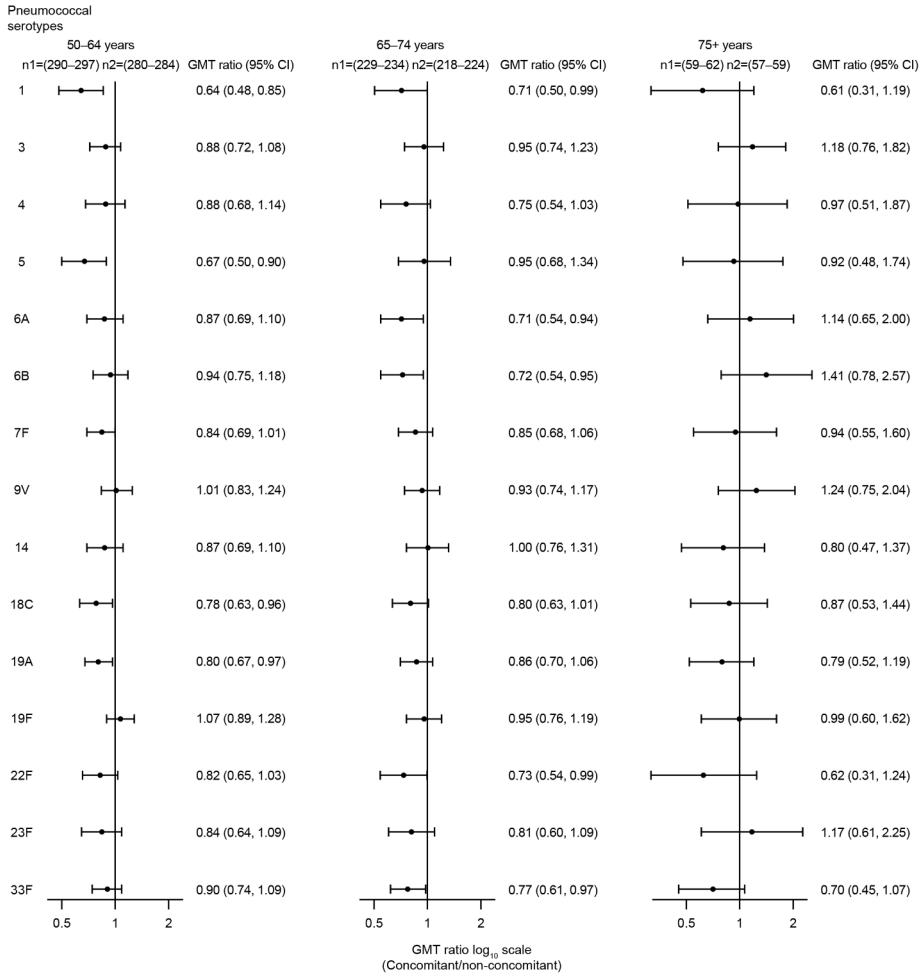

Figure 7. Estimated serotype-specific OPA GMTs 30 days after vaccination with V114 by age group. The forest plot depicts serotype-specific OPA GMT ratios with the corresponding 95% CIs within each age group. GMTs, GMT ratios, and 95% CIs were estimated from a constrained longitudinal data analysis model. n1 is the number of subjects contributing to the analysis from the concomitant group across all 15 serotypes. n2 is the number of subjects contributing to the analysis from the non-concomitant group across all 15 serotypes. CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity; V114, 15-valent pneumococcal conjugate vaccine.

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Author contributions

Severance R, Schwartz H, and Davis M: enrollment of participants and/or data collection; review of the manuscript.

Li J and Buchwald UK: study concept and design; preparation of the manuscript.

Connor L, Pedley A, Sterling TM, Nolan KM, and Tamms GM: analysis and interpretation of data; preparation of the manuscript.

Dagan R, Hartzel J, and Musey LK: study concept and design; analysis and interpretation of data; review of the manuscript.

Data sharing

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Disclosure of potential conflicts of interest

Connor L, Li J, Pedley A, Hartzel J, Sterling TM, Nolan KM, Tamms GM, Musey LK, and Buchwald UK are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA. Dagan R has received grants/research support from Pfizer, Merck Sharp & Dohme, and Medimmune, has been a scientific consultant for Pfizer, MeMed, Merck Sharp & Dohme Corp, and BiondVax, has served on advisory boards of Pfizer, Merck Sharp & Dohme Corp, and BiondVax, and has been a speaker for Pfizer. Severance R has received research support from Merck Sharp & Dohme Corp.

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