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Subgroup Analysis of a Randomized Phase III Trial (PNEU-AGE)

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Safety and Immunogenicity of V114, a 15-valent Pneumococcal Conjugate Vaccine, Compared With 13-valent Pneumococcal Vaccine in Japanese Adults Aged ≥65 Years: Subgroup Analysis of a Randomized Phase III Trial (PNEU-AGE)

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Running title: V114 in Japanese adults

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Keywords: pneumococcal vaccine; V114; 15-valent PCV; adults; PCV13
ABSTRACT

The safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine (PCV), was assessed in a pivotal Phase III trial in healthy adults ≥50 years of age (NCT03950622, Japic-CTI 194845). We report a subgroup analysis of 245 Japanese participants (all ≥65 years of age). Participants were randomized 1:1 to receive a single dose of V114 or 13-valent PCV (PCV13). Immune responses were evaluated at baseline and 30 days post-vaccination. Non-serious and serious adverse events (AEs) were evaluated post-vaccination through 14 days and 6 months, respectively. Proportions of participants experiencing solicited and serious AEs were comparable for both vaccines; all solicited AEs were mild or moderate in severity. Serotype-specific opsonophagocytic activity (OPA) geometric mean titers at 30 days post-vaccination were comparable between groups for all 13 shared serotypes and higher with V114 for the unique serotypes 22F and 33F. Proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from pre-vaccination to 30 days post-vaccination were higher with V114 than PCV13 for serotypes 3, 22F, and 33F. V114 was well tolerated and immunogenic in Japanese adults ≥65 years of age, with safety and immunogenicity profiles consistent with that seen in the overall study population.
INTRODUCTION

Pneumococcal disease caused by *Streptococcus pneumoniae* is associated with significant morbidity and mortality worldwide (1). Adults ≥65 years of age are one of the most vulnerable age groups, due to the effects of immunosenescence and age-related physiological changes to the respiratory system (2, 3), as well as an increased incidence of comorbid at-risk conditions (4). In Japan, approximately 65–70% of adults diagnosed with invasive pneumococcal disease (IPD) are ≥65 years of age (5, 6), and case fatality rates for IPD in Japanese adults are approximately 20% (6). In addition, the incidence of pneumococcal pneumonia is estimated to range from 5–17 cases per 1,000 Japanese adults ≥65 years of age, rising with increasing age (7), and around 70% of community-onset pneumonia cases in Japanese adults lead to hospitalization (7).

The 23-valent pneumococcal polysaccharide vaccine (PPSV23; PNEUMOVAX®23, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is provided for the prevention of pneumococcal disease in adults ≥65 years of age in Japan as part of the national immunization program (8, 9), and has been shown to be moderately effective in the prevention of pneumococcal pneumonia (9, 10). The 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar13®, Wyeth LLC, marketed by Pfizer, New York, NY, USA) is also approved for the prevention of pneumococcal disease in adults ≥65 years of age in Japan, although it is not yet included in the national immunization program (9, 11). However, PCV13 was introduced into the Japanese infant vaccination program in 2013 (8), which has resulted in a significant reduction in IPD caused by serotypes included in the vaccine, but also in the emergence of disease caused by non-vaccine serotypes...
across age groups (5, 8, 12). Non-PCV13 serotypes now account for more than 60% of all isolates in adult patients with IPD in Japan (5, 8). In addition, serotype 3, which is included in PCV13, remains responsible for 18% of all cases of pneumococcal pneumonia and 12–17% of IPD cases in Japanese adults (5, 6, 8, 10, 13), and is present in 19% of non-invasive isolates (14).

To cover the broader burden of pneumococcal disease associated with non-vaccine serotypes, new pneumococcal conjugate vaccines (PCVs) have recently been developed, including a 20-valent PCV (PCV20) and a 15-valent PCV (V114). V114 (VAXNEUVANCE™, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) contains serotypes 22F and 33F, in addition to the 13 serotypes included in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) (15). V114 was developed to provide broader serotype coverage while maintaining strong immune responses to the serotypes included in PCV13. Serotypes 22F and 33F are important causes of pneumococcal disease globally; serotype 22F has been among the most common causes of IPD in Europe and North America in recent years, and serotype 33F has been frequently associated with IPD in young children in the United States (16-18). In adult populations in Japan, serotype 22F was responsible for approximately 5–10% of adult IPD cases from 2010 to 2018 (5, 6, 8). Both serotypes 22F and 33F are associated with invasive disease (19), and serotype 33F is also associated with multidrug resistance (20).

V114 has been evaluated in an extensive Phase III clinical development program, including studies in adults (15, 21-23), and studies in pediatric populations. As part of this program, a pivotal Phase III trial compared the safety and immunogenicity of V114 and PCV13 in healthy adults ≥50 years of age in the United
States, Japan, Spain, Canada, and Taiwan (15). The objective of the current analysis was to assess the safety and immunogenicity of V114 compared with PCV13 in Japanese participants from this pivotal Phase III study.
MATERIALS AND METHODS

Study design: PNEU-AGE was a Phase III, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 compared with PCV13 in healthy pneumococcal-vaccine naïve adults ≥50 years of age (Protocol V114-019, NCT03950622, EudraCT 2018–004316-22, Japic-CTI 194845). Here, the results of safety and immunogenicity analyses in the subgroup of Japanese participants are reported.

Detailed methodology of the main study has been previously published (15). In brief, participants were randomized 1:1 to receive a single dose (0.5 mL) of V114 or PCV13 administered intramuscularly. Randomization was stratified by age at enrollment (50–64 years, 65–74 years, and ≥75 years of age); all Japanese participants were required to be ≥65 years of age, in line with current Japanese pneumococcal vaccine recommendations. Participants were in generally good health and/or had stable underlying medical conditions and were naïve to pneumococcal vaccines. The study was conducted in accordance with the principals of Good Clinical Practice and was approved by the appropriate Institutional Review Boards and Regulatory Agencies. Written informed consent was obtained from each participant prior to any study procedure.

Study assessments: Solicited injection-site adverse events (AEs) and maximum daily body temperature were recorded by participants by electronic vaccination report card during days 1–5 after vaccination, and solicited systemic AEs were recorded during days 1–14 after vaccination. Participants were followed for all other (non-solicited) injection-site and systemic AEs during days 1–14 after vaccination. Severity of solicited AEs was categorized as previously reported (24).
Serious AEs (SAEs) and deaths were collected from time of signed consent to end of study (approximately 6 months after vaccination). All injection-site AEs were considered to be vaccine related.

For immunogenicity assessments, serum samples were drawn at baseline and at 30 days post-vaccination. Functional antibodies were measured using serotype-specific opsonophagocytic killing activity by validated microcolony multiplex opsonophagocytic assay (mMOPA) (25), and serotype-specific pneumococcal capsular polysaccharide immunoglobulin G (IgG) antibodies were evaluated using a validated multiplexed electrochemiluminescence (ECL) assay (26).

**Study endpoints and statistical methods:** Safety analyses were conducted in the All Participants as Treated (APaT) population, which consisted of all randomized participants who received study vaccination. Safety endpoints included proportions of participants with solicited injection-site AEs, solicited systemic AEs, and any AE, SAE, or vaccine-related SAE. Point estimates were provided for all safety endpoints and 95% confidence intervals (CI) and P values were provided for between-treatment differences in the proportion of participants with solicited AEs using the unstratified Miettinen and Nurminen method (27).

The Per-Protocol (PP) population served as the primary population for the analysis of immunogenicity data and consisted of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The primary immunogenicity objectives in the main PNEU-AGE study were to demonstrate non-inferiority of immune responses to V114 compared with PCV13 for shared serotypes and superiority of immune response for serotypes unique to V114 in terms of serotype-specific opsonophagocytic activity.
(OPA) at 30 days post-vaccination. A secondary objective was to demonstrate superiority of V114 compared with PCV13 for serotype 3. Serotype-specific IgG responses at 30 days following vaccination for all 15 serotypes included in V114 were also assessed as a secondary objective.

Subgroup analyses were performed to assess consistency of the results of the main study in the subpopulation of Japanese participants. Such analyses were not prespecified and the study was not specifically designed or powered to assess non-inferiority or superiority for this subgroup. As such, descriptive summaries of serotype-specific OPA geometric mean titers (GMTs) and GMT ratios at 30 days post-vaccination for all 15 serotypes, and proportions of participants with a ≥4-fold rise in OPA GMT from pre-vaccination to 30 days post-vaccination for serotypes 22F, 33F, and 3 are provided.

OPA GMTs, IgG geometric mean concentrations (GMCs), and OPA GMT and IgG GMC ratios (with corresponding 95% CIs) were estimated using serotype-specific constrained longitudinal data analysis (cLDA) models, as previously reported (15, 28). Between-treatment differences in proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination and corresponding 95% CIs were calculated using the Miettinen and Nurminen method.

All analyses were performed using SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).
RESULTS

**Study population:** In total, 245 Japanese participants were enrolled in PNEU-AGE, of whom 121 were randomized to receive V114 and 124 were randomized to receive PCV13. Consistent with the overall PNEU-AGE trial population (15), demographics and baseline characteristics of Japanese participants were similar between the two vaccination groups (Table 1). The median age of Japanese participants was 70.0 years (range 65–83 years). Approximately 18% of participants were ≥75 years of age, and approximately 52% were female.

**Safety:** The proportions of Japanese participants experiencing one or more AE were 69.4% in the V114 group and 58.1% in the PCV13 group (Table 2). The proportions of participants reporting solicited AEs were generally similar between the V114 and PCV13 groups. The most frequently reported solicited injection-site AE was injection-site pain, reported in 43.8% of participants who received V114 and 37.1% of participants who received PCV13. The most frequently reported solicited systemic AE was myalgia, reported in 11.6% and 5.6% of V114 and PCV13 recipients, respectively. The majority of solicited AEs reported by participants receiving V114 and PCV13 were mild in severity (Fig. 1) and were of short duration (≤3 days, data not shown). No participants reported a solicited AE rated as severe. The majority of participants (99.2%) had a maximum body temperature of <100.4°F (38.0°C) and no participants had maximum body temperature of ≥101.3°F (38.5°C).

Two participants in the Japanese study population who received V114 reported SAEs (back pain and meniscus injury reported by one participant each; Table 2). Both events occurred ≥60 days after vaccination and were considered by the
investigators not to be vaccine related. No Japanese participants died during the study.

**Immunogenicity**: Serotype-specific OPA GMTs at 30 days post-vaccination were generally comparable between the V114 and PCV13 groups for the 13 shared serotypes (with the exception of serotype 3, for which OPA GMTs were higher with V114) and higher among recipients of V114 for the two unique serotypes, 22F and 33F (Fig. 2). For the two unique serotypes, the proportion of participants with a ≥4-fold rise in serotype-specific OPA responses from pre-vaccination to 30 days post-vaccination was higher following administration of V114 compared with PCV13 (percentage point differences 59.1% for serotype 22F and 47.1% for serotype 33F; Table 3). For serotype 3, the proportion of participants with a ≥4-fold rise in OPA titer was also higher, compared with PCV13 (percentage point difference 27.4%).

Trends observed for serotype-specific IgG GMCs at 30 days post-vaccination were generally consistent with the OPA GMT primary analysis results (Fig. 3).
DISCUSSION

In this analysis of Japanese participants ≥65 years of age from the PNEU-AGE trial, V114 was generally well tolerated, with a safety profile comparable to that of PCV13. V114 was immunogenic for all 15 serotypes included in the vaccine, with higher immune responses to the unique serotypes, 22F and 33F, compared with PCV13. Serotype 22F has emerged as an important cause of pneumococcal disease in Japanese adults since the introduction of PCV13 into the infant vaccination program (5, 6, 8). Therefore, V114 has the potential to broaden protection against pneumococcal disease caused by an important serotype in older Japanese adults, while demonstrating a comparable safety profile to PCV13 and maintaining protection against the serotypes shared between the two vaccines. The higher immune responses to serotype 3 observed among recipients of V114 compared with recipients of PCV13 in this study suggest that V114 may provide improved protection against this serotype, which continues to cause disease in Japanese adults, despite inclusion in PCV13 (5, 6, 8, 10, 13).

In this analysis, the majority of solicited AEs with V114 were mild and of short duration, which is consistent with the safety profile observed in the overall PNEU-AGE trial population and in the subgroup of adults ≥65 years of age from PNEU-AGE (15). It is also consistent with observations from another Phase III clinical trial of V114 in healthy adults ≥50 years of age (PNEU-PATH) (21). No SAEs considered by the investigators to be related to study vaccine and no deaths were reported among the PNEU-AGE Japanese participants.

Consistent with the overall PNEU-AGE trial population, the subgroup of adults ≥65 years of age, and the PNEU-PATH trial, OPA GMTs in Japanese participants
≥65 years of age were comparable between the V114 and PCV13 groups for the 13 shared serotypes (with the exception of serotype 3, for which was OPA GMTs were higher with V114) and were higher for the two serotypes unique to V114 (serotypes 22F and 33F) (15, 21). The larger proportion of participants with a ≥4 fold rise in serotype-specific OPA responses to serotypes 22F, 33F, and 3 from pre-vaccination to 30 days post-vaccination in the V114 group observed in Japanese participants is also consistent with the overall PNEU-AGE population and subgroup of adults ≥65 years of age (15), although the between-group difference for serotype 3 was larger in the Japanese participants compared with the other two populations. Notably, in the overall PNEU-AGE population, OPA responses to serotype 3 in recipients of V114 were superior to those of PCV13 recipients (15), although this finding is yet to be confirmed in a real-world effectiveness study. Serotype-specific IgG responses were consistent with OPA responses in Japanese participants and the other populations studied (15, 21).

Limitations of the Phase III trial have been previously described (15). First, as immune correlates of protection have not been established for adults, the immunogenicity findings cannot be directly translated to protection from pneumococcal disease caused by serotypes in V114. Second, the immunogenicity data were limited to 30 days post-vaccination; thus, long-term persistence of antibody responses was not assessed. However, durability of immune responses to V114 in healthy adults for up to 1 year post-vaccination has been demonstrated in another global study (29). An additional limitation of the current analysis is the small number of Japanese participants, which was not statistically powered to make conclusions on non-inferiority or superiority.
In conclusion, the findings of this analysis show that V114 is well tolerated and immunogenic in Japanese adults ≥65 years of age, with safety and immunogenicity profiles consistent with that seen in an overall population of healthy adults aged ≥50 years that included participants from Europe, North America, and elsewhere in Asia.
Acknowledgements

The authors would like to thank the patients, their families, and all investigators involved in the PNEU-AGE study in Japan.

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The PNEU-AGE study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conflicts of interest

Kishino H., Sawata M., Igarashi R., and Shirakawa M. are employees of MSD K.K., Tokyo, Japan. Musey L.K., Pedley A, Platt H.L., and Buchwald U.K. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

Author contributions

Kishino H, Igarashi R: study concept and design for Japanese subgroup analysis; analysis, acquisition, and interpretation of data; preparation and review of the manuscript.

Sawata M, Shirakawa M: study concept and design for Japanese subgroup analysis; analysis and interpretation of data; preparation and review of the manuscript
Pedley A, Platt HL: study concept and design; analysis, acquisition, and interpretation of data; review of the manuscript.

Musey LK, Buchwald UK: 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., Rahway, 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.
References


**Fig. 1.** Proportions of participants with solicited AEs after vaccination with V114 or PCV13 by severity.

Solicited AEs collected post-vaccination (days 1–5 for injection-site events and days 1–14 for systemic events) are shown with severity grades (V114 $N = 121$; PCV13 $N = 124$). The height of the stacked bar represents the total percentage of participants reporting the AE. The severity grades (mild, moderate, or severe) within the bar indicate the proportion of the total attributed. AE, adverse event; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.
**Fig. 2.** Estimated OPA GMTs 30 days after V114 or PCV13 vaccination.

Forest plot depict the V114/PCV13 GMT ratios with corresponding 95% CIs. The 13 shared serotypes are displayed in the upper panel. The two serotypes unique to V114 are shown in the lower panel. GMTs, GMT ratios, and 95% CIs are estimated from a constrained longitudinal data analysis model. CI, confidence interval; GMT, geometric mean titer (1/dil); OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.
**Fig. 3.** Estimated IgG GMCs 30 days after V114 or PCV13 vaccination.

Forest plot depict the V114/PCV13 GMC ratios with corresponding 95% CIs. The 13 shared serotypes are displayed in the upper panel. The two serotypes unique to V114 are shown in the lower panel. GMCs, GMC ratios, and 95% CIs are estimated from a constrained longitudinal data analysis model. CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.
Table 1. Baseline participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>V114 (N = 121)</th>
<th>PCV13 (N = 124)</th>
<th>Total (N = 245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74, n (%)</td>
<td>99 (81.8)</td>
<td>102 (82.3)</td>
<td>201 (82.0)</td>
</tr>
<tr>
<td>≥75, n (%)</td>
<td>22 (18.2)</td>
<td>22 (17.7)</td>
<td>44 (18.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>70.8 (3.8)</td>
<td>70.5 (4.1)</td>
<td>70.6 (4.0)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>71.0 (65–83)</td>
<td>70.0 (65–81)</td>
<td>70.0 (65–83)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>57 (47.1)</td>
<td>61 (49.2)</td>
<td>118 (48.2)</td>
</tr>
<tr>
<td>Female</td>
<td>64 (52.9)</td>
<td>63 (50.8)</td>
<td>127 (51.8)</td>
</tr>
</tbody>
</table>

N, number of participants randomized and vaccinated.

PCV13, 13-valent pneumococcal conjugate vaccine; SD, standard deviation; V114, 15-valent pneumococcal conjugate vaccine. Table includes all vaccinated participants.
Table 2. Number and proportion of participants with AEs following vaccination with V114 or PCV13

<table>
<thead>
<tr>
<th></th>
<th>V114 (N = 121)</th>
<th>PCV13 (N = 124)</th>
<th>Difference vs PCV13</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>84 (69.4)</td>
<td>72 (58.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>70 (57.9)</td>
<td>60 (48.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>36 (29.8)</td>
<td>25 (20.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vaccine-related AE</td>
<td>78 (64.5)</td>
<td>67 (54.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>70 (57.9)</td>
<td>60 (48.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>26 (21.5)</td>
<td>16 (12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SAE</td>
<td>2 (1.7)†</td>
<td>1 (0.8)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vaccine-related SAE</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solicited injection-site AEs (Day 1–5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>53 (43.8)</td>
<td>46 (37.1)</td>
<td>6.7 (−5.6, 18.8)</td>
<td>0.286</td>
</tr>
<tr>
<td>Injection-site swelling</td>
<td>20 (16.5)</td>
<td>13 (10.5)</td>
<td>6.0 (−2.6, 14.9)</td>
<td>0.167</td>
</tr>
<tr>
<td>Injection-site erythema</td>
<td>21 (17.4)</td>
<td>20 (16.1)</td>
<td>1.2 (−8.3, 10.8)</td>
<td>0.798</td>
</tr>
<tr>
<td>Solicited systemic AEs (Day 1–14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (7.4)</td>
<td>5 (4.0)</td>
<td>3.4 (−2.7, 10.0)</td>
<td>0.252</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (5.0)</td>
<td>6 (4.8)</td>
<td>0.1 (−5.9, 6.2)</td>
<td>0.965</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14 (11.6)</td>
<td>7 (5.6)</td>
<td>5.9 (−1.2, 13.6)</td>
<td>0.098</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (0.8)</td>
<td>3 (2.4)</td>
<td>−1.6 (−6.2, 2.4)</td>
<td>0.326</td>
</tr>
</tbody>
</table>

Estimated differences, CIs, and P values are calculated based on the unstratified Miettinen & Nurminen method.

N, number of participants randomized and vaccinated; n, number of participants with one or more adverse events.

†Back pain and meniscus injury reported by one participant each. ‡Ureterolithiasis reported by one participant.
AE, adverse event; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.
Table 3. Proportion of participants with a ≥4-fold rise in OPA GMT from pre-vaccination to 30 days after V114 or PCV13 vaccination

<table>
<thead>
<tr>
<th>Serotype</th>
<th>V114 (N = 121)</th>
<th>PCV13 (N = 124)</th>
<th>Difference (V114−PCV13) % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m/n</td>
<td>%</td>
<td>m/n</td>
</tr>
<tr>
<td>22F</td>
<td>78/110</td>
<td>70.9</td>
<td>12/102</td>
</tr>
<tr>
<td>33F</td>
<td>61/119</td>
<td>51.3</td>
<td>5/120</td>
</tr>
<tr>
<td>3</td>
<td>88/118</td>
<td>74.6</td>
<td>57/121</td>
</tr>
</tbody>
</table>

Estimated differences and CIs are calculated based on the unstratified Miettinen & Nurminen method.

N, number of participants randomized and vaccinated; n, number of participants contributing to the analysis; m, number of participants with indicated response.

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

<table>
<thead>
<tr>
<th>Injection-site</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>V114 PCV13</td>
<td>V114 PCV13</td>
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<tr>
<td>V114 PCV13</td>
<td>V114 PCV13</td>
</tr>
</tbody>
</table>

Pain: 43.8% (Mild), 37.1% (Moderate)
Swelling: 16.5% (Mild), 10.5% (Moderate)
Erythema: 17.4% (Mild), 16.1% (Moderate)
Fatigue: 7.4% (Mild), 4.0% (Moderate)
Myalgia: 11.6% (Mild), 5.6% (Moderate)
Headache: 5.0% (Mild), 4.8% (Moderate)
Arthralgia: 0.8% (Mild), 2.4% (Moderate)
### Pneumococcal serotype

#### 13 shared serotypes

<table>
<thead>
<tr>
<th>Serotype</th>
<th>GMT (95% CI)</th>
<th>Serotype</th>
<th>GMT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>157.8</td>
<td>120</td>
<td>167.2</td>
</tr>
<tr>
<td>3</td>
<td>233.4</td>
<td>120</td>
<td>708.1</td>
</tr>
<tr>
<td>4</td>
<td>363.7</td>
<td>120</td>
<td>397.6</td>
</tr>
<tr>
<td>5</td>
<td>3228.5</td>
<td>120</td>
<td>2736.5</td>
</tr>
<tr>
<td>6A</td>
<td>2543.1</td>
<td>120</td>
<td>1631.2</td>
</tr>
<tr>
<td>6B</td>
<td>4209.4</td>
<td>120</td>
<td>4545.8</td>
</tr>
<tr>
<td>7F</td>
<td>1564.0</td>
<td>120</td>
<td>1476.3</td>
</tr>
<tr>
<td>9V</td>
<td>1328.0</td>
<td>120</td>
<td>1490.0</td>
</tr>
<tr>
<td>14</td>
<td>1981.2</td>
<td>120</td>
<td>1880.3</td>
</tr>
<tr>
<td>18C</td>
<td>2100.8</td>
<td>120</td>
<td>2701.9</td>
</tr>
<tr>
<td>19A</td>
<td>1159.4</td>
<td>120</td>
<td>1257.7</td>
</tr>
<tr>
<td>19F</td>
<td>1364.4</td>
<td>120</td>
<td>942.7</td>
</tr>
</tbody>
</table>

#### 2 serotypes unique to V114

<table>
<thead>
<tr>
<th>Serotype</th>
<th>GMT (95% CI)</th>
<th>Serotype</th>
<th>GMT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22F</td>
<td>1950.5</td>
<td>120</td>
<td>66.4</td>
</tr>
<tr>
<td>33F</td>
<td>6373.0</td>
<td>120</td>
<td>862.5</td>
</tr>
</tbody>
</table>

**GMT ratio log_{10} scale (V114/PCV13)**
Pneumococcal serotype
13 shared serotypes

<table>
<thead>
<tr>
<th>Serotype</th>
<th>V114 GMC</th>
<th>PCV13 GMC</th>
<th>GMC ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.35</td>
<td>7.12</td>
<td>0.75 (0.55, 1.03)</td>
</tr>
<tr>
<td>3</td>
<td>0.94</td>
<td>0.46</td>
<td>2.04 (1.61, 2.57)</td>
</tr>
<tr>
<td>4</td>
<td>1.76</td>
<td>2.14</td>
<td>0.83 (0.60, 1.13)</td>
</tr>
<tr>
<td>5</td>
<td>4.05</td>
<td>6.07</td>
<td>0.67 (0.49, 0.91)</td>
</tr>
<tr>
<td>6A</td>
<td>8.28</td>
<td>6.62</td>
<td>1.25 (0.87, 1.79)</td>
</tr>
<tr>
<td>6B</td>
<td>7.32</td>
<td>5.23</td>
<td>1.40 (0.98, 2.00)</td>
</tr>
<tr>
<td>7F</td>
<td>5.07</td>
<td>6.95</td>
<td>0.73 (0.55, 0.97)</td>
</tr>
<tr>
<td>9V</td>
<td>4.20</td>
<td>4.70</td>
<td>0.90 (0.65, 1.22)</td>
</tr>
<tr>
<td>14</td>
<td>7.69</td>
<td>9.88</td>
<td>0.78 (0.57, 1.06)</td>
</tr>
<tr>
<td>18C</td>
<td>6.57</td>
<td>8.83</td>
<td>0.74 (0.54, 1.02)</td>
</tr>
<tr>
<td>19A</td>
<td>10.41</td>
<td>13.43</td>
<td>0.78 (0.56, 1.08)</td>
</tr>
<tr>
<td>19F</td>
<td>6.58</td>
<td>7.98</td>
<td>0.83 (0.58, 1.17)</td>
</tr>
<tr>
<td>23F</td>
<td>6.03</td>
<td>5.95</td>
<td>1.01 (0.73, 1.40)</td>
</tr>
</tbody>
</table>

2 serotypes unique to V114

<table>
<thead>
<tr>
<th>Serotype</th>
<th>V114 GMC</th>
<th>PCV13 GMC</th>
<th>GMC ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22F</td>
<td>2.86</td>
<td>0.31</td>
<td>9.15 (7.06, 11.85)</td>
</tr>
<tr>
<td>33F</td>
<td>11.35</td>
<td>1.51</td>
<td>7.50 (5.86, 9.60)</td>
</tr>
</tbody>
</table>