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# Immunogenicity and Safety of MMRV and PCV-7 Administered Concomitantly in Healthy Children

**AUTHORS:** Michael Leonardi, MD,<sup>a</sup> Kenneth Bromberg, MD,<sup>b</sup> Roger Baxter, MD,<sup>c</sup> Julie L. Gardner, BS,<sup>d</sup> Stephanie Klopfer, PhD,<sup>a</sup> Ouzama Nicholson, MD,<sup>d</sup> Michael Brockley, BA,<sup>e</sup> James Trammel, MS,<sup>e</sup> Vicky Leamy, MPH,<sup>f</sup> Wendy Williams, MS,<sup>d</sup> Barbara Kuter, PhD, MPH,<sup>d</sup> and Florian Schödel, MD<sup>d</sup>

<sup>a</sup>Palmetto Pediatrics, North Charleston, South Carolina; <sup>b</sup>Brooklyn Hospital Center, Brooklyn, New York; <sup>c</sup>Kaiser Permanente Vaccine Study Center, Oakland, California; <sup>d</sup>Merck Research Laboratories, North Wales, Pennsylvania; <sup>e</sup>i3 Statprobe, Ann Arbor, Michigan; and <sup>f</sup>i3 Research, Cary, North Carolina

## KEY WORDS

measles, mumps, rubella, varicella, vaccine, MMRV, pneumococcal 7-valent conjugate vaccine, PCV-7, immunization, concomitant administration

## ABBREVIATIONS

ACIP—Advisory Committee on Immunization Practices

MMR—measles mumps rubella vaccine

MMRV—measles mumps rubella and varicella vaccine

PCV-7—pneumococcal 7-valent conjugate vaccine

AE—adverse experience

VRC—vaccination report card

VZV—varicella-zoster virus

ELISA—enzyme-linked immunosorbent assay

gpELISA—glycoprotein antigen-based ELISA

GMT—geometric mean titer

CI—confidence interval

Drs Kuter, Schödel, Klopfer, and Williams were involved in the study concept and design and analysis and interpretation of data; Drs Leonardi, Bromberg, Baxter, and Leamy were involved in enrollment of subjects and data collection and analysis and interpretation of data; and Drs Trammel, Nicholson, and Gardner were involved in analysis and interpretation of data. The report was primarily drafted by Drs Leonardi, Gardner, Klopfer, Nicholson, and Kuter. All coauthors approved the final version of the manuscript.

This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT00109343, V221, Protocol 019).

Dr Nicholson's current affiliation is GlaxoSmithKline, Philadelphia, PA.

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Address correspondence to Barbara Kuter, PhD, MPH, Merck & Co, Inc, PO Box 4, West Point, PA 19486. E-mail: [barbara\\_kuter@merck.com](mailto:barbara_kuter@merck.com)

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**FINANCIAL DISCLOSURE:** Drs Gardner, Nicholson, Williams, Kuter, and Schödel, current and former employees of the sponsor, may own stock or stock options in the company;

(Continued on last page)



**WHAT'S KNOWN ON THIS SUBJECT:** It is recommended that between 12 and 15 months of age children should receive a fourth dose of pneumococcal 7-valent conjugate vaccine and the first dose of a measles, mumps, rubella, and varicella vaccine.



**WHAT THIS STUDY ADDS:** This study found that both measles, mumps, rubella, and varicella and pneumococcal 7-valent conjugate vaccines could be administered concomitantly in healthy children 12 to 15 months of age without affecting the safety or the antibody response to any of the components of either vaccine.

## abstract

**OBJECTIVE:** We assessed the immunogenicity and safety of a combination measles, mump, rubella, and varicella vaccine (MMRV) (ProQuad [Merck & Co, Inc, West Point, PA]) administered to healthy children concomitantly with a pneumococcal 7-valent conjugate vaccine (PCV-7) (Prevnar [Pfizer, Philadelphia, PA]).

**PATIENTS AND METHODS:** Healthy 12- to 15-month-old children who lacked vaccination and clinical histories for measles, mumps, rubella, varicella, and zoster but had written documentation of receipt of a 3-dose primary series of PCV-7 were randomly assigned in a 2:1:1 ratio to receive either the MMRV and PCV-7 (group 1), PCV-7 followed 6 weeks later by MMRV (group 2), or MMRV followed 6 weeks later by PCV-7 (group 3). The primary safety analysis was 56 days (28 days after each visit). Immunogenicity was evaluated 6 weeks after each vaccination.

**RESULTS:** A total of 1027 children were enrolled (group 1: 510; group 2: 258; group 3: 259). For all 3 groups, the antibody response rate was  $\geq 96.8\%$  for measles, mumps, and rubella,  $\geq 88.0\%$  for varicella-zoster virus, and  $\geq 98.3\%$  for all of the 7 *Streptococcus pneumoniae* serotypes. The immune responses to all antigens present in MMRV and PCV-7 were similar whether administered concomitantly or sequentially. The incidence of local and systemic adverse experiences (AEs) was comparable between group 1 and groups 2 and 3 combined. No vaccine-related serious AEs were reported.

**CONCLUSIONS:** Concomitant administration of the MMRV and PCV-7 is highly immunogenic and generally well tolerated. Similar immune responses between the groups support concomitant administration of the MMRV and PCV-7 to healthy children 12 to 15 months of age. *Pediatrics* 2011;128:e1387–e1394

The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of vaccines for measles, mumps, rubella, and varicella as soon as possible after the first birthday.<sup>1</sup> A second dose of a measles, mumps, rubella (MMR)-containing vaccine as well as a second dose of a varicella-containing vaccine are recommended at 4 to 6 years of age.<sup>2,3</sup> On the basis of data obtained from the US National Immunization Survey in 2008 among children 19 to 35 months of age, it is estimated that the coverage rate with 1 or more doses is 92% for MMR (85.9%–95.6% according to state) and 90% for varicella vaccine (77.0%–94.4% according to state).<sup>4</sup> Data derived in 2008 from private national vaccine usage claims for US physician offices and ambulatory care suggest that among children 4 to 6 years of age, compliance with the 2-dose varicella vaccine recommendation is ~65% to 70 (unpublished data, Merck & Co, Inc). This coverage rate is lower than the estimated 90% to 95% second-dose coverage for MMR (unpublished data, Merck & Co, Inc). Use of the currently licensed combination MMR and varicella vaccine (MMRV) provides an option for improving compliance with ACIP recommendations for either dose of MMR and varicella vaccine without increasing the number of injections. Currently, the ACIP does not express a preference for MMRV over separate administration of MMR and varicella vaccines for the first dose because of a small increase in febrile seizures among recipients of MMRV compared with MMR and varicella vaccines.<sup>5</sup> Because no increase in febrile seizures was found after the second dose; MMRV is the preferred vaccine for the second dose of each vaccine.

In February 2000, a pneumococcal 7-valent conjugate vaccine (PCV-7) (Prevnar [Pfizer, Philadelphia, PA]) was licensed in the United States for

use in infants and young children. The ACIP recommends that the vaccine be administered in a 4-dose series for all children 2 to 23 months of age and for children 24 to 59 months of age who are at increased risk for pneumococcal disease.<sup>6</sup> A single dose of PCV-7 is also recommended for all healthy children 24 to 59 months of age who have not completed any recommended schedule for PCV-7.<sup>7</sup>

On the basis of these recommendations, in the United States concomitant administration of MMRV and PCV-7 could occur at 12 months and 4 to 6 years of age. To evaluate the safety and immunogenicity of the concomitant administration of MMRV and PCV-7, a randomized multicenter trial was conducted to assess whether both vaccines could be administered concomitantly in children 12 to 15 months of age without affecting the safety or the antibody response to any of the components of either vaccine.

## PATIENTS AND METHODS

### Study Subjects

The study was conducted at 24 centers in the United States from March 2006 (first subject enrolled) through September 2007 (last subject visit completed). Approximately 1000 children were recruited at the time of routine child well visits. Written informed consent was obtained from the parent or legal guardian of each child before enrollment. Healthy children 12 to 15 months of age were eligible to participate if they had no clinical history of measles, mumps, rubella, varicella, or herpes zoster infection; no previous vaccination with MMR or varicella vaccine; and a 3-dose primary series of PCV-7. Children were excluded if they had recent exposure to measles, mumps, rubella, varicella, or herpes zoster; allergy to any vaccine component; immunodeficiency or neoplastic disease; inactivated/conjugate vac-

cine  $\leq 14$  days or live vaccine  $\leq 30$  days before enrollment; received immunoglobulin or any blood-derived product  $\leq 5$  months before the study or planned to receive such products during the study; history of any seizure; any coagulation disorder that would contraindicate intramuscular injections; recent febrile illness; and participation in other clinical trials. The study was conducted in accordance with the principles of good clinical practice and approved by the appropriate institutional review boards and regulatory agencies.

### Vaccine/Randomization

ProQuad (MMRV, Merck & Co, Inc, West Point, PA) is a sterile, lyophilized preservative-free, live-virus vaccine that contains measles, mumps, rubella and varicella viruses. After reconstitution it is administered as a 0.5-mL subcutaneous injection. Prevnar (PCV-7) is a pneumococcal 7-valent conjugate (diphtheria CRM197 protein) vaccine for immunization against *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F and is administered as a 0.5-mL intramuscular injection.

Subjects were randomly assigned to 1 of 3 vaccination groups in a 2:1:1 ratio according to a computer-generated allocation schedule. Subjects in group 1 received MMRV and a fourth dose of PCV-7 concomitantly at separate injection sites on day 1 (visit 1); no vaccine was administered at day 43 (visit 2). Subjects in group 2 received a fourth dose of PCV-7 on day 1 (visit 1) and received MMRV on day 43 (visit 2). Subjects in group 3 received MMRV on day 1 (visit 1) and a fourth dose of PCV-7 on day 43 (visit 2). All subjects received a second dose of MMRV  $\geq 90$  days after the first dose.

The allocation schedule for all sites was held at a central location. Randomization to 1 of the 3 groups was

disclosed immediately before vaccination through a telephone call to the central location. The parent/legal guardian of the subject enrolled in the clinical study, the investigator, the clinical study-site personnel, and all sponsor and sponsor designee personnel were unblinded to the group assignment for each subject once randomization occurred.

### Safety Surveillance

All participants were to be followed for safety for 28 days after visit 1 and 2. For the purpose of this analysis, these 2 safety follow-up periods were combined into a 56-day follow-up window that was used to assess safety associated with the concomitant administration of MMRV and PCV-7 versus administration of the 2 vaccines 6 weeks apart. Parents/legal guardians were asked to record their child's adverse experiences (AEs) on a vaccination report card (VRC). The VRC prompted for injection-site pain/tenderness, redness (erythema), and swelling for 5 days after each vaccination and numeric temperatures for 28 days after each visit. When a child's temperature was  $\geq 101.0^{\circ}\text{F}$  ( $\geq 38.3^{\circ}\text{C}$ ) axillary or  $\geq 103.0^{\circ}\text{F}$  ( $\geq 39.4^{\circ}\text{C}$ ) rectal ( $\geq 102.0^{\circ}\text{F}$  [ $\geq 39.0^{\circ}\text{C}$ ] oral equivalent), study personnel recorded the fever as an AE. Parents also recorded all local and systemic AEs for 28 days after each visit. The investigator assessed each reported AE as to seriousness, action taken, and causal relationship to the study vaccine.

All children with rashes and mumps-like symptoms were evaluated by study personnel. The maximum number and types of skin lesions (if present) and any other associated complaints were recorded on the VRC. On the basis of the appearance of the rash and parental history, study personnel determined whether the rash was con-

sidered to be like that of measles, rubella, varicella, or zoster.

### Laboratory Methods

A 3- to 7-mL blood sample was collected from each child before receipt of any vaccines on day 1 and  $\sim 6$  weeks later (study day 43). To determine measles, mumps, rubella, and varicella-zoster virus (VZV) antibody levels, serum samples were tested by using appropriately sensitive enzyme-linked immunosorbent assay (ELISA) methods.<sup>8–10</sup> Antibody levels  $< 255$  mIU/mL for measles,  $< 10$  antibody U/mL for mumps,  $< 10$  IU/mL for rubella, and  $< 1.25$  glycoprotein antigen-based ELISA U/mL for VZV were considered seronegative. For measles, mumps, and rubella, the antibody response rates were defined as the proportion of subjects who were seronegative before vaccination who became seropositive after vaccination. The antibody response rate for VZV was defined as the proportion of subjects who were seronegative at baseline and whose postvaccination titer was  $\geq 5$  gpELISA U/mL (a value correlated with long-term protection).<sup>11,12</sup> For PCV-7, the geometric mean titers (GMTs) to *S pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F at 6 weeks postvaccination were evaluated by using the pneumococcal polysaccharide ELISA.<sup>13</sup> The percentage with response  $\geq 0.2$   $\mu\text{g}/\text{mL}$  and  $\geq 0.35$   $\mu\text{g}/\text{mL}$  also were summarized. All assays were performed by Merck Research Laboratories, Wayne, PA.

### Statistical Methods

Three formal statistical hypotheses were evaluated to assess immunogenicity responses: (1) noninferiority between groups for the antigens in MMRV as measured by antibody response rates; (2) acceptability of the antibody response rates in the investigational group for the antigens in MMRV; and (3) noninferiority between groups for the antigens in PCV-7. Suc-

cess of the trial required satisfying all 3 immunogenicity hypotheses, and success within a hypothesis required demonstrating either noninferiority or acceptability for all components being tested.

The primary immunogenicity analysis was performed on a per protocol basis. The analysis of antibody response rates to measles, mumps, rubella, and varicella was based on comparison of group 1 (investigational group) to group 3 (control group) by using the 1-sided noninferiority test developed by Miettinen and Nurminen<sup>14</sup> with study center stratification (at the  $\alpha = .025$  level). The statistical criteria for noninferiority for each of the 4 antigens required that the lower bound of the 95% confidence interval (CI) for the difference in response rates (group 1 minus group 3) was more than  $-10$  percentage points. The statistical criteria for an acceptable antibody response rate required that for subjects in group 1, the lower bound of the 2-sided 95% exact 1-sample binomial CI for the antibody response rate be  $> 90\%$  for measles, mumps, and rubella and  $> 76\%$  for varicella. The analysis of noninferiority of the GMTs to the 7 serotypes in PCV-7 was based on comparison of group 1 to group 2 (control group) using an analysis of covariance (ANCOVA) model for each antigen. The dependent variable in each ANCOVA model was the natural log-transformed postvaccination titer, with treatment group, study center, and the natural log-transformed prevaccination titer as independent variables. To conclude noninferiority of the concomitant administration of MMRV and PCV-7 with respect to the 7 *S pneumoniae* serotypes, the GMTs in the investigational group could be no more than 2.0-fold lower than the GMTs in group 2 for all antigens, which required that the lower bound of the 95% CI for the ratio of GMTs (group 1 divided by group 2) be  $> 0.5$ .

Power for the 3 primary immunogenicity hypotheses was calculated on the

basis of the following assumptions (unpublished data, Merck & Co, Inc):<sup>1</sup> 5% of the subjects had a baseline measles antibody titer  $\geq 255$  mIU/mL, a baseline mumps antibody titer  $\geq 10$  mIU/mL, or a baseline rubella antibody titer  $\geq 10$  IU/mL, and 10% had a baseline varicella antibody titer  $\geq 1.25$  gpELISA U/mL<sup>2</sup>; an additional 10% of subjects had nonevaluable serology at either baseline or postvaccination because of drop-out or other protocol violations<sup>3</sup>; the expected response rates in both groups for measles, mumps, rubella, and varicella were 95%, 95%, 95%, and 90%, respectively<sup>4</sup>; the SDs of the natural logarithms of the 6-week antibody titers for *S pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were not  $> 1.3$  in each group<sup>5</sup>; and the 15 primary immunogenicity comparisons were independent. These conditions resulted in  $\sim 425$  subjects in group 1,  $\sim 225$  subjects in group 2, and  $\sim 212$  subjects in group 3 available for these comparisons; overall, the power for the 3 primary immunogenicity hypotheses was  $\sim 91.7\%$ .

To address the primary safety hypothesis, the safety profile of group 1 was compared with that of groups 2 and 3 combined. Two 28-day follow-up periods after visits 1 and 2 were combined for each subject to produce a 56-day follow-up period during which all subjects received the first dose of MMRV and the fourth dose of PCV-7. Group 1 did not receive a vaccine at visit 2 but was included to assess safety for the same period of time for all subjects.

For injection-site AEs that occurred on days 1 to 5 after vaccination and for systemic clinical AEs (incidence  $\geq 5\%$  in any vaccination group) that occurred during the 56-day follow-up period, risk differences were estimated, and the 95% 2-sided CI was provided. Injection-site reactions; measles-like, rubella-like, varicella-like, and zoster-like rashes; mumps-like symptoms;

and elevated temperature ( $\geq 102.2^\circ\text{F}$  or  $\geq 38.9^\circ\text{C}$  oral equivalent) were prompted for on the VRC and risk differences and 95% CIs were summarized regardless of incidence rate.

## RESULTS

### Subject Characteristics

A total of 1027 subjects were enrolled in the study: 510 subjects were randomly assigned to group 1 (MMRV and PCV-7); 258 were randomly assigned to group 2 (PCV-7 followed by MMRV); and 259 were randomly assigned to group 3

(MMRV followed by PCV-7) (Figure 1). Although not formally tested, the 3 treatment groups were generally comparable with respect to age, race, and gender, and had similar study completion rates (Figure 1, Table 1).

### Immunogenicity

The antibody response rates and GMTs to measles, mumps, rubella, and varicella (Table 2) were similar when MMRV was administered concomitantly with PCV-7 (group 1) and when MMRV was administered alone (group

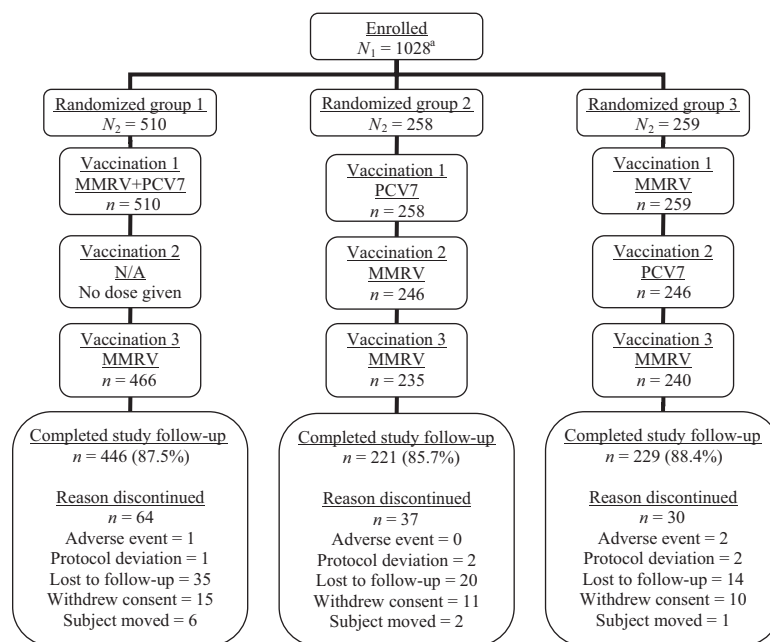


FIGURE 1

Subject accounting.

TABLE 1 Subject Demographics

	Group 1, MMRV + PCV-7 (N = 510)	Group 2, PCV Followed by MMRV (N = 258)	Group 3, MMRV Followed by PCV-7 (N = 259)
Gender, n (%)			
Male	280 (54.9)	138 (53.5)	142 (54.8)
Female	230 (45.1)	120 (46.5)	117 (45.2)
Age at study entry, mo			
Mean (SD)	12.6 (0.96)	12.5 (0.93)	12.6 (0.98)
Median	12	12	12
Range	12–15	12–15	12–15
Race/ethnicity, n (%)			
Caucasian	83 (16.3)	36 (14.0)	36 (13.9)
Asian	18 (3.5)	5 (1.9)	8 (3.1)
African American	335 (65.7)	161 (62.4)	174 (67.2)
Hispanic	46 (9.0)	31 (12.0)	26 (10.0)
Other	28 (5.5)	25 (9.7)	15 (5.8)

**TABLE 2** Summary of Antibody Responses to MMRV 6 Weeks After Vaccination

Antigen/Parameter	Group 1, MMRV + PCV-7 (N = 510)	Group 3, MMRV Followed by PCV-7 (N = 259)
<b>Measles</b>		
≥255 mIU/mL, n/N (% [95% CI])	395/406 (97.3 [95.2–98.6])	203/204 (99.5 [97.3–100.0])
GMT (95% CI)	2969.9 (2704.7–3261.1)	3420.4 (3084.1–3796.3)
<b>Mumps</b>		
≥10 mIU/mL, n/N (% [95% CI])	390/403 (96.8 [94.5–98.3])	205/208 (98.6 [95.8–99.7])
GMT (95% CI)	93.4 (84.9–102.6)	103.8 (92.1–116.9)
<b>Rubella</b>		
≥10 mIU/mL, n/N (% [95% CI])	372/377 (98.7 [96.9–99.6])	191/195 (97.9 [94.8–99.4])
GMT (95% CI)	60.1 (55.8–64.9)	52.5 (47.0–58.6)
<b>Varicella</b>		
≥5 gpELISA U/mL, n/N (% [95% CI])	350/379 (92.3 [89.2–94.8])	169/192 (88.0 [82.6–92.3])
GMT (95% CI)	14.2 (13.1–15.4)	12.9 (11.4–14.5)

Noninferiority for MMRV was established because the lower bound of the 95% CI for the estimated risk difference (RD) in response rates was more than  $-10.0$  for each antigen. For measles, the RD was  $-2.2$  (95% CI:  $-4.6$  to  $0.2$ ). For mumps, the RD was  $-1.9$  (95% CI:  $-4.5$  to  $1.0$ ). For rubella, the RD was  $0.9$  (95% CI:  $-1.3$  to  $4.1$ ). For varicella, the RD was  $4.5$  (95% CI:  $-0.4$  to  $10.4$ ). *N* indicates the number of subjects vaccinated in each treatment group; *n*, number of seronegative subjects at baseline and with postvaccination serology contributing to the per-protocol analysis; Ab, antibody.

**TABLE 3** Summary of Antibody Response to *S pneumoniae* Serotypes 6 Weeks After Vaccination

Serotype/Parameter	Group 1, MMRV + PCV-7 (N = 510)	Group 2, PCV Followed by MMRV (N = 258)
<b>4</b>		
≥0.2 μg/mL, n/N (% [95% CI])	403/410 (98.3 [96.5–99.3])	193/193 (100.0 [98.1–100.0])
≥0.35 μg/mL, n/N (% [95% CI]), n/N (% [95% CI])	390/410 (95.1 [92.6–97.0])	181/193 (93.8 [89.4–96.7])
GMT (95% CI)	1.54 (1.41–1.67)	1.34 (1.19–1.51)
<b>6B</b>		
≥0.2 μg/mL, n/N (% [95% CI])	408/410 (99.5 [98.2–99.9])	192/192 (100 [98.1–100.0])
≥0.35 μg/mL, n/N (% [95% CI])	408/410 (99.5 [98.2–99.9])	192/192 (100 [98.1–100.0])
GMT (95% CI)	9.17 (8.40–10.02)	8.22 (7.17–9.41)
<b>9V</b>		
≥0.2 μg/mL, n/N (% [95% CI])	407/409 (99.5 [98.2–99.9])	193/193 (100 [98.1–100.0])
≥0.35 mcg/mL, n/N (% [95% CI])	407/409 (99.5 [98.2–99.9])	193/193 (100 [98.1–100.0])
GMT (95% CI)	2.98 (2.76–3.21)	2.71 (2.44–3.02)
<b>14</b>		
≥0.2 μg/mL, n/N (% [95% CI])	407/408 (99.8 [98.6–100.0])	193/193 (100 [98.1–100.0])
≥0.35 μg/mL, n/N (% [95% CI])	407/408 (99.8 [98.6–100.0])	192/193 (99.5 [97.1–100.0])
GMT (95% CI)	6.88 (6.32–7.48)	5.61 (4.95–6.36)
<b>18C</b>		
≥0.2 μg/mL, n/N (% [95% CI])	404/408 (99.0 [97.5–99.7])	191/193 (99.0 [96.3–99.9])
≥0.35 μg/mL, n/N (% [95% CI])	399/408 (97.8 [95.9–99.0])	189/193 (97.9 [94.8–99.4])
GMT (95% CI)	2.35 (2.14–2.58)	2.23 (1.96–2.55)
<b>19F</b>		
≥0.2 μg/mL, n/N (% [95% CI])	407/408 (99.8 [98.6–100.0])	192/192 (100 [98.1–100.0])
≥0.35 μg/mL, n/N (% [95% CI])	406/408 (99.5 [98.2–99.9])	192/192 (100 [98.1–100.0])
GMT (95% CI)	3.59 (3.31–3.91)	3.22 (2.85–3.64)
<b>23F</b>		
≥0.2 μg/mL, n/N (% [95% CI])	412/413 (99.8 [98.7–100.0])	194/197 (98.5 [95.6–99.7])
≥0.35 μg/mL, n/N (% [95% CI])	409/413 (99.0 [97.5–99.7])	192/197 (97.5 [94.2–99.2])
GMT (95% CI)	4.24 (3.85–4.67)	3.71 (3.16–4.36)

Noninferiority for the 7 serotypes in PCV-7 was established because the lower bound of the 95% CI for the estimated GMT fold difference (FD) was  $>0.5$  for each serotype. The FDs ranged from 1.1- to 1.2-fold across the 7 serotypes, and the corresponding lower 95% CI limits ranged from 0.9- to 1.0-fold. *N* indicates number of subjects vaccinated in each treatment group; *n*, number of subjects contributing to the per-protocol analysis for the given serotype.

3). The lower bounds of the 95% CI for the response rate difference (group 1 minus group 3) were  $-4.6$ ,  $-4.5$ ,  $-1.3$ ,

and  $-0.4$  percentage points for measles, mumps, rubella, and varicella, respectively. Thus, the prespecified crite-

ria for noninferiority (95% CI lower bound more than  $-10$  percentage points) were met for each of the 4 antigens in MMRV. In addition, the lower bounds of the 95% CI for the antibody response rates for measles, mumps, rubella, and varicella when MMRV was administered concomitantly with PCV-7 (95.2%, 94.5%, 96.9%, and 89.2%, respectively) met the prespecified acceptability criteria. The GMTs for the 7 *S pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) in group 1 were noninferior compared with those in group 2 (Table 3). The lower bounds of the 95% CI for the GMT fold difference (group 1 divided by group 2) ranged from 0.9-fold to 1.0-fold, thus meeting the noninferiority requirement of being  $>0.5$ -fold.

## Safety

The overall rate of serious AEs in group 1 (0.6%) versus groups 2 and 3 combined (0.8%) was not significantly different. None of the serious AEs were considered vaccine related. In group 3, stage IV neuroblastoma was diagnosed in 1 subject 8 days after receipt of the MMRV vaccine; this subject's participation in the study was discontinued, and the subject died 218 days after receiving the vaccination. The event was not considered by the investigator to be related to the study vaccine.

During the 56-day follow-up period, the proportion of subjects in group 1 versus groups 2 and 3 combined was comparable in terms of 1 or more AEs (82.5% vs 85.2%), systemic AEs (71.1% vs 74.2%), and injection-site AEs (48.0% vs 52.3%), respectively (Table 4). The most commonly reported systemic AEs were pyrexia, otitis media, and upper respiratory infection. Group 1 and groups 2 and 3 combined were comparable with respect to the incidence rates of systemic AEs with 2 exceptions. Both nasopharyngitis and in-

**TABLE 4** Unsolicited and Solicited Clinical AEs That Occurred During the 56-Day Safety Follow-up Window

	Group 1, MMRV + PCV-7 Concomitantly (N = 510), n (%)	Group 2 + Group 3 MMRV + PCV-7 Nonconcomitantly (N = 517), n (%)	Risk Difference, Concomitant vs Nonconcomitant, 95% CI <sup>a</sup>
Subjects with follow-up	498 (97.6)	507 (98.1)	
Subjects with			
≥1 AE	411 (82.5)	432 (85.2)	-2.7 (-7.3 to 1.9)
Systemic AEs	354 (71.1)	376 (74.2)	-3.1 (-8.6 to 2.4)
Injection-site AEs	239 (48.0)	265 (52.3)	-4.3 (-10.4 to 1.9)
Unsolicited systemic AEs (incidence ≥5% in either treatment group)			
Pyrexia	150 (30.1)	159 (31.4)	-1.2 (-6.9 to 4.5)
Upper respiratory tract infection	85 (17.1)	87 (17.2)	-0.1 (-4.8 to 4.6)
Otitis media	53 (10.6)	56 (11.0)	-0.4 (-4.3 to 3.5)
Cough	35 (7.0)	40 (7.9)	-0.9 (-4.2 to 2.4)
Diarrhea	39 (7.8)	38 (7.5)	0.3 (-3.0 to 3.7)
Rhinorrhea	35 (7.0)	35 (6.9)	0.1 (-3.1 to 3.3)
Dermatitis diaper	34 (6.8)	26 (5.1)	1.7 (-1.3 to 4.7)
Irritability	27 (5.4)	34 (6.7)	-1.3 (-4.3 to 1.7)
Rash (nonspecific)	27 (5.4)	31 (6.1)	-0.7 (-3.7 to 2.3)
Nasopharyngitis	24 (4.8)	42 (8.3)	-3.5 (-6.6 to -0.4)
Vomiting	22 (4.4)	33 (6.5)	-2.1 (-5.0 to 0.7)
Solicited systemic AEs (incidence > 0% in either treatment group)			
Measles-like rash	27 (5.4)	30 (5.9)	-0.5 (-3.4 to 2.4)
Mumps-like symptoms	0	0	NA
Rubella-like rash	4 (0.8)	4 (0.8)	0.0 (-1.3 to 1.4)
Varicella-like rash	11 (2.2)	6 (1.2)	1.0 (-0.6 to 2.9)
Solicited injection-site AEs (incidence > 0% in either treatment group) <sup>b</sup>			
Injection-site rash, MMRV injection site	6 (1.2)	12 (2.4)	-1.2 (-3.1 to 0.5)
Injection-site rash, PCV-7 injection site	5 (1.0)	3 (0.6)	0.4 (-0.9 to 1.8)

Percentages were calculated on the basis of the number of subjects with follow-up. Although a subject may have had ≥2 AEs, the subject was counted only once within a category. The same subject may appear in different categories.

<sup>a</sup> Risk differences and CIs are based on the pooled incidence rates across all study centers.

<sup>b</sup> Does not include injection-site redness (erythema), pain/tenderness and swelling, which were solicited during days 1 to 5 postvaccination only. These AEs are summarized in TABLE 5

95% CI was not calculated if no events were observed.

**TABLE 5** Injection-Site AEs Prompted for on the Vaccination Report Card, Days 1 to 5 After Administration of MMRV and PCV-7

	Group 1, MMRV + PCV-7 Concomitantly (N = 510), n (%)	Group 2 + Group 3, MMRV + PCV-7 Nonconcomitantly (N = 517), n (%)	Risk Difference, Concomitant vs Nonconcomitant, 95% CI <sup>a</sup>
Subjects with follow-up	498 (97.6)	495 (95.7)	
Subjects with ≥1 injection-site AE after MMRV	163 (32.7)	144 (29.1)	Not applicable
Erythema	63 (12.7)	63 (12.7)	-0.1 (-4.3 to 4.1)
Pain/tenderness	125 (25.1)	127 (25.7)	-0.6 (-6.0 to 4.9)
Swelling	55 (11.0)	52 (10.5)	0.5 (-3.4 to 4.4)
Subjects with ≥1 injection-site AE after PCV-7	203 (40.8)	198 (40.1)	Not applicable
Erythema	106 (21.3)	114 (23.1)	-1.8 (-7.0 to 3.4)
Pain/tenderness	157 (31.5)	148 (30.0)	1.6 (-4.2 to 7.3)
Swelling	92 (18.5)	101 (20.4)	-2.0 (-6.9 to 3.0)

Percentages were calculated on the basis of the number of subjects with follow-up. Although a subject may have had 2 or more distinct episodes of the same specific injection-site AE, the subject was counted only once in the overall total for that specific AE.

<sup>a</sup> Risk differences and CIs are based on the pooled incidence rates across all study centers.

somnia were reported at a statistically significantly lower rate by subjects in group 1 compared with subjects in groups 2 and 3 combined. The rate of vaccine-associated rashes (measles like, rubella like, varicella zoster like, and injection-site rashes) and mumps-like symptoms were comparable for group 1 versus groups 2 and 3 combined (Table 4).

The rates of injection-site AEs on days 1 to 5 (Table 5) were comparable for AEs reported at the MMRV injection site (32.7% for group 1 and 29.1% for groups 2 and 3 combined) and AEs reported at the PCV-7 injection site (40.8% for group 1 and 40.1% for groups 2 and 3 combined).

Overall, 22.3% of subjects in group 1 and groups 2 and 3 combined reported a maximum temperature ≥102.2°F (39.0°C), oral equivalent (no statistical difference).

## DISCUSSION

The immunogenicity and safety data from this study support the concomitant administration of MMRV and PCV-7 to healthy children 12 to 15 months of age. This study demonstrated that the concomitant administration of the 2 vaccines elicits adequate antibody responses to measles, mumps, rubella, varicella, and all 7 *S pneumoniae* serotypes found in PCV-7 on the basis of prespecified noninferiority criteria. The study also showed that MMRV and PCV-7 were well tolerated when administered concomitantly. There were no clinically significant differences in safety profiles among the groups. The most common systemic AE considered related to vaccination was fever, reported after vaccination in ~22% of all study subjects. There was no evidence that concomitant administration of MMRV and PCV-7 increased the rate of fever compared with separate administration of the vaccines. The most common

injection-site AEs were injection-site swelling, redness, and pain, which were mild and short in duration (<3 days). Of the vaccine-associated rashes and mumps-like symptoms, measles-like rash was the most commonly reported AE and occurred in ~5% of subjects. Occurrence of these AEs did not differ statistically among the concomitant and nonconcomitant study groups. The AEs rates reported in this study were generally similar to those reported in earlier studies of MMRV.<sup>15</sup>

The strength of this study is that it was adequately powered and well controlled, and more than 85% of subjects completed all required follow-up. A limitation of the study is that the majority of subjects were white, although earlier studies showed little difference in immune responses according to ethnicity.<sup>15</sup> Parental completion of a diary card for 28 days also may have resulted in reporting fatigue over time.

The current ACIP recommendations describe a small increased risk of febrile seizures 5 to 12 days after the first dose of MMRV compared with the first dose of MMR and varicella vaccines given concomitantly (0.7 vs 0.3 per 1000 children).<sup>16</sup> Two children who participated in this study were re-

ported to have had a febrile seizure after receipt of the vaccine (days 9 and 29); neither event was considered by the investigator to be vaccine related.

Although the coverage rates for MMR are generally high in many parts of the world, many countries have yet to implement varicella vaccine, and some have implemented use of a single dose only. Use of the MMRV for either the first or second, or for both doses would allow for varicella vaccine to be included in the routine immunization schedule without an increase in the number of injections

In a previous study, MMRV was administered with diphtheria-tetanus-acellular pertussis (DTaP) vaccine and with the combined *Haemophilus influenzae* type B conjugate vaccine and hepatitis B (Hib/Hep B) vaccines without any impact on safety or immunogenicity.<sup>17</sup> The data from this study support the administration of MMRV with PCV-7, 1 of several vaccines routinely administered as part of the childhood immunization schedule in many countries.

## CONCLUSIONS

Concomitant administration of MMRV and PCV-7 is highly immunogenic and generally well tolerated. Similar immune responses between the groups

evaluated support concomitant administration of MMRV and PCV-7 to healthy children 12 to 15 months of age.

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## REFERENCES

- Centers for Disease Control and Prevention. Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. *MMWR Morb Mortal Wkly Rep.* 2008;57(10):258–260
- Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. Measles, mumps, and rubella: vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 1998;47(1):1–57
- Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2007;56(1):1–40, CE-1–CE-4
- Centers for Disease Control and Prevention. National, state, and local area vaccination coverage among children aged 19–35 months: United States, 2008. *MMWR Morb Mortal Wkly Rep.* 2009;58(33):921–926
- National Center for Immunization and Respiratory Diseases. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Surveill Summ.* 2011;60(2):3–61
- Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2000;49(RR-9):1–35, CE-1–CE-6
- Centers for Disease Control and Prevention. Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV-7) in children aged 24–59 months who are not completely vaccinated. *MMWR Morb Mortal Wkly Rep.* 2008;57(13):343–344
- Wasmuth EH, Miller WJ. Sensitive enzyme-linked immunosorbent assay for antibody to varicella-zoster virus using purified VZV glycoprotein antigen. *J Med Virol.* 1990; 32(3):189–193
- Provost PJ, Krah DL, Kuter BJ, et al. Antibody assays suitable for assessing immune re-

- sponses to live varicella vaccine. *Vaccine*. 1991;9(2):111–116
10. Keller PM, Lonergan K, Neff BJ, Morton DA, Ellis RW. Purification of individual varicella-zoster virus (VZV) glycoproteins gpI, gpII, and gpIII and their use in ELISA for detection of VZV glycoprotein-specific antibodies. *J Virol Methods*. 1986;14(2):177–188
  11. Li S, Chan ISF, Matthews H, et al. Inverse relationship between six week postvaccination varicella antibody response to vaccine and likelihood of long term breakthrough infection. *Pediatr Infect Dis J*. 2002;21(4):337–342
  12. White CJ, Kuter BJ, Ngai A, et al. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatr Infect Dis J*. 1992;11(1):19–23
  13. Marchese RD, Jain NT, Antonello J, et al. Enzyme-linked immunosorbent assay for measuring antibodies to pneumococcal polysaccharides for the PNEUMOVAX 23 Vaccine: assay operating characteristics and correlation to the WHO international assay [published correction appears in *Clin Vaccine Immunol*. 2008;15(6):1034]. *Clin Vaccine Immunol*. 2006;13(8):905–912
  14. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985;4(2):213–226
  15. Kuter BJ, Brown ML, Hartzel J, et al; Study Group for ProQuad. Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). *Hum Vaccin*. 2006;2(5):205–214
  16. Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine*. 2009;27(34):4656–4661
  17. Shinefield H, Black S, Thear M, et al. Safety and immunogenicity of a measles, mumps, rubella, and varicella vaccine given with combined Haemophilus influenzae type B conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J*. 2006;25(4):287–292

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## Immunogenicity and Safety of MMRV and PCV-7 Administered Concomitantly in Healthy Children

Michael Leonardi, Kenneth Bromberg, Roger Baxter, Julie L. Gardner, Stephanie Klopfer, Ouzama Nicholson, Michael Brockley, James Trammel, Vicky Leamy, Wendy Williams, Barbara Kuter and Florian Schödel

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