Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines

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abstract

BACKGROUND: This study in 11- to 15-year-old boys and girls compared the immunogenicity and safety of GARDASIL 9 (9-valent human papillomavirus [9vHPV] vaccine) administered either concomitantly or nonconcomitantly with 2 vaccines routinely administered in this age group (Menactra [MCV4; *Neisseria meningitidis* serotypes A/C/Y/W-135] or Adacel [Tdap; diphtheria/tetanus/acellular pertussis]).

METHODS: Participants received 9vHPV vaccine at day 1 and months 2 and 6; the concomitant group (n = 621) received MCV4/Tdap concomitantly with 9vHPV vaccine at day 1; the nonconcomitant group (n = 620) received MCV4/Tdap at month 1. Antibodies to HPV-, MCV4-, and Tdap-relevant antigens were determined. Injection-site and systemic adverse events (AEs) were monitored for 15 days after any vaccination; serious AEs were monitored throughout the study.

RESULTS: The geometric mean titers for all HPV types in 9vHPV vaccine 4 weeks after dose 3, proportion of subjects with a fourfold rise or greater in titers for 4 *N meningitidis* serotypes 4 weeks after injection with MCV4, proportion of subjects with antibody titers to diphtheria and tetanus ≥0.1 IU/mL, and geometric mean titers for pertussis antigens 4 weeks after injection with Tdap were all noninferior in the concomitant group compared with the nonconcomitant group. Injection-site swelling occurred more frequently in the concomitant group. There were no vaccine-related serious AEs.

CONCLUSIONS: Concomitant administration of 9vHPV vaccine with MCV4/Tdap was generally well tolerated and did not interfere with the antibody response to any of these vaccines. This strategy would minimize the number of visits required to deliver each vaccine individually.

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WHAT'S KNOWN ON THIS SUBJECT: Previous studies have shown that concomitant administration of the quadrivalent human papillomavirus vaccine with MCV4 and Tdap was generally well tolerated and did not interfere with the immune responses to the respective vaccines.

WHAT THIS STUDY ADDS: Concomitant administration of the novel 9-valent human papillomavirus vaccine with MCV4 and Tdap, 2 vaccines that are currently recommended for routine vaccination of adolescents, did not compromise the safety, tolerability, and immunogenicity of the individual vaccines.

A 9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus (HPV; 9vHPV) vaccine was developed to cover 7 cancer-causing HPV types (HPV 16, 18, 31, 33, 45, 52, 58) that are together responsible for ~90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers, and 2 HPV types (HPV 6 and 11) that are responsible for 90% of genital warts.[1–5] In clinical studies, the 9vHPV vaccine prevented persistent infection and disease due to the HPV vaccine types in females 16 to 26 years of age[6]; efficacy findings were extended to girls and boys 9 to 15 years of age based on noninferior immunogenicity.[7] The 9vHPV vaccine was licensed in the United States in December 2014 under the name GARDASIL9 (Merck & Co., Inc., Kenilworth, NJ).[8] In February 2015, the Advisory Committee on Immunization Practices included GARDASIL9 in its recommendations for routine HPV vaccination of boys and girls at age 11 or 12 years and catchup vaccination in females 13 to 26 years and males 13 to 21 years not vaccinated previously.[9] Epidemiologic studies have demonstrated the acquisition of HPV soon after sexual initiation.[10] The median age of sexual debut is in the late teens (15–19 years) in most countries.[11] Thus, preadolescent boys and girls ≤15 years of age represent the ideal HPV vaccination population.

Most vaccine schedules worldwide rely on the concomitant administration of vaccines to improve the adherence to vaccination and to lower the cost of the programs, both in childhood and in adolescent vaccination. Because adolescents and adults need to maintain the protection given by several childhood vaccines, such as diphtheria, tetanus, and whooping cough, and need to be protected against *Neisseria meningitidis* before exposure to new populations such as those in high schools, college, or military service, etc, a booster dose of the diphtheria, tetanus, and acellular pertussis vaccines and routine vaccination for meningococcal serogroups A/C/Y/W-135 are recommended for adolescents in several countries.[12–14] A logical step was to include the 9vHPV vaccine in those already-established programs.

This study in boys and girls 11 to 15 years of age was designed to evaluate the immunogenicity and safety of the concomitant administration of a first dose of the 9vHPV vaccine with MCV4 (Menactra [meningococcal polysaccharide conjugate serogroups A/C/Y/W-135, Sanofi-Pasteur Inc, Lyon France]) and Tdap (Adacel [tetanus, diphtheria, acellular pertussis, Sanofi-Pasteur Inc]), 2 vaccines that are also recommended by the Advisory Committee on Immunization Practices for routine vaccination of preadolescents and adolescents and thereby help inform decisions by those who would be administering these vaccines together (Merck Protocol V503-005; NCT00988884).

METHODS

Study Population

Between October 22, 2009, and February 22, 2011, 1241 healthy boys and girls aged 11 to 15 who denied any sexual activity (and who were not planning on becoming sexually active through the course of the study) from 41 sites located in Chile (n = 100), Colombia (n = 140), Mexico (n = 200), Peru (n = 100), and the United States (n = 701) participated in the study. Reasons for exclusion from the study included pregnancy (determined by urine or serum β-human chorionic gonadotropin testing), known allergy to any vaccine component, thrombocytopenia, and immunosuppression/prior immunosuppressive therapy or previous receipt of an HPV vaccine. Subjects must not have been immunized against diphtheria, tetanus, and pertussis in the past 5 years or received a meningococcal vaccine. The study was conducted in conformity with applicable national or local requirements regarding ethical committee review, informed consent, and the protection of the rights and welfare of human subjects participating in biomedical research. An external data monitoring committee assessed safety findings throughout the study.

Study Design

This was an open-label, randomized, multicenter, comparative study. Subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups (concomitant group [Group A] or nonconcomitant group [Group B]) in a 1:1 ratio. At day 1, subjects in Group A received the first dose of 9vHPV vaccine in the deltoid muscle of the nondominant arm and MCV4 and Tdap in the deltoid muscle of the opposite arm. Subjects in Group B received the first dose of the 9vHPV vaccine on day 1 in the nondominant arm and MCV4 and Tdap 1 month later (month 1) in the dominant arm. All subjects received the second dose of the 9vHPV vaccine at month 2 and the third dose at month 6. The compositions of the 3 vaccines have been described previously.[6,15,16]

Blood samples were drawn immediately before vaccination at day 1, month 1, month 2 (Group B only), and month 7. Serum collected from all subjects at day 1 and month 7 underwent analysis of anti-HPV responses with a competitive Luminex Immunoassay, performed by PPD Vaccines and Biologics (Wayne, PA).[17] Serum collected at day 1 and month 1 for Group A and month 1 and month 2 for Group B underwent antibody testing for *N meningitidis* serogroups A/C/Y/W-135, diphtheria, tetanus, and pertussis. *N meningitidis* serogroups A/C/Y/W-135 serum bactericidal antibody assay was performed by the Health Protection Agency, Manchester Medical Microbiology Partnership (Manchester, United Kingdom). Diphtheria antibodies were measured by a diphtheria antitoxin cell culture assay performed by CSL Limited

TABLE 1 Noninferiority Criteria Corresponding to the Primary Hypotheses Related to Immunogenicity

Antigen	Paramater[a]	Expected Rates/SDs	Noninferiority Margin	Power
HPV type 6, 11, 16, 18, 31, 33, 45, 52, 58[b]	GMT	σ = 1.2	Twofold decrease	>99.9%
N meningitidis Serogroup A	% with fourfold or greater rise in titer	90%	10 percentage points	99.8%
N meningitidis Serogroup C	% with fourfold or greater rise in titer	90%	10 percentage points	99.8%
N meningitidis Serogroup Y	% with fourfold or greater rise in titer	80%	10 percentage points	95.1%
N meningitidis Serogroup W-135	% with fourfold or greater rise in titer	95%	10 percentage points	>99.9%
Diphtheria	% with titer >0.1 IU/mL	95%	10 percentage points	>99.9%
Tetanus	% with titer >0.1 IU/mL	92%	10 percentage points	99.8%
Pertussis PT	GMT	σ = 1.0	1.5-fold decrease	>99.9%
Pertussis FHA	GMT	σ = 0.8	1.5-fold decrease	>99.9%
Pertussis PRN	GMT	σ = 1.3	1.5-fold decrease	>99.9%
Pertussis FIM	GMT	σ = 1.5	1.5-fold decrease	97.0%

[a] Noninferiority of anti-HPV GMTs was measured at 4 weeks after dose 3 of 9vHPV vaccine. Noninferiority of *N meningitidis* serogroups A/C/Y/W-135, diphtheria, tetanus, and pertussis was measured 4 weeks postvaccination with MCV4 and Tdap.

[b] Each HPV type is tested separately

(Parkville, Australia) and calibrated against the First International Standard for Diphtheria Antitoxin. Tetanus antibodies were measured by a tetanus antitoxin enzyme immunoassay performed by CSL Limited and calibrated against the First International Standard for Tetanus Immunoglobulin. Pertussis antibodies were measured by an anti–pertussis toxin (PT) enzyme-linked immunosorbent assay (ELISA), anti–filamentous hemagglutinin (FHA) ELISA, anti-pertactin (PRN) ELISA, and anti–fimbriae 2/3 (FIM) ELISA performed by Michael E. Pichichero Laboratory, Rochester General Hospital Research Institute (Rochester, NY). The anti-PT ELISA, anti-FHA ELISA, and anti-FIM ELISA were calibrated against the US Food and Drug Administration Pertussis reference lot 3, and the anti-PRN ELISA was calibrated against the US Food and Drug Administration Pertussis reference lot 4.

Safety Measurements

All subjects received a vaccination report card (VRC) at the day 1 and months 1, 2, and 6 visits. VRCs for all the subjects were to be completed after the month-1 visit to provide a common period of follow-up even though subjects in the Group A were not vaccinated at month 1. On the VRC, the parent/guardian was asked to record (1) the subject's oral temperature in the evening of the day of each study vaccination and daily for a total of 5 days and (2) injection-site and systemic adverse events (AEs) for a total of 15 days including the day of vaccination after each study vaccination. Serious AEs were collected for the whole duration of the study regardless of causality and were followed for outcome. For all injection-site AEs, except erythema and swelling, subjects were instructed by the VRC to estimate the severity of AEs as mild (awareness of symptom but easily tolerated), moderate (discomfort enough to cause interference with usual activities), or severe (incapacitating with inability to work or do usual activity). For erythema and swelling, subjects were instructed by the VRC to measure an injection-site reaction at its greatest width ("maximum size") from edge to edge in maximum units ranging from 0 to >7 inches (17.5 cm) on the VRC, rounding up to the next unit if in between 2 units (each unit on the VRC measured ~1 inch [2.5 cm]).

Statistical Analysis

Primary immunogenicity analyses were done "per-protocol". Subjects in per-protocol analyses for the 9vHPV vaccine analyses had to receive all 3 doses of 9vHPV vaccine within acceptable day ranges and 1 dose of MCV4 and Tdap. In addition, for per-protocol analysis for 9vHPV vaccine, subjects had to (1) have at least 1 postdose 3 serology result within acceptable day ranges; (2) in analyses for the HPV6 and HPV11 components, be seronegative to both

TABLE 2 Summary of Subject Characteristics by Vaccination Group at Enrollment

Characteristic	Group A[a] (Concomitant) (*N* = 621)	Group B[a] (Nonconcomitant) (*N* = 620)
	n (%)	*n* (%)
Gender		
Male	310 (49.9)	310 (50.0)
Female	311 (50.1)	310 (50.0)
Age (y)		
Mean (SD)	12.2 (1.4)	12.1 (1.3)
Median (range)	12.0 (11 to 15)	12.0 (11 to 15)
Region		
North America	344 (55.4)	357 (57.6)
Latin America	277 (44.6)	263 (42.4)
Race		
American Indian or Alaska Native	60 (9.7)	59 (9.5)
Asian	6 (1.0)	8 (1.3)
Black or African American	38 (6.1)	41 (6.6)
Multiracial	217 (34.9)	217 (35.0)
Native Hawaiian or Other Pacific Islander	2 (0.3)	5 (0.8)
White	298 (48.0)	290 (46.8)

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as above and MCV4 and Tdap at month 1.

HPV6 and 11 at day 1; (3) in analyses for the other vaccine HPV types, be seronegative at day 1 only for the HPV type being analyzed; and (4) have no protocol violations that were considered to affect the immune responses. For per-protocol analysis for MCV4 and Tdap, subjects had to (1) have received MCV4 and Tdap within acceptable day ranges; (2) have at least 1 serology result after administration of MCV4 and Tdap within acceptable day ranges; and (3) have no protocol violations that were considered to affect the immune responses.

The primary and secondary end points for evaluating antibody responses to the 9vHPV vaccine were geometric mean titers (GMTs) to HPV6/11/16/18/31/33/45/52/58 and the percentages of subjects who seroconverted for each HPV type by 4 weeks after the third dose of 9vHPV vaccine. Anti-HPV cutoffs for determining serostatus were 30, 16, 20, 24, 10, 8, 8, 8, and 8 milli-Merck units/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. The primary end points for evaluating antibody response to MCV4 and Tdap were the proportions of subjects who achieved acceptable serological responses to *N meningitidis* serogroups A/C/Y/W-135, diphtheria, and tetanus and GMTs for pertussis (anti-PT, anti-FHA, anti-PRN, and anti-FIM) 4 weeks postvaccination with MCV4 and Tdap.

Noninferiority criteria for each immunogenicity hypothesis are shown in Table 1. Noninferiority of anti-HPV GMTs 4 weeks postdose 3 and pertussis GMTs 4 weeks postvaccination with MCV4 and Tdap was based on 1-sided tests of noninferiority (conducted at the 0.025 significance level) comparing GMTs between Group A and Group B for each component. An analysis of variance model (1 for each component) was used with a response of $\log_e$ individual titers and fixed effects for vaccination group and gender. Noninferiority of anti-HPV seroconversion rates and of serologic responses to *N meningitidis* serogroups

TABLE 3 Summary of Exclusions[a] From the Per-Protocol Immunogenicity Populations for 9vHPV Vaccine and MCV4 and Tdap

	Concomitant (Group A),[b] *N* = 619	Nonconcomitant (Group B),[b] *N* = 618
Exclusions for the 9vHPV vaccine		
Number randomized who received ≥1 injection, *n*	619	618
Number excluded from the per-protocol immunogenicity analyses, *n* (%)		
HPV6/11	117 (18.9)	104 (16.8)
HPV16	106 (17.1)	88 (14.2)
HPV18	103 (16.6)	83 (13.4)
HPV31	105 (17.0)	82 (13.3)
HPV33	99 (16.0)	81 (13.1)
HPV45	96 (15.5)	79 (12.8)
HPV52	98 (15.8)	80 (12.9)
HPV58	100 (16.2)	81 (13.1)
Reasons for exclusion, *n* (%)		
Did not receive MCV4 or Tdap	0 (0.0)	18 (2.9)
Received incorrect clinical material	0 (0.0)	2 (0.3)
Received nonstudy vaccination[c]	6 (1.0)	8 (1.3)
Received immunosuppressives before month 7	0 (0.0)	2 (0.3)
Incorrectly randomized	2 (0.3)	0 (0.0)
History of immune disorder	1 (0.2)	3 (0.5)
Did not complete the 3-dose regimen of 9vHPV vaccine	32 (5.2)	29 (4.7)
Received ≥1 dose of 9vHPV vaccine outside the acceptable day range	10 (1.6)	7 (1.1)
Serum sample or results missing at day 1	3 (0.5)	2 (0.3)
Serum sample or results missing at month 7	78 (12.6)	60 (9.7)
Day 1 seropositive,[d] *n* (%)		n (%)
HPV6/11[e]	27 (4.4)	31 (5.0)
HPV16	13 (2.1)	16 (2.6)
HPV18	10 (1.6)	8 (1.3)
HPV31	11 (1.8)	5 (0.8)
HPV33	5 (0.8)	4 (0.6)
HPV45	2 (0.3)	2 (0.3)
HPV52	4 (0.6)	3 (0.5)
HPV58	9 (1.5)	5 (0.8)
Exclusions for MCV4 and Tdap		
Number randomized who received ≥1 injection	619	618
Number excluded from the per-protocol immunogenicity analyses, *n* (%)	24 (3.9)	52 (8.4)
Reason for exclusion, *n* (%)		
Did not receive MCV4 or Tdap	0 (0.0)	18 (2.9)
Received incorrect clinical material	0 (0.0)	2 (0.3)
Received nonstudy vaccination[c]	3 (0.5)	8 (1.3)
Received immunosuppressives before month 7	0 (0.0)	2 (0.3)
Incorrectly randomized	2 (0.3)	0 (0.0)
With history of immune disorder	1 (0.2)	3 (0.5)
Received MCV4 and Tdap outside the acceptable day range	0 (0.0)	13 (2.1)
Serum sample or results missing at 4 wk postinjection of Tdap-IPV vaccine	18 (2.9)	31 (5.0)
Received incorrect Tdap dose[f]	0 (0.0)	1 (0.2)

[a] A subject may appear in >1 category.

[b] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6, and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as with Group A together with MCV4 and Tdap at month 1.

[c] Includes (1) any live vaccine received 21 d before or 14 d after study vaccine or (2) any inactivated or recombinant vaccine received within 14 d of study vaccine.

[d] Seropositive at day 1 to the relevant HPV types(s) applies to the per protocol population for the relevant HPV type(s) only.

[e] Because the L1 proteins for HPV6 and HPV11 are 92% homologous at the amino acid level, all participants were required to be seronegative to both HPV6 and HVP11 to be included in either of the HPV6 and HPV11 per-protocol immunogenicity populations.

[f] Excluded from the per protocol immunogenicity population for Tdap; not excluded from the per protocol immunogenicity population for MCV4.

A/C/Y/W-135, diphtheria, and tetanus was tested by 1-sided tests of noninferiority comparing proportions between Group A and Group B for each component. These tests were conducted based on methods developed by Miettinen and Nurminen.[18] All tests were conducted at the 0.025 significance level. Success in this study was declared if the primary hypotheses of noninferiority were demonstrated for all components of 9vHPV vaccine and at least 1 of MCV4 and Tdap. With 620 subjects per group (1240 total), this study had an overall power >99% for the primary immunogenicity hypotheses (Table 1).

All subjects who received at least 1 study vaccination and had follow-up data were included in safety analyses. AEs were summarized descriptively as frequencies and percentages by participant groups.

RESULTS

A total of 1254 subjects residing in Latin America and North America were screened for inclusion in this study and 1241 were randomized (621 to Group A and 620 to Group B). The numbers of subjects who were randomized, vaccinated, and completed or discontinued the study are shown in Supplemental Figure 1. Both vaccination groups were comparable with respect to baseline demographics (Table 2). Approximately 6.4% (79 of 1241) of patients were African American, and 1.1% (14/1241) were Asian.

The most common reason for exclusion from the per-protocol analyses was having a serum sample or result missing at 4 weeks postinjection (Table 3). Few subjects (0.3%–4.7%) were excluded from the per-protocol analyses for 9vHPV vaccine because of testing positive for HPV on Day 1.

Month 7 anti-HPV GMTs against all HPV types were comparable in Group A and Group B, with fold differences (ie, Group A/Group B) ranging from 0.97 for HPV6 and HPV11 to 1.10 for HPV45 (Table 4). The noninferiority criteria for the anti-HPV GMT responses in Group A relative to Group B were achieved. Seroconversion rates were 100% for all HPV types in both groups and were noninferior in Group A compared with Group B (Table 5).

At least 75% of subjects achieved a fourfold or higher rise in titers to *N meningitidis* serogroup A in both Group A and Group B, and at least 89% of subjects achieved a fourfold or higher rise in titers to *N meningitidis* serogroups C, Y, and W-135 in both Group A and Group B (Table 6). The noninferiority criterion was met for all 4 *N meningitidis* serogroups. More than 99.8% of subjects in both Group A and Group B achieved a diphtheria and tetanus titer ≥0.1 IU/mL at 4 weeks postvaccination with Tdap. There was a 0 to 0.2 percentage point difference (Group A – Group B) in the percentage of subjects who achieved titers ≥0.1 IU/mL, and the noninferiority criteria for both antigens were met (Table 7).

TABLE 4 Anti-HPV GMTs and Estimated Fold Difference at 4 Weeks After Dose 3 in the HPV Per-Protocol Populations

Antigen	Concomitant (Group A),[a] *N* = 619		Nonconcomitant (Group B),[a] *N* = 618		Estimated Fold Difference Group A/Group B[b] (95% Confidence Interval)
	n	Estimated GMT (mMU/mL)	*n*	Estimated GMT (mMU/mL)	
HPV6	501	2198.7	514	2260.7	0.97 (0.88 to 1.08)
HPV11	502	1495.0	514	1547.2	0.97 (0.87 to 1.07)
HPV16	513	8882.6	530	9027.6	0.98 (0.89 to 1.09)
HPV18	516	2610.4	535	2633.9	0.99 (0.88 to 1.12)
HPV31	514	2439.4	536	2334.3	1.04 (0.93 to 1.17)
HPV33	520	1268.5	537	1276.3	0.99 (0.89 to 1.11)
HPV45	523	947.8	539	863.8	1.10 (0.97 to 1.25)
HPV52	521	1082.7	538	1103.7	0.98 (0.88 to 1.10)
HPV58	519	1532.8	537	1555.1	0.99 (0.88 to 1.10)

mMU, milliMerck units; *N*, number of subjects randomized to the respective vaccination group who received ≥1 injection; *n* = number of subjects contributing to the analysis.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and MCV4 and Tdap at month 1.

[b] *P* value for noninferiority <.001 for all 9 antigens. The noninferiority criterion for GMT end points reported in this table was defined as statistically less than a twofold decrease in Group A compared with Group B. Noninferiority of GMT in Group A relative to Group B was demonstrated if the lower limit of the 95% confidence interval for the fold difference was >0.5.

TABLE 5 Seroconversion Rates and Estimated Percent Difference at 4 Weeks After Dose 3 in the HPV Per-Protocol Populations

Antigen	Concomitant (Group A),[a] *N* = 619		Nonconcomitant (Group B),[a] *N* = 618		Estimated Percent Difference Group A – Group B[b] (95% confidence interval)
	m/n	Response (%)	*m/n*	Response (%)	
HPV6	501/501	100	514/514	100	0.0 (–0.8 to 0.7)
HPV11	502/502	100	514/514	100	0.0 (–0.8 to 0.7)
HPV16	513/513	100	530/530	100	0.0 (–0.7 to 0.7)
HPV18	516/516	100	535/535	100	0.0 (–0.7 to 0.7)
HPV31	514/514	100	536/536	100	0.0 (–0.7 to 0.7)
HPV33	520/520	100	537/537	100	0.0 (–0.7 to 0.7)
HPV45	523/523	100	539/539	100	0.0 (–0.7 to 0.7)
HPV52	521/521	100	538/538	100	0.0 (–0.7 to 0.7)
HPV58	519/519	100	537/537	100	0.0 (–0.7 to 0.7)

m = number of subjects with the indicated response; *N*, number of subjects randomized to the respective vaccination group who received at least 1 injection; *n*, number of subjects contributing to the analysis. Seropositive is defined as anti-HPV serum levels (assessed by competitive Luminex immunoassay) greater or equal to 30, 16, 20, 24, 10, 8, 8, 8, 8 milliMerck units/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and MCV4 and Tdap at month 1.

[b] *P* value for noninferiority <.001 for all 9 antigens. The noninferiority criterion for seroconversion end points reported in this table was defined as statistically <5 percentage points decrease in Group A compared with Group B. Noninferiority of seroconversion rates in Group A relative to Group B was demonstrated if the lower limit of the 95% confidence interval for the percentage point difference was greater than –5.

TABLE 6 Estimated Percentage Point Difference in the Per-Protocol Population for MCV4 for Percent of Subjects With Fourfold or Greater Rise in Titers for *N meningitidis* Serogroups at 4 Weeks Postvaccination

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Percentage Point Difference Group A − Group B (97.5% CI)
	m/n	%	97.5% CI	*m/n*	%	97.5% CI	
Serogroup A	466/590	79.0	(75.0 to 82.6)	425/564	75.4	(71.0 to 79.3)	3.8 (−1.7 to 9.3)[b]
Serogroup C	548/590	92.9	(90.1 to 95.1)	538/566	95.1	(92.6 to 96.9)	−2.1 (−5.4 to 1.1)[b]
Serogroup W-135	563/589	95.6	(93.3 to 97.3)	553/566	97.7	(95.9 to 98.9)	−2.1 (−4.7 to 0.3)[b]
Serogroup Y	540/590	91.5	(88.6 to 93.9)	506/566	89.4	(86.1 to 92.1)	2.1 (−1.8 to 6.1)[b]

m = number of subjects with the indicated response; N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as above and Tdap-IPV vaccine at month 1.

[b] *P* value for noninferiority <.001 for all antigens. The noninferiority criterion for end points reported in this table was defined as statistically <10 percentage points decrease in Group A compared with Group B. Noninferiority of percent of subjects with fourfold or greater rise in titers for *N meningitidis* serogroups in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the percentage point difference was greater than −10.

With respect to pertussis antigens the per-protocol immunogenicity analysis also showed that anti-PT, anti-FHA, anti-PRN, and anti-FIM GMTs were noninferior in Group A compared with Group B (Table 8).

Few subjects (~0.2%) discontinued because of an AE, and no deaths were reported (Table 9). Throughout the study period, 5 subjects (0.8%) in Group A and 5 subjects (0.8%) in Group B reported nonfatal serious AEs; none were vaccine related. Regarding injection-site AEs, a higher proportion of subjects in Group A reported swelling (14.4%) at the 9vHPV vaccination site compared with Group B (9.4%), and the difference between the groups was statistically significant (P = .007; Table 10). Comparable proportions of subjects reported swelling at MCV4 and Tdap vaccination site in Group A and Group B (P = .526; Table 10).

Most of the swelling was mild to moderate in intensity (ie, with a maximum size <5 cm) both at the 9vHPV vaccine injection site and the MCV4 and Tdap injection site. Most subjects in each group (Group A: 92.3%; Group B: 91.9%) reported a maximum temperature <37.8°C (<100°F) within 5 days of the first vaccination. The proportions with elevated temperatures (≥37.8°C) within 5 days of the first vaccination were similar between the 2 groups (risk difference: –0.4; 95% confidence interval: –3.5 to 2.7). No subject became pregnant during the study.

DISCUSSION

This study demonstrated that when the first dose of 9vHPV vaccine is administered concomitantly with MCV4 and Tdap at a separate injection site, the immune response to all vaccine components is noninferior to the immune response achieved when the 3 vaccines are administered nonconcomitantly. Specifically, GMTs to all 9 vaccine HPV types were noninferior in Group A compared with Group B, and all subjects in both vaccination groups seroconverted after the third dose of 9vHPV vaccine. Also, antibody responses to *N meningitidis* serogroups A/C/Y/W-135, diphtheria, tetanus, and pertussis at 4 weeks after administration of MCV4 and Tdap were noninferior in Group A compared with Group B.

Concomitant administration of the first dose of 9vHPV vaccine with MCV4 and Tdap was generally well tolerated. The proportion of subjects reporting injection site AEs postvaccination 1 was similar in the concomitant vaccination group (85.3%) and the nonconcomitant vaccination group (85.1%). Significantly more subjects reported swelling at the

TABLE 7 Estimated Percentage Point Difference in the Per-Protocol Population for Tdap for Percent of Subjects With Diphtheria and Tetanus Titers ≥0.1 IU/mL at 4 Weeks Postvaccination

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Percentage Point Difference Group A − Group B (97.5% CI)
	m/n	%	97.5% CI	*m/n*	%	97.5% CI	
Diphtheria titer ≥0.1 IU/mL							
Day 1	403/593	68.0	(63.5 to 72.2)	391/564	69.3	(64.8 to 73.6)	
4 wk postvaccination	595/595	100	(99.3 to 100)	566/566	100	(99.2 to 100)	0.0 (−0.8 to 0.9)[b]
Tetanus titer ≥0.1 IU/mL							
Day 1	460/573	80.3	(76.3 to 83.9)	450/548	82.1	(78.1 to 85.6)	
4 wk postvaccination	593/594	99.8	(98.9 to 100)	562/562	100	(99.2 to 100)	−0.2 (−1.2 to 0.7)[b]

m = number of subjects with the indicated response; N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and Tdap-IPV vaccine at month 1.

[b] *P* value for non-inferiority <0.001 for all antigens. The non-inferiority criterion for endpoints reported in this table was defined as statistically less than 10 percentage points decrease in Group A compared with Group B. Non-inferiority of percent with titer ≥ 0.1 IU/mL in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the percentage point difference was greater than −10.

TABLE 8 Antipertussis GMTs and Estimated Fold Difference at 4 Weeks Postvaccination in the Per-Protocol Population for Tdap

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Fold Difference Group A/Group B (97.5% CI)
	n	Estimated GMT (ELU/m)	97.5% CI	*n*	Estimated GMT (ELU/m)	97.5% CI	
Anti-PT							
Day 1	594	7.5	(6.8 to 8.2)	564	7.1	(6.5 to 7.8)	
4 wk postvaccination	595	28.5	(25.8 to 31.5)	566	35.7	(32.3 to 39.6)	0.80 (0.69 to 0.92)[b]
Anti-FHA							
Day 1	594	33.0	(30.4 to 35.8)	564	32.8	(30.1 to 35.7)	
4 wk postvaccination	595	184.1	(171.8 to 197.4)	566	201.4	(187.6 to 216.3)	0.91 (0.83 to 1.01)[b]
Anti-PRN							
Day 1	594	20.9	(19.2 to 22.8)	564	20.4	(18.6 to 22.4)	
4 wk postvaccination	595	328.4	(300.6 to 358.8)	566	344.0	(314.2 to 376.7)	0.95 (0.84 to 1.08)[b]
Anti-FIM							
Day 1	594	16.1	(14.3 to 18.2)	564	15.8	(13.9 to 18.1)	
4 wk postvaccination	595	653.0	(556.0 to 767.1)	566	681.4	(577.8 to 803.7)	0.96 (0.76 to 1.21)[b]

N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.
[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and Tdap-IPV vaccine at month 1.
[b] *P* value for noninferiority <.001 for all antigens with the exception of anti-pertussis toxin, where *P* for noninferiority was .003. The noninferiority criterion for end points reported in this table was defined as statistically <1.5-fold decrease in Group A compared with Group B. Noninferiority of GMT in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the fold difference was >0.67.

9vHPV vaccine injection site after the first vaccination in the concomitant group. Injection-site swelling at the 9vHPV vaccine injection site was mostly mild to moderate in intensity. Moreover, there were few discontinuations due to an AE. Thus, the finding of increased rates of injection-site swelling is likely to be of minor clinical significance. In another study that investigated concomitant administration of 9vHPV vaccine with a diphtheria/tetanus/pertussis/polio vaccine, more subjects also reported swelling at the 9vHPV vaccine injection site in the concomitant vaccination group.[19] This suggests that the increase in injection-site swelling may be due to the concomitant administration of diphtheria/tetanus/pertussis antigens (rather than meningococcal antigens) with 9vHPV vaccine.

The results of this study are similar to those of a previous study of concomitant administration of the quadrivalent HPV (types 6/11/16/18) vaccine and MCV4 and Tdap,

TABLE 9 AEs Reported Day 1 Through 15 After the Respective Vaccination Visit

	Postvaccination 1[a]		Postvaccination 2[b]		Postvaccination 3[b]	
	Concomitant (Group A)[c]	Nonconcomitant (Group B)[c]	Concomitant (Group A)[c]	Nonconcomitant (Group B)[c]	Concomitant (Group A)[c]	Nonconcomitant (Group B)[c]
Subjects with follow-up, *n*	613	611	591	593	583	581
Subjects with ≥1 AE, *n* (%)	523 (85.3)	520 (85.1)	307 (51.9)	299 (50.4)	323 (55.4)	307 (52.8)
Injection-site	496 (80.9)	491 (80.4)	276 (46.7)	276 (46.5)	304 (52.1)	281 (48.4)
Systemic	264 (43.1)	259 (42.4)	95 (16.1)	89 (15.0)	86 (14.8)	94 (16.2)
Serious[d]	1[e] (0.2)	1[f] (0.2)	1[g] (0.2)	0 (0.0)	1[h] (0.2)	0 (0.0)
Serious vaccine-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to an AE, *n* (%)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to death, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

All subjects who received ≥1 injection and had follow-up data were included in the primary analysis of safety. The number and percent of subjects reporting the following were compared between Group A and Group B: systemic AEs on days 1 through 15 after any vaccination and the number of subjects reporting clinical serious AEs from days 1 to 15 after any vaccination or vaccine-related clinical serious AE at any time during the study.
[a] Postvaccination 1 is defined as the follow-up period for safety after vaccination at day 1 and after vaccination/visit at month 1. These data represent AEs reported for the 2 vaccines combined.
[b] Because 9vHPV vaccine was the only vaccine administered in a 3-dose regimen, AEs reported postvaccination 2 and 3 would be specific to 9vHPV vaccination.
[c] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and a 0.5-mL dose of MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and MCV4 and Tdap at month 1. Two subjects randomized into the nonconcomitant group received 9vHPV vaccine at day 1 but did not receive MCV4 and Tdap at month 1 and are excluded from this table.
[d] There were 7 additional serious AE reported outside the day 1 to 15 time window. Group A: appendicitis 27 d postdose 2 of 9vHPV vaccine (5-d duration); appendicitis 93 d postdose 2 of 9vHPV vaccine (4-d duration). Group B: appendicitis 61 d postdose 1 of 9vHPV vaccine (1.3-wk duration); orthostatic hypotension 193 d postdose 1 of 9vHPV vaccine (3-d duration); depression 40-d postdose 2 of 9vHPV vaccine (3-d duration); dengue fever 47 d postdose 2 of 9vHPV vaccine (1.6-wk duration); bronchitis 127 d postdose 2 of 9vHPV vaccine (6-d duration). Thus, throughout the study period, there were 11 serious non–vaccine-related AEs reported for 10 subjects: 5 subjects (0.8%) in Group A and 5 subjects (0.8%) in Group B (1 subject experienced 2 serious AEs: gastroenteritis and orthostatic hypotension). All serious AEs were considered not related to any of the 3 study vaccines by the study investigators (investigators were instructed to assign causality to AEs on the basis of exposure, time course, likely cause, and consistency with the vaccine's known profile; vaccine-related AEs were those that were determined by the investigator to be possibly, probably, or definitely vaccine related).
[e] Seroma 9 d postdose 1 of 9vHPV vaccine (4.3-wk duration).
[f] Gastroenteritis 6 d postdose 1 of 9vHPV vaccine (2-d duration).
[g] Affective disorder 1 d postdose 2 of 9vHPV vaccine (1.1-wk duration).
[h] Testicular torsion 8 d postdose 3 (2-d duration).

TABLE 10 Injection-Site AEs Prompted for on the VRC

	Concomitant (Group A)[a]	Nonconcomitant (Group B)[a]	% Difference Group A vs Group B (95% CI)	*P*
9vHPV injection site (reported d 1–5 postdose 1)				
Subjects contributing to the analysis, *n*	611	609		
Erythema, *n* (%)	61 (10.0)	54 (8.9)	1.1 (–2.2 to 4.4)	.505
Pain, *n* (%)	356 (58.3)	335 (55.0)	3.3 (–2.3 to 8.8)	.251
Swelling, *n* (%)	88 (14.4)	57 (9.4)	5.0 (1.4 to 8.7)	.007
MCV4 and Tdap injection site (reported d 1–5 postvaccination)				
Subjects contributing to the analysis, *n*	611	598		
Erythema, *n* (%)	159 (26.0)	152 (25.4)	0.6 (–4.3 to 5.5)	.810
Pain, *n* (%)	439 (71.8)	406 (67.9)	4.0 (–1.2 to 9.1)	.134
Swelling, *n* (%)	188 (30.8)	174 (29.1)	1.7 (–3.5 to 6.8)	.526

All subjects who received ≥1 injection and had follow-up data were included in the primary analysis of safety. The number and percent of subjects reporting injection-site AEs were compared between Group A and Group B. Risk differences, 95% CIs and *P* values were calculated for injection site AEs between day 1 and day 5 for both groups. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and a 0.5-mL dose of MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and MCV4 and Tdap at month 1. Two subjects randomized into the nonconcomitant group received 9vHPV vaccine at day 1 but did not did not receive MCV4 and Tdap at month 1 and are excluded from this table.

which showed that concomitant administration of dose 1 of quadrivalent HPV vaccine and MCV4 and Tdap was generally well tolerated and did not interfere with the antibody response to any of the vaccine antigens; similar to this study, increased rates in injection-site swelling were also noted in the concomitant vaccination group.[20]

The primary limitation of this study was its unblinded nature. As such, safety assessment could have been biased toward an overestimation of AEs being reported in the concomitant vaccination group because subjects who are receiving 2 injections on the same day may more likely report injection-site or systemic AEs compared with subjects who receive only 1 injection. Another limitation of this study is that the coadministration of Tdap and MCV4 was assessed only with the first dose of HPV vaccine and not with subsequent doses.

Even though only 1 Tdap vaccine was assessed in this study, one can reasonably assume that the results may be generalizable to other Tdap vaccines. Differences in antigen and aluminum dose between diphtheria/tetanus/pertussis vaccines such as Adacel, Boostrix-IPV, or Repevax are relatively modest and therefore expected to have limited impact on 9vHPV vaccine immunogenicity. A limited impact on 9vHPV vaccine immunogenicity is unlikely to have clinical significance: the 9vHPV vaccine efficacy findings in young women were extended to adolescents based on the demonstration of noninferior anti-HPV responses[7]; anti-HPV responses in adolescents were actually much higher than in young women. Even if concomitant administration of a different diphtheria/tetanus/pertussis vaccine were associated with a small decrease in 9vHPV vaccine immunogenicity, anti-HPV responses would still be substantially higher than in young women, and therefore protection elicited by 9vHPV vaccine would not be compromised.

When the study was initiated in 2009, other meningococcal serotype A/C/Y/W-135 vaccines (Menveo and Nimenrix) had not yet been licensed. Although Menactra, Menveo, and Nimenrix contain similar amounts of polysaccharide and carrier protein, they use different carrier proteins; thus, it is difficult to speculate whether results obtained in this study can be extrapolated to other meningococcal vaccines. Regulatory guidelines caution against such extrapolation for conjugated polysaccharide vaccines.[21]

This study demonstrates that concomitant administration of 9vHPV vaccine and MCV4 and Tdap was generally well tolerated and the immune responses to components of either vaccine were noninferior compared with nonconcomitant administration. Providing vaccinations to adolescents is challenging because they make infrequent health care visits. Concomitant administration would minimize the number of visits required to deliver each vaccine individually and therefore facilitate adherence to recommended vaccination regimens. In the United States, coverage for the first dose of HPV vaccine remains substantially lower (by ~20–25 percentage points) than coverage for other vaccines recommended by the Advisory Committee on Immunization Practices for children 11 to 12 years of age.[22,23] It is estimated that coadministration of HPV vaccine with other vaccines such as diphtheria, tetanus, pertussis, meningococcal conjugate, and influenza vaccines could increase coverage for the first dose of HPV vaccine to >90%.[24]

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ABBREVIATIONS

9vHPV: 9-valent HPV (6/11/16/18/31/33/45/52/58) L1 virus-like particle vaccine
AEs: adverse events
ELISA: enzyme-linked immunosorbent assay
FHA: filamentous hemagglutinin
FIM: fimbriae 2/3
GMT: geometric mean titers
HPV: human papillomavirus
PRN: pertactin
PT: pertussis toxin
VRC: vaccination report card

Drs Huicho and Luxembourg substantially contributed to interpretation of the results and drafting of the manuscript and reviewed and revised the manuscript for important intellectual content; Dr Sobanjo-ter Meulen substantially contributed to conception, design and planning of the study and interpretation of the results and reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

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