Immunogenicity and Safety of a 9-Valent HPV Vaccine

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abstract

OBJECTIVES: Prophylactic vaccination of youngwomen aged 16 to 26 years with the 9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus (HPV) virus-like particle (9vHPV) vaccine prevents infection and disease. We conducted a noninferiority immunogenicity study to bridge the findings in young women to girls and boys aged 9 to 15 years.

METHODS: Subjects (N = 3066) received a 3-dose regimen of 9vHPV vaccine administered at day 1, month 2, and month 6. Anti-HPV serologic assays were performed at day 1 and month 7. Noninferiority required that the lower bound of 2-sided 95% confidence intervals of geometric mean titer ratios (boys:young women or girls:young women) be >0.67 for each HPV type. Systemic and injection-site adverse experiences (AEs) and serious AEs were monitored.

RESULTS: At 4 weeks after dose 3, >99% of girls, boys, and young women seroconverted for each vaccine HPV type. Increases in geometric mean titers to HPV types 6/11/16/18/31/33/45/52/58 were elicited in all vaccine groups. Responses in girls and boys were noninferior to those of young women. Persistence of anti-HPV responses was demonstrated through 2.5 years after dose 3. Administration of the 9vHPV vaccine was generally well tolerated. A lower proportion of girls (81.9%) and boys (72.8%) than young women (85.4%) reported injection-site AEs, most of which were mild to moderate in intensity.

CONCLUSIONS: These data support bridging the efficacy findings with 9vHPV vaccine in young women 16 to 26 years of age to girls and boys 9 to 15 years of age and implementing gender-neutral HPV vaccination programs in preadolescents and adolescents.

WHAT'S KNOWN ON THIS SUBJECT: Prophylactic vaccination of young women 16 to 26 years of age with the 9-valent human papillomavirus (HPV)–like particle (9vHPV) vaccine prevents infection and disease with vaccine HPV types.

WHAT THIS STUDY ADDS: These data support bridging the efficacy findings with 9vHPV vaccine in young women 16 to 26 years of age to girls and boys 9 to 15 years of age and implementation of gender-neutral HPV vaccination programs in preadolescents and adolescents.

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Human papillomavirus (HPV) causes premalignant and malignant lesions of the cervix,[1,2] vagina,[3,4] vulva,[4,5] anus,[4,6] penis,[7] and oropharynx,[8] as well as genital warts.[9,10] HPV is responsible for ~5% of the global cancer disease burden.[11] Prophylactic vaccines directed against the 2 most common high-risk HPV types are now widely recommended on the basis of clinical trial results and postlicensure data.[12] The quadrivalent HPV (6/11/16/18) virus-like particle (qHPV) vaccine is highly efficacious in preventing infection and cervical, vaginal, vulvar, and anal dysplasia caused by HPV 6/11/16/18 as well as HPV 6/11–related condyloma,[13–16] and the bivalent HPV (16/18) vaccine is highly efficacious against HPV 16/18–related infection and cervical dysplasia.[17] Postlicensure studies have shown a rapid decrease in the incidence of high-grade cervical abnormalities,[18–21] prevalence of vaccine HPV types,[22–26] and incidence of genital warts[27–31] in vaccinees. Data have shown that prophylactic HPV vaccination is generally safe and well tolerated.[32–38]

The median age of sexual debut is in the late teens (15–19 years) in most countries.[39] Virginal adolescents (≤15 years old) were not included in HPV vaccine efficacy evaluations because of low HPV exposure and ethical constraints. Therefore, qHPV vaccine efficacy findings in subjects aged 16 to 26 years were bridged to subjects aged 9 to 15 years on the basis of the demonstration of noninferior immunogenicity.[40]

Current HPV vaccines address ~70% of cervical cancers via protection from HPV 16/18. Partial cross-protection against nonvaccine HPV types has been reported for both licensed vaccines, although its clinical significance remains uncertain.[41] The 9-valent HPV (6/11/16/18/31/33/45/52/58) virus-like particle (9vHPV) vaccine includes 5 additional oncogenic HPV types compared with the qHPV vaccine (HPV 31/33/45/52/58), potentially increasing cervical cancer prevention to 90%.[2,42] The 9vHPV vaccine may also provide increased protection against an extra ~5% to 10% of vulvar, vaginal, and anal cancers and high-grade vulvar, vaginal, and anal intraepithelial neoplasia.[4,43,44]

Prophylactic administration of a 3-dose regimen of 9vHPV vaccine to HPV-naive women aged 16 to 26 years is highly efficacious against vaccine HPV type-related infection and disease.[45] In this report we evaluated whether the 9vHPV vaccine induces noninferior serum antibody responses in boys and girls 9 to 15 years of age (the ideal prophylactic HPV vaccination population) compared with adolescent females/women (ie, young women) 16 to 26 years of age (the population used to establish 9vHPV vaccine efficacy).

METHODS

Population

This study (protocol V503-002; NCT00943722) is an international, multicentered immunogenicity and tolerability study in girls and boys (9–15 years of age) who received the 9vHPV vaccine compared with young women (16–26 years of age). The study was initiated in August 2009, and data are current through visits that occurred before or in April 2013. Subjects were enrolled from 72 sites in 17 countries (Austria, Belgium, Brazil, Chile, Colombia, Costa Rica, Finland, India, Peru, Poland, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand and the United States). The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. An external data monitoring committee assessed safety findings during the study.

The study enrolled 3 cohorts: girls 9 to 15 years of age, boys 9 to 15 years of age, and young women 16 to 26 years of age. For the 2 younger cohorts, participants were required to be generally healthy and sexually naive at enrollment and throughout the vaccination period (through month 7). For the older cohort, participants were required to be generally healthy and have no history of abnormal Papanicolaou test results, no more than 4 lifetime sexual partners, and no previous abnormal cervical biopsy results.

Reasons for exclusions from the study included pregnancy, known allergy to any vaccine component, thrombocytopenia, immunosuppression/previous immunosuppressive therapy, or previous receipt of an HPV vaccine.

Vaccine Dosing

All subjects received 9vHPV vaccine administered (in the deltoid) as a 0.5-mL intramuscular injection. A dose of 9vHPV vaccine contained 30 μg of HPV 6, 40 μg of HPV 11, 60 μg of HPV 16, 40 μg of HPV 18, 20 μg of HPV 31, 20 μg of HPV 33, 20 μg of HPV 45, 20 μg of HPV 52, and 20 μg of HPV 58 virus-like particles, and 500 μg of amorphous aluminum hydroxyphosphate sulfate.

Study Design

The study was designed to enroll 1800 girls 9 to 15 years of age, 600 boys 9 to 15 years of age, and 400 young women 16 to 26 years of age. After informed consent and determination that all inclusion criteria and none of the exclusion criteria were met, eligible subjects received an allocation number. An interactive voice response system was used to allocate study subjects and balance randomization between sites. The interactive voice response system assigned the subject an allocation number from 1 of 3 allocation schedules as determined by the sponsor. Subjects, investigators (and staff), laboratory staff, and sponsor were blinded to vaccine lot number.

All subjects were administered a 3-dose regimen of 9vHPV vaccine

(day 1, month 2, and month 6). All participants were required to be afebrile (oral temperature <37.8°C) within 24 hours before each injection. Young women were instructed to use effective contraception through month 7. All female participants underwent pregnancy testing (urine or serum analyses for β-human chorionic gonadotropin) before each vaccination. Participants found to be pregnant were not vaccinated.

All participants were assessed for immunogenicity at day 1 and month 7. In addition, young women 16 to 26 years of age underwent polymerase chain reaction (PCR) testing of cervical and external genital samples at day 1 and month 7 for detection of HPV DNA, including the 9 vaccine types and 5 additional oncogenic HPV types (HPV 35/39/51/56/59). HPV seropositivity at day 1 or PCR positivity at day 1 and month 7 was not a reason for exclusion from the study; however, the results were part of the criteria to define analysis populations.

The study consisted of 2 immunogenicity substudies (Fig 1): (1) an adult-adolescent immunobridging substudy to compare 9vHPV vaccine immunogenicity at month 7 in girls versus young women and boys versus young women and (2) a lot consistency substudy to demonstrate consistent immunogenicity at month 7 in subjects randomly assigned to 3 different vaccine lots of the final manufacturing process.

The lot consistency substudy was conducted in girls. All enrolled girls were randomly assigned equally to 3 vaccine lots (termed lots 1, 2, and 3). Boys and young women did not participate in the lot consistency substudy and were all assigned to lot 1. Girls who were assigned to lot 1 participated in both substudies. This report is focused on the adult-adolescent immunobridging substudy, antibody persistence through month 36, and safety. The results of the lot consistency substudy will be published separately.

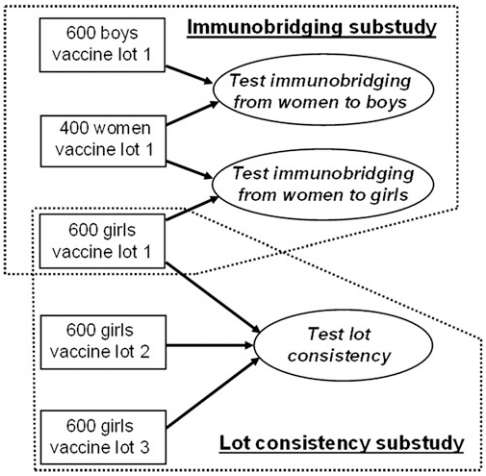

FIGURE 1
Subject distribution between the adult-adolescent immunobridging substudy and the lot consistency substudy.

Assessment

Serum samples obtained at day 1 and month 7 from all subjects and at months 12, 24, and 36 from ~600 randomly selected girls (random selection made before unblinding) and from all boys were tested for vaccine HPV type antibodies by competitive Luminex immunoassay (cLIA).[46] A subject was defined as anti-HPV 6/11/16/18/31/33/45/52/58 positive if his or her anti-HPV serum level was ≥30, ≥16, ≥20, ≥24, ≥10, ≥8, ≥8, ≥8, or ≥8 milli Merck units (mMU)/mL for the 9 types, respectively.

Participants were observed for 30 minutes after each vaccination for any immediate reaction. All subjects received a vaccination report card (VRC) at the day 1, month 2, and

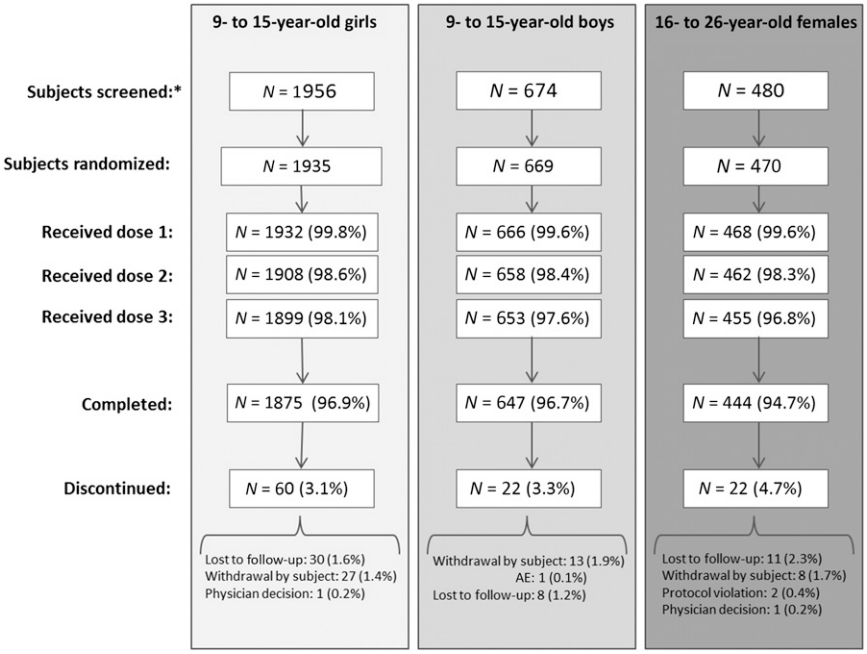

FIGURE 2
Disposition of subjects. *One screened, non-randomized subject could not be included in this count because his/her gender was not reported in the database.

TABLE 1 Subject Characteristics

	Girls (9–15 Years Old)	Boys (9–15 Years Old)	Young Women (16–26 Years Old)
n	1935	669	470
Gender, *n* (%)			
Male	0 (0.0)	669 (100.0)	0 (0.0)
Female	1935 (100.0)	0 (0.0)	470 (100.0)
Age			
9–12 Years, *n* (%)	1304 (67.4)	450 (67.3)	0 (0.0)
13–15 Years, *n* (%)	631 (32.6)	219 (32.7)	0 (0.0)
16–26 Years, *n* (%)	0 (0.0)	0 (0.0)	470 (100.0)
Mean (SD), y	11.6 (1.8)	11.7 (1.8)	21.3 (2.7)
Median (range), y	11.0 (9–15)	12.0 (9–15)	21.0 (16–26)
Race, *n* (%)			
American Indian Or Alaska Native	2 (0.1)	2 (0.3)	0 (0.0)
Asian	430 (22.2)	186 (27.8)	128 (27.2)
Black or African American	161 (8.3)	37 (5.5)	48 (10.2)
Multi-Racial	258 (13.3)	149 (22.3)	53 (11.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	3 (0.4)	1 (0.2)
White	1084 (56.0)	292 (43.6)	240 (51.1)
Weight, kg			
Mean	45.3	45.4	60.0
SD	13.6	15.1	13.1
Median	43.5	42.0	58.0
Range	18.0–152.0	15.4–115.2	35.0–126.1
BMI			
Subjects with data, *n*	1934	669	468
Mean (SD), kg/m^2	19.8 (4.4)	19.6 (4.2)	22.6 (4.6)
Median (range), kg/m^2	18.9 (5.6–58.8)	18.6 (10.1–43.0)	21.6 (15.4–47.5)
Region, *n* (%)			
Africa	95 (4.9)	30 (4.5)	40 (8.5)
Asia-Pacific	423 (21.9)	185 (27.7)	125 (26.6)
Europe	573 (29.6)	143 (21.4)	183 (38.9)
Latin America	408 (21.1)	160 (23.9)	60 (12.8)
North America	436 (22.5)	151 (22.6)	62 (13.2)

Analyses in a subset of all study sites may be conducted for regulatory purposes.

month 6 study vaccination visits. On the VRC, the subject or (for the 9- to 15-year-olds) the parent/guardian was asked to record the subject's oral temperature in the evening after each study vaccination and daily for 4 days. Also, beginning after each study vaccination and for a total of 15 days, the subject was asked to record injection-site and systemic adverse experiences (AEs) on the VRC. Investigators assigned causality to AEs on the basis of exposure, time course, likely cause, and consistency with the vaccine's known profile. Vaccine-related AEs were determined by the investigator to be possibly, probably, or definitely vaccine-related. For each AE, participants rated the symptom as mild (awareness of symptom but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating with inability to work or do usual activity); injection-site AEs of swelling and erythema were rated by size. Serious AEs were predefined as any AE that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing in-patient hospitalization, or was a congenital anomaly, a cancer, or an "other important medical event." Serious AEs were collected regardless of causality from day 1 through 6 months after the last vaccination. Deaths and serious vaccine-related AEs were collected throughout the study.

Statistical Methodology

To be included in the immunogenicity analyses, subjects had to meet the following requirements: (1) be seronegative at day 1 and (for 16- to 26-year-old young women)

TABLE 2 Noninferiority of GMTs at Month 7 in the PPI Population

Assay (cLIA)	Girls (9–15 Years Old) (*N* = 646)		Boys (9–15 Years Old) (*N* = 666)		Young Women (16–26 Years Old) (*N* = 468)		GMT Ratio (95% CI)[a]	
	n	GMT, mMU/mL	*n*	GMT, mMU/mL	*n*	GMT, mMU/mL	Girls:Young Women	Boys:Young Women
Anti-HPV 6	517	1715.4	559	2084.7	328	900.8	1.90 (1.70–2.14)	2.31 (2.07–2.59)
Anti-HPV 11	517	1295.1	559	1487.1	332	706.6	1.83 (1.63–2.06)	2.10 (1.88–2.36)
Anti-HPV 16	529	6979.8	569	8628.9	329	3522.6	1.98 (1.77–2.22)	2.45 (2.19–2.74)
Anti-HPV 18	531	2153.7	567	2822.8	345	882.7	2.44 (2.13–2.80)	3.20 (2.80–3.65)
Anti-HPV 31	522	1891.6	564	2221.2	340	753.9	2.51 (2.21–2.85)	2.95 (2.60–3.34)
Anti-HPV 33	534	980.4	567	1198.7	354	466.8	2.10 (1.87–2.36)	2.57 (2.29–2.88)
Anti-HPV 45	534	714.4	570	907.0	368	272.2	2.62 (2.27–3.03)	3.33 (2.89–3.84)
Anti-HPV 52	533	932.9	568	1037.8	337	419.6	2.22 (1.97–2.51)	2.47 (2.19–2.79)
Anti-HPV 58	531	1286.7	566	1567.7	332	590.5	2.18 (1.93–2.45)	2.66 (2.37–2.98)

Analyses in a subset of all study sites may be conducted for regulatory purposes. mMU, milli Merck units; *N*, number of subjects assigned to the respective vaccination group who received at least 1 injection; *n*, number of subjects contributing to the analysis; The per-protocol immunogenicity (PPI) population included subjects who were seronegative at day 1 (and for young women PCR-negative from day 1 through month 7) to the HPV type being analyzed, who received 3 doses of vaccine during prespecified visit intervals, and from whom the month 7 sample was obtained within a prespecified interval.

[a] The *P* value for noninferiority was <.001 for all comparisons.

PCR-negative from day 1 through month 7 only for the HPV type being analyzed (for HPV 6 and HPV 11 immunogenicity analyses, subjects had to be seronegative and PCR-negative for both HPV 6 and HPV 11); (2) receive all 3 doses of the correct clinical material within acceptable day ranges; and (3) have a post–dose 3 serology result within acceptable day ranges.

Noninferiority of month 7 geometric mean titers (GMTs) in girls and boys versus young women (primary immunogenicity objective) was tested by constructing a 95% confidence interval (CI) for the ratio of GMTs. The statistical criterion for noninferiority was established when the lower bound of the 2-sided 95% CI of the GMT ratio (girls:young women or boys:young women) was >0.67 for each HPV type. Separately for each anti-HPV type, the 95% CI of the GMT ratio was derived from an analysis of variance model with the log of antibody titers as the response and vaccination group as the fixed effect. With the planned sample size, this study has >99% power for the primary immunogenicity hypothesis on all 9 HPV types for a true GMT ratio of at least 1.2 for all 9 types. Noninferiority of seroconversion rates in girls and boys versus young women (secondary immunogenicity objective) was based on 9 one-sided tests of noninferiority (1 corresponding to each vaccine HPV type) at the 0.025 level conducted by using the method of Miettinen and Nurminen.[47] The statistical criterion for noninferiority was established when the lower bound of the 2-sided 95% CI for the differences in seroconversion rates (% girls minus % young women or % boys minus % young women) was greater than −5 percentage points for each HPV type.

All subjects who received at least 1 study vaccination and had follow-up data were included in the analysis of safety. Analyses on a subset of all study sites may be conducted for regulatory purposes.

RESULTS

A total of 3111 subjects were screened for inclusion in this study, and 3074 were included in the study from 72 sites. A summary of the number of subjects who were randomly assigned, vaccinated, and completed or discontinued the study is shown in Fig 2. A summary of baseline subject characteristics is provided in Table 1. All cohorts were comparable with respect to geographic region and race.

At enrollment, serum antibody titers for HPV 6/11/16/18/31/33/45/52/58 that were greater than the predefined seropositive threshold values for ≥1 HPV type (indicative of previous exposure to the respective vaccine HPV types) were detected in 8.5% (163 of 1920), 5.6% (37 of 666), and 32.4% (151 of 466) of girls, boys, and young women, respectively. At enrollment, 22.7% of young women were PCR-positive for at least 1 vaccine HPV type. Overall, 40.9% (184 of 450) of young women were positive for at least 1 vaccine HPV type by serology or PCR at day 1.

Table 2 displays the month 7 HPV cLIA GMTs for each vaccine HPV type. The lower bound exceeded 0.67 for all HPV types, with *P* values <.001, indicating that cLIA GMT responses in girls and boys were noninferior to those of young women. For all 9 vaccine HPV types, the month 7 GMTs in girls and boys were higher than those in young women. More than 99% of participants seroconverted by month 7 to all 9 HPV types (Table 3), meeting the criterion for noninferior antibody responses for this secondary endpoint.

Anti-HPV GMTs in girls and boys were highest at month 7 and decreased by ~70% at month 12 (Table 4). At months 24 and 36, GMTs were ~10% to 20% of month 7 GMTs. More than 90% of subjects were seropositive at month 36 for each of the 9 vaccine HPV types (Table 5).

The 3-dose regimen of the 9vHPV vaccine was generally well tolerated

TABLE 3 Noninferiority of Seroconversion at Month 7 in the PPI Population

Assay (cLIA)	Girls (9–15 Years Old) (*N* = 646)		Boys (9–15 Years Old) (*N* = 666)		Young Women (16–26 Years Old) (*N* = 468)		Difference (95% CI)[a]	
	n	Seropositive, %	*n*	Seropositive, %	*n*	Seropositive, %	Girls−Young Women	Boys−Young Women
Anti-HPV 6	517	99.8	559	99.8	328	99.7	0.1 (−0.8, 1.5)	0.1 (−0.7, 1.5)
Anti-HPV 11	517	100.0	559	100.0	332	100.0	0.0 (−0.7, 1.2)	0.0 (−0.7, 1.2)
Anti-HPV 16	529	100.0	569	100.0	329	100.0	0.0 (−0.7, 1.2)	0.0 (−0.7, 1.2)
Anti-HPV 18	531	99.8	567	100.0	345	99.7	0.1 (−0.8, 1.5)	0.3 (−0.4, 1.6)
Anti-HPV 31	522	100.0	564	100.0	340	99.7	0.3 (−0.4, 1.7)	0.3 (−0.4, 1.7)
Anti-HPV 33	534	100.0	567	100.0	354	99.7	0.3 (−0.4, 1.6)	0.3 (−0.4, 1.6)
Anti-HPV 45	534	99.8	570	100.0	368	99.5	0.4 (−0.6, 1.8)	0.5 (−0.1, 2.0)
Anti-HPV 52	533	100.0	568	100.0	337	99.7	0.3 (−0.4, 1.7)	0.3 (−0.4, 1.7)
Anti-HPV 58	531	100.0	566	100.0	332	100.0	0.0 (−0.7, 1.2)	0.0 (−0.7, 1.2)

Analyses in a subset of all study sites may be conducted for regulatory purposes. Seropositive was defined as anti-HPV serum cLIA levels ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 milli Merck units (mMU)/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. *N*, number of subjects assigned to the respective vaccination group who received at least 1 injection; *n*, number of subjects with evaluable serology data and who were eligible for the indicated analysis population; The per-protocol immunogenicity (PPI) population included subjects who were seronegative at day 1 (and for young women PCR-negative from day 1 through month 7) to the HPV type being analyzed, who received 3 doses of vaccine during prespecified visit intervals, and from whom the month 7 sample was obtained within a prespecified interval.

[a] The *P* value for noninferiority was <.001 for all comparisons.

TABLE 4 Summary of Anti-HPV cLIA GMTs Over Time

Assay (cLIA) and Time Point	9vHPV Vaccine			
	Girls (9–15 Years Old)		Boys (9–15 Years Old)	
	n	GMT (95% CI), mMU/mL	*n*	GMT (95% CI), mMU/mL
Anti-HPV 6				
Day 1	1597	<16 (<16, <16)	559	<16 (<16, <16)
Month 07	1597	1712.0 (1638.9–1788.4)	559	2084.7 (1940.9–2239.2)
Month 12	437	616.1 (571.3–664.5)	491	692.4 (639.9–749.3)
Month 24	416	312.9 (288.7–339.2)	470	336.6 (310.8–364.6)
Month 36	407	252.8 (232.1–275.3)	457	262.7 (241.4–285.8)
Anti-HPV 11				
Day 1	1597	<6 (<6, <6)	559	<6 (<6, <6)
Month 07	1597	1278.7 (1223.1–1336.8)	559	1487.1 (1385.0–1596.7)
Month 12	439	393.3 (360.4–429.1)	495	456.6 (419.2–497.4)
Month 24	418	179.7 (163.6–197.5)	471	201.1 (183.7–220.2)
Month 36	411	145.8 (132.6–160.2)	463	156.6 (142.4–172.1)
Anti-HPV 16				
Day 1	1627	<12 (<12, <12)	569	<12 (<12, <12)
Month 07	1627	7071.6 (6776.1–7380.1)	569	8628.9 (8077.5–9218.0)
Month 12	444	2428.5 (2256.0–2614.2)	505	2847.1 (2639.5–3071.0)
Month 24	423	1078.7 (985.8–1180.3)	481	1230.8 (1126.3–1345.1)
Month 36	416	857.4 (779.8–942.8)	472	944.1 (856.4–1040.8)
Anti-HPV 18				
Day 1	1641	<8 (<8, <8)	567	<8 (<8, <8)
Month 07	1641	2081.2 (1978.8–2188.9)	567	2822.8 (2609.0–3054.2)
Month 12	446	494.1 (445.3–548.2)	503	769.2 (699.1–846.3)
Month 24	425	210.2 (188.1–234.8)	479	317.3 (286.7–351.1)
Month 36	418	167.8 (149.5–188.3)	470	244.2 (219.1–272.2)
Anti-HPV 31				
Day 1	1617	<4 (<4, <4)	564	<4 (<4, <4)
Month 07	1617	1879.3 (1791.3–1971.6)	564	2221.2 (2056.4–2399.1)
Month 12	443	574.1 (521.3–632.2)	500	689.4 (628.1–756.7)
Month 24	421	252.2 (226.2–281.2)	476	300.2 (270.3–333.3)
Month 36	414	216.6 (194.0–241.8)	467	246.3 (221.4–274.1)
Anti-HPV 33				
Day 1	1637	<4 (<4, <4)	567	<4 (<4, <4)
Month 07	1637	944.1 (904.3–985.7)	567	1198.7 (1117.3–1285.9)
Month 12	441	278.2 (255.5–302.9)	503	368.8 (338.6–401.6)
Month 24	419	115.6 (104.5–127.8)	479	151.5 (137.6–166.8)
Month 36	412	94.1 (84.9–104.2)	471	120.8 (109.3–133.6)
Anti-HPV 45				
Day 1	1647	<3 (<3, <3)	570	<3 (<3, <3)
Month 07	1647	737.1 (698.4–777.8)	570	907.0 (830.0–991.2)
Month 12	448	195.2 (174.3–218.5)	506	254.1 (227.6–283.7)
Month 24	426	77.3 (68.2–87.5)	482	99.5 (88.1–112.5)
Month 36	419	64.7 (57.1–73.4)	473	76.7 (67.4–87.1)
Anti-HPV 52				
Day 1	1642	<3 (<3, <3)	568	<3 (<3, <3)
Month 07	1642	970.5 (927.1–1016.0)	568	1037.8 (962.9–1118.6)
Month 12	448	295.3 (270.3–322.7)	505	313.3 (285.6–343.6)
Month 24	426	134.7 (122.7–148.0)	481	136.3 (124.1–149.7)
Month 36	419	109.6 (99.7–120.4)	472	104.9 (94.9–115.8)
Anti-HPV 58				
Day 1	1630	<4 (<4, <4)	566	<4 (<4, <4)
Month 07	1630	1277.7 (1222.0–1336.0)	566	1567.7 (1461.2–1682.0)
Month 12	446	424.0 (390.1–460.9)	502	526.9 (483.7–574.0)
Month 24	424	178.0 (161.5–196.3)	478	220.7 (201.0–242.3)
Month 36	417	147.4 (133.0–163.2)	470	170.9 (154.5–189.0)

mMU, milli Merck units; *n*, number of subjects contributing to the analysis.

in each participant group (Table 6). Discontinuations from study vaccination due to an AE were rare (1 total). The incidence of serious vaccine-related AEs was low (2 total). The proportions of participants with injection-site or systemic AEs were numerically lower among girls and boys than among young women. The most common (incidence ≥2%) injection-site AEs were pain, swelling, erythema, and pruritus; most were mild to moderate in intensity. The most common (incidence ≥2%) vaccine-related systemic AEs among girls and boys were headache and pyrexia. The proportions of participants with a fever (≥37.8°C) within 5 days of any injection were comparable between the 3 cohorts (Table 7). Five participants (3 girls, 1 boy, and 1 woman) experienced a maximum oral temperature between 39.9°C and 40.9°C. For one of the girls, the fever was deemed not related to the vaccine because it occurred 5 days after vaccination. For the 4 other subjects, fever occurred within 2 days of vaccination and resolved within 1 to 2 days.

Serious AEs by system organ class are shown in Table 8. One subject died during the study: this subject, a 17-year-old woman at the time of the event, was diagnosed with acute myeloid leukemia 481 days after receiving dose 3. She was hospitalized twice for chemotherapy and died of sepsis 559 days after receiving dose 3, or 7 days after the second round of chemotherapy was initiated. The death was not considered related to the study vaccine. Two serious AEs were judged by the reporting investigator to be vaccine-related. The first, a 10-year-old boy with a previous medical history of seasonal allergy and bronchial asthma experienced an asthma exacerbation 1 day after receiving dose 1, was hospitalized the next day for medical treatment, and fully recovered the following day. The second, a 21-year-old woman, experienced a severe headache on the day she received dose 3; was hospitalized the next day with neck stiffness, headache, and fever (39.0°C); received symptomatic treatment; was diagnosed with viral infection or an AE due to study vaccination; was discharged from the

TABLE 5 Summary of Anti-HPV Seropositivity Over Time

Assay (cLIA) and Time Point	9vHPV Vaccine			
	Girls (9–15 Years Old)		Boys (9–15 Years Old)	
	n	Seropositive (95% CI), %	*n*	Seropositive (95% CI), %
Anti-HPV 6				
Day 1	1597	0.0 (0.0–0.2)	559	0.0 (0.0–0.7)
Month 07	1597	99.6 (99.2–99.9)	559	99.8 (99.0–100)
Month 12	437	99.8 (98.7–100)	491	99.8 (98.9–100)
Month 24	416	99.3 (97.9–99.9)	470	99.6 (98.5–99.9)
Month 36	407	98.5 (96.8–99.5)	457	98.7 (97.2–99.5)
Anti-HPV 11				
Day 1	1597	0.0 (0.0–0.2)	559	0.0 (0.0–0.7)
Month 07	1597	99.9 (99.5–100)	559	100 (99.3–100)
Month 12	439	100 (99.2–100)	495	100 (99.3–100)
Month 24	418	99.5 (98.3–99.9)	471	99.2 (97.8–99.8)
Month 36	411	99.3 (97.9–99.8)	463	98.3 (96.6–99.3)
Anti-HPV 16				
Day 1	1627	0.0 (0.0–0.2)	569	0.0 (0.0–0.6)
Month 07	1627	99.9 (99.6–100)	569	100 (99.4–100)
Month 12	444	100 (99.2–100)	505	100 (99.3–100)
Month 24	423	99.8 (98.7–100)	481	100 (99.2–100)
Month 36	416	99.8 (98.7–100)	472	99.6 (98.5–99.9)
Anti-HPV 18				
Day 1	1641	0.0 (0.0–0.2)	567	0.0 (0.0–0.6)
Month 07	1641	99.8 (99.5–100)	567	100 (99.4–100)
Month 12	446	99.3 (98.0–99.9)	503	100 (99.3–100)
Month 24	425	96.9 (94.8–98.4)	479	98.5 (97.0–99.4)
Month 36	418	94.5 (91.9–96.5)	470	96.6 (94.5–98.0)
Anti-HPV 31				
Day 1	1617	0.0 (0.0–0.2)	564	0.0 (0.0–0.7)
Month 07	1617	99.9 (99.7–100)	564	100 (99.3–100)
Month 12	443	100 (99.2–100)	500	100 (99.3–100)
Month 24	421	99.3 (97.9–99.9)	476	99.4 (98.2–99.9)
Month 36	414	99.3 (97.9–99.9)	467	98.5 (96.9–99.4)
Anti-HPV 33				
Day 1	1637	0.0 (0.0–0.2)	567	0.0 (0.0–0.6)
Month 07	1637	99.9 (99.6–100)	567	100 (99.4–100)
Month 12	441	100 (99.2–100)	503	100 (99.3–100)
Month 24	419	99.0 (97.6–99.7)	479	99.6 (98.5–99.9)
Month 36	412	98.5 (96.9–99.5)	471	98.7 (97.2–99.5)
Anti-HPV 45				
Day 1	1647	0.0 (0.0–0.2)	570	0.0 (0.0–0.6)
Month 07	1647	99.8 (99.5–100)	570	100 (99.4–100)
Month 12	448	99.3 (98.1–99.9)	506	99.6 (98.6–100)
Month 24	426	95.5 (93.1–97.3)	482	95.4 (93.2–97.1)
Month 36	419	93.8 (91.0–95.9)	473	93.0 (90.3–95.1)
Anti-HPV 52				
Day 1	1642	0.0 (0.0–0.2)	568	0.0 (0.0–0.6)
Month 07	1642	99.9 (99.6–100)	568	100 (99.4–100)
Month 12	448	100 (99.2–100)	505	100 (99.3–100)
Month 24	426	99.5 (98.3–99.9)	481	99.4 (98.2–99.9)
Month 36	419	99.0 (97.6–99.7)	472	97.9 (96.1–99.0)
Anti-HPV 58				
Day 1	1630	0.0 (0.0–0.2)	566	0.0 (0.0–0.6)
Month 07	1630	99.9 (99.6–100)	566	100 (99.4–100)
Month 12	446	100 (99.2–100)	502	100 (99.3–100)
Month 24	424	99.8 (98.7–100)	478	100 (99.2–100)
Month 36	417	99.0 (97.6–99.7)	470	99.1 (97.8–99.8)

Seropositive was defined as anti-HPV serum cLIA levels ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 milli Merck units (mMU)/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. *n*, number of subjects contributing to the analysis.

hospital after 2 days; and fully recovered 8 days later. It was noted that she was bitten by a spider 5 days before dose 3 and was still being treated for an infected spider bite when she received dose 3.

A total of 37 participants became pregnant during the course of the study, representing a total of 39 pregnancies. The outcomes of 36 pregnancies were known: 23 resulted in a live birth, and 13 resulted in fetal loss (1 ectopic pregnancy, 2 spontaneous abortions, 1 late fetal death, and 9 elective abortions). One infant was born with a congenital anomaly (unspecified cardiac disease); the estimated date of conception was ~27 months after dose 3, and the congenital anomaly was considered not related to the study vaccine.

DISCUSSION

This study represents the first analysis of 9vHPV vaccine immunogenicity in girls and boys 9 to 15 years of age, the primary target population for immunoprophylaxis to prevent HPV-related precancers and cancers of the anogenital tract. Seroconversion for all 9 HPV vaccine types was achieved in >99% of participants in the study. The antibody responses in 9- to 15-year-old boys and girls was shown to be noninferior to those observed in 16- to 26-year-old young women (the population used to establish 9vHPV vaccine efficacy[45]), thereby supporting the bridging of efficacy findings from 16- to 26-year-old women to 9- to 15-year- old boys and girls. Antibody responses for all vaccine HPV types were numerically greater in girls and boys than in young women. Antibody responses persisted over time, with >90% girls and boys remaining seropositive through 2.5 years after the third vaccination. Administration of 9vHPV vaccine was generally well tolerated in each group.

A limitation of the current study is the lack of clinical efficacy data. Although prophylactic administration of 9vHPV vaccine is highly efficacious against

TABLE 6 AE Summary

	Girls (9–15 Years Old) (*N* = 1923)		Boys (9–15 Years Old) (*N* = 662)		Young Women (16–26 Years Old) (*N* = 466)	
	Count	(%)	Count	(%)	Count	(%)
With ≥1 AEs	1666	(86.6)	536	(81.0)	420	(90.1)
Injection-site event[a]	1575	(81.9)	482	(72.8)	398	(85.4)
Pain[b]	1545	(80.3)	465	(70.2)	391	(83.9)
Mild	915	(47.6)	342	(51.7)	240	(51.5)
Moderate	552	(28.7)	120	(18.1)	139	(29.8)
Severe	78	(4.1)	3	(0.5)	12	(2.6)
Swelling	668	(34.7)	172	(26.0)	151	(32.4)
Mild (0 to ≤2.5 cm)	439	(22.8)	111	(16.8)	105	(22.5)
Moderate (>2.5 to ≤5.0 cm)	143	(7.4)	28	(4.2)	29	(6.2)
Severe (>5.0 cm)	86	(4.5)	33	(5.0)	17	(3.6)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	567	(29.5)	160	(24.2)	132	(28.3)
Mild (0 to ≤2.5 cm)	445	(23.1)	127	(19.2)	100	(21.5)
Moderate (>2.5 to ≤5.0 cm)	79	(4.1)	21	(3.2)	25	(5.4)
Severe (>5 cm)	42	(2.2)	12	(1.8)	5	(1.1)
Unknown	1	(0.1)	0	(0.0)	2	(0.4)
Pruritus[b]	62	(3.2)	6	(0.9)	16	(3.4)
Mild	48	(2.5)	5	(0.8)	13	(2.8)
Moderate	13	(0.7)	0	(0.0)	3	(0.6)
Severe	1	(0.1)	1	(0.2)	0	(0.0)
Systemic event[c]	865	(45.0)	277	(41.8)	266	(57.1)
Vaccine-related systemic event	401	(20.9)	144	(21.8)	121	(26.0)
Headache	183	(9.5)	60	(9.1)	46	(9.9)
Pyrexia	128	(6.7)	57	(8.6)	32	(6.9)
Fatigue	19	(1.0)	3	(0.5)	12	(2.6)
Serious event	17	(0.9)	11	(1.7)	15	(3.2)
Vaccine-related event	0	(0.0)	1	(0.2)	1	(0.2)
Death[d]	1	(0.1)	0	(0.0)	0	(0.0)
Discontinuation because of an AE	0	(0.0)	1	(0.2)	0	(0.0)
Because of a vaccine-related event	0	(0.0)	1	(0.2)	0	(0.0)
Because of a serious event	0	(0.0)	1	(0.2)	0	(0.0)
Because of a serious vaccine-related event	0	(0.0)	1	(0.2)	0	(0.0)

N, number of subjects as-treated who received at least 1 dose of the indicated vaccine and had at least 1 follow-up visit for an AE.
[a] Days 1–5 after any vaccination visit.
[b] Intensities of pain and itching are defined as follows: mild is an awareness of sign or symptom but easily tolerated; moderate is discomfort enough to cause interference with usual activity; severe is incapacitating with inability to work or do usual activity.
[c] Days 1–15 after any vaccination visit.
[d] The death was not considered by the study investigator to be vaccine-related and was a result of sepsis (occurring 557 days after vaccination dose 3).

infection and disease related to vaccine HPV types in women aged 16 to 26 years,[45] efficacy studies of HPV vaccines are not conducted in children (eg, ≤15 years) due to low exposure to HPV and other technical reasons. Instead, efficacy findings in adults are extended to adolescents on the basis of similar immunogenicity. This approach is similar to that previously used to support licensure of the qHPV vaccine[40] and is consistent with the recommendations from the World Health Organization on prophylactic HPV vaccine development.[48]

TABLE 7 Maximum Temperatures

Maximum Temperature (Oral)[a]	Girls (9–15 Years Old) (*N* = 1908)		Boys (9–15 Years Old) (*N* = 660)		Young Women (16–26 Years Old) (*N* = 463)	
	Count	(%)	Count	(%)	Count	(%)
≤37.8°C	1748	(91.6)	594	(90.0)	424	(91.6)
37.8° to <38.9°C	133	(7.0)	57	(8.6)	31	(6.7)
38.9° to <39.9°C	24	(1.3)	8	(1.2)	7	(1.5)
39.9° to <40.9°C	3	(0.2)	1	(0.2)	1	(0.2)
≥40.9°C	0	(0.0)	0	(0.0)	0	(0.0)

The summaries provided are counts of subjects, and the percentages were calculated relative to the number of subjects with temperature data. *N*, number of subjects with temperature data who received at least 1 dose of the indicated vaccine.
[a] Days 1–5 after any vaccination visit.

In other studies, the 9vHPV vaccine and the qHPV vaccine elicited similar anti-HPV 6/11/16/18 responses both in young women aged 16 to 26 years and in girls 9 to 15 years of age.[45,49] In another study, administration of a 2-dose regimen of qHPV vaccine in girls 9 to 13 years of age induced anti-HPV GMTs that were noninferior to those elicited by administration of a 3-dose regimen in young women 16 to 26 years of age.[50] This finding supports that a 2-dose regimen with the 9vHPV vaccine may be an acceptable alternative, which is currently under study. Another study was conducted to assess the safety of the 9vHPV vaccine in previous recipients of a 3-dose regimen of qHPV vaccine. The 9vHPV vaccine appeared to be generally well tolerated in previous qHPV vaccine recipients (A. Luxembourg, MD, PhD, unpublished results, 2014). The study results will be reported separately.

Follow-up was limited in duration. Duration of protection is particularly relevant to HPV vaccines because individuals remain at risk of HPV-related disease throughout life. Studies with qHPV vaccine found no evidence of waning immunity in long-term cohorts (through at least 96 months),[51–53] which suggests that the 9vHPV vaccine could also offer long-term protection. Planned longer-term immunogenicity and effectiveness follow-up of subjects vaccinated with 9vHPV vaccine should provide essential information on durability of protection. In addition, we do not present direct vaccine efficacy data, because those results have already been published.[45]

TABLE 8 Subjects with Serious AEs, by System Organ Class

	Girls (9–15 Years Old) (*N* = 1923)		Boys (9–15 Years Old) (*N* = 662)		Young Women (16–26 Years Old) (*N* = 466)	
	Count	(%)	Count	(%)	Count	(%)
Days 1–15 after any vaccination visit						
With ≥1 serious AEs	3	(0.2)	5	(0.8)	2	(0.4)
Infections and infestations	1	(0.1)	2	(0.3)	0	(0.0)
Injury, poisoning, and procedural complications	1	(0.1)	1	(0.2)	1	(0.2)
Nervous system disorders	0	(0.0)	0	(0.0)	1	(0.2)
Psychiatric disorders	0	(0.0)	1	(0.2)	0	(0.0)
Respiratory, thoracic, and mediastinal disorders	1	(0.1)	1	(0.2)	0	(0.0)
Any time during the study						
With ≥1 serious AEs	17	(0.9)	11	(1.7)	15	(3.2)
Gastrointestinal disorders	3	(0.2)	0	(0.0)	1	(0.2)
General disorders and administration site conditions	1	(0.1)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	0	(0.0)	0	(0.0)	1	(0.2)
Infections and infestations	9	(0.5)	5	(0.8)	1	(0.2)
Injury, poisoning, and procedural complications	1	(0.1)	3	(0.5)	3	(0.6)
Nervous system disorders	0	(0.0)	1	(0.2)	1	(0.2)
Pregnancy, puerperium, and perinatal conditions	0	(0.0)	0	(0.0)	4	(0.9)
Psychiatric disorders	1	(0.1)	1	(0.2)	0	(0.0)
Reproductive system and breast disorders	0	(0.0)	0	(0.0)	1	(0.2)
Respiratory, thoracic, and mediastinal disorders	2	(0.1)	1	(0.2)	0	(0.0)
Surgical and medical procedures	1	(0.1)	0	(0.0)	5	(1.1)

Per protocol, serious AEs were reportable regardless of causality from day 1 through 180 days after vaccination dose 3; events of fetal loss were to be reported as serious AEs for any pregnancy with last menstrual period before 180 days after vaccination dose 3; and deaths, and serious vaccine-related AEs, were to be reported for the entire duration of the study. The summaries provided are counts of subjects, and the percentages were calculated relative to the number of subjects as-treated. System organ class categories reported are those with an incidence >0% in any vaccination group. A subject is counted once within a category and may be counted in >1 category. *N*, number of subjects as-treated who received at least 1 dose of the indicated vaccine and had at least 1 follow-up visit for an AE.

Licensed HPV vaccines have been introduced in the national vaccination programs of >40 countries.[54] Although the age range of the primary target age group varies by country, all of these programs target young adolescents. The 9vHPV vaccine has the potential to provide additional benefit compared with existing vaccines by extending coverage to 5 additional high-risk HPV types. Antibody response to the 9vHPV vaccine in girls and boys aged 9 to 15 years is noninferior to that of young women aged 16 to 26 years, which supports bridging the efficacy findings in young women 16 to 26 years of age to girls and boys 9 to 15 years of age. The 9vHPV vaccine appears to be generally well tolerated in all groups. The 9vHPV vaccine was licensed in 2014 in the United States under the name Gardasil 9 (Merck & Co., Inc, Kenilworth, NJ).

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ABBREVIATIONS

AE: adverse experience
CI: 95% confidence interval
cLIA: competitive Luminex immunoassay
GMT: geometric mean titer
HPV: human papillomavirus
qHPV: quadrivalent human papillomavirus (6/11/16/18) virus-like particle
PCR: polymerase chain reaction
9vHPV: 9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus virus-like particle
VRC: vaccination report card

reviewing or revising the manuscript, and provision of study materials and patients; Dr Luxembourg contributed to the conception, design, or planning of the study; analysis and interpretation of the data; and drafting and reviewing or revising the manuscript; Mr Maansson contributed to the analysis of the data and reviewing or revising the manuscript; Ms Moeller and Dr Sun contributed to the conception, design, or planning of the study and reviewing or revising the manuscript; Dr Pitisuttithum contributed to acquisition of the data and reviewing or revising the manuscript; Dr Van Damme contributed to the analysis, acquisition, and interpretation of the data; reviewing or revising the manuscript; and provision of study materials and patients as well as administrative logistical or technical support; Dr Vuocolo contributed to the interpretation of the results and drafting of the manuscript; and all authors reviewed and approved the final manuscript as

submitted and are in agreement with its content and submission. They further verify that they had access to relevant study data and related analyses and vouch for the completeness and accuracy of the data presented.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00943722).

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