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Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women

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IMPORTANCE Human papillomavirus (HPV) infections cause anogenital cancers and warts. The 9-valent HPV vaccine provides protection against 7 high-risk types of HPV responsible for 90% of cervical cancers and 2 other HPV types accounting for 90% of genital warts.

OBJECTIVE To determine whether HPV type–specific antibody responses would be noninferior among girls and boys aged 9 to 14 years after receiving 2 doses of the 9-valent HPV vaccine compared with adolescent girls and young women aged 16 to 26 years receiving 3 doses.

DESIGN, SETTING, AND PARTICIPANTS Open-label, noninferiority, immunogenicity trial conducted at 52 ambulatory care sites in 15 countries. The study was initiated on December 16, 2013, with the last participant visit for this report on June 19, 2015. Five cohorts were enrolled: (1) girls aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (2) boys aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (3) girls and boys aged 9 to 14 years to receive 2 doses 12 months apart (n = 301); (4) girls aged 9 to 14 years to receive 3 doses over 6 months (n = 301); and (5) a control group of adolescent girls and young women aged 16 to 26 years to receive 3 doses over 6 months (n = 314).

INTERVENTIONS Two doses of the 9-valent HPV vaccine administered 6 or 12 months apart or 3 doses administered over 6 months.

MAIN OUTCOMES AND MEASURES The primary end point was prespecified as the antibody response against each HPV type assessed 1 month after the last dose using a competitive immunoassay. Each of the three 2-dose regimens was compared with the standard 3-dose schedule in adolescent girls and young women using a noninferiority margin of 0.67 for the ratio of the antibody geometric mean titers.

RESULTS Of the 1518 participants (753 girls [mean age, 11.4 years]; 451 boys [mean age, 11.5 years]; and 314 adolescent girls and young women [mean age, 21.0 years]), 1474 completed the study and data from 1377 were analyzed. At 4 weeks after the last dose, HPV antibody responses in girls and boys given 2 doses were noninferior to HPV antibody responses in adolescent girls and young women given 3 doses ($P < .001$ for each HPV type). Compared with adolescent girls and young women who received 3 doses over 6 months, the 1-sided 97.5% CIs for the ratio of HPV antibody geometric mean titers at 1 month after the last dose across the 9 HPV subtypes ranged from 1.36 to ∞ to 2.50 to ∞ for girls who received 2 doses 6 months apart; from 1.37 to ∞ to 2.55 to ∞ for boys who received 2 doses 6 months apart; and from 1.61 to ∞ to 5.36 to ∞ for girls and boys who received 2 doses 12 months apart.

CONCLUSIONS AND RELEVANCE Among girls and boys aged 9 to 14 years receiving 2-dose regimens of a 9-valent HPV vaccine separated by 6 or 12 months, immunogenicity 4 weeks after the last dose was noninferior to a 3-dose regimen in a cohort of adolescent girls and young women. Further research is needed to assess persistence of antibody responses and effects on clinical outcomes.

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Editorial
Supplemental content

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Diseases related to the human papillomavirus (HPV) impose a substantial health care burden on both the developing and developed world.[1] A 9-valent HPV vaccine was developed to prevent infection and disease from the 9 HPV types (HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58) responsible for causing approximately 90% of cervical cancers and other HPV-related anogenital cancers and 90% of genital warts,[1-4] thus providing broader coverage than the earlier bivalent (HPV-16, HPV-18) and quadrivalent (HPV-6, HPV-11, HPV-16, HPV-18) vaccines. In the pivotal trial[5] in young women, 3 doses of the 9-valent HPV vaccine reduced infection and disease from all 9 vaccine types.

Clinical efficacy cannot be directly tested during early adolescence because of limited exposure to HPV. Efficacy of all HPV vaccines has been demonstrated as a 3-dose series in young women.[5,6] In contrast, efficacy in young adolescents has been inferred from the demonstration of noninferior HPV antibody responses compared with young women (immunobridging). With the bivalent and quadrivalent vaccines, antibody responses 1 month after the second dose in girls within the 9- to 14-year age range who received a 2-dose regimen were noninferior to responses in adolescent girls and young women within the 15- to 26-year age range given 3 doses.[7-12] Based on these results, vaccine efficacy previously established in young women receiving 3 doses was inferred for younger age groups receiving 2 doses. In 2014, the World Health Organization changed its recommendation for routine HPV vaccination of girls aged 9 to 14 years from a 3-dose to a 2-dose schedule based on data from clinical trials with the bivalent and quadrivalent vaccines.[13]

In this study, immunogenicity of a 2-dose regimen of the 9-valent HPV vaccine was assessed using standard immunobridging criteria by comparing antibody responses to vaccine types in girls and boys given 2 doses separated by 6 or 12 months vs antibody responses in adolescent girls and young women given the standard 3-dose regimen.

Key Points

Question Are 2 doses of the 9-valent human papillomavirus (HPV) vaccine in girls and boys aged 9 to 14 years noninferior to 3 doses in adolescent girls and young women aged 16 to 26 years?

Findings In this international, open-label, noninferiority trial involving 1518 participants, antibody responses measured 4 weeks after the last dose in girls and boys given 2 doses separated by 6 or 12 months were noninferior to responses in adolescent girls and young women given 3 doses.

Meaning Short-term immune responses after 2 doses of 9-valent HPV vaccine in girls and boys aged 9 to 14 years were noninferior to immune responses after 3 doses in adolescent girls and young women. Persistence of response and clinical outcomes need to be studied.

Methods

Study Design

An international clinical trial was conducted of the immunogenicity and safety of the 9-valent HPV vaccine in girls and boys aged 9 to 14 years given 2 doses 6 or 12 months apart compared with a control group of adolescent girls and young women aged 16 to 26 years given the standard 3-dose schedule. The protocol is available in Supplement 1. This study assessed whether a 2-dose regimen of the 9-valent HPV vaccine in girls and boys would likely be protective by bridging antibody responses to the older group of adolescent girls and young women shown to be protected against HPV infection and disease. Such an approach allows direct comparison with antibody geometric mean titers (GMTs) proven to be effective against clinically meaningful end points.

The trial was initiated on December 16, 2013, at 52 ambulatory care sites in 15 countries and was conducted according to good clinical practice principles. The protocol was approved by the regulatory agencies of all participating countries and by the institutional review boards with jurisdiction over the study sites. All participants or their parents or guardians signed informed consent at entry. Enrollment was concluded on April 18, 2014, but follow-up is ongoing to assess antibody persistence through month 36. The last participant visit contributing to the current report occurred on June 19, 2015.

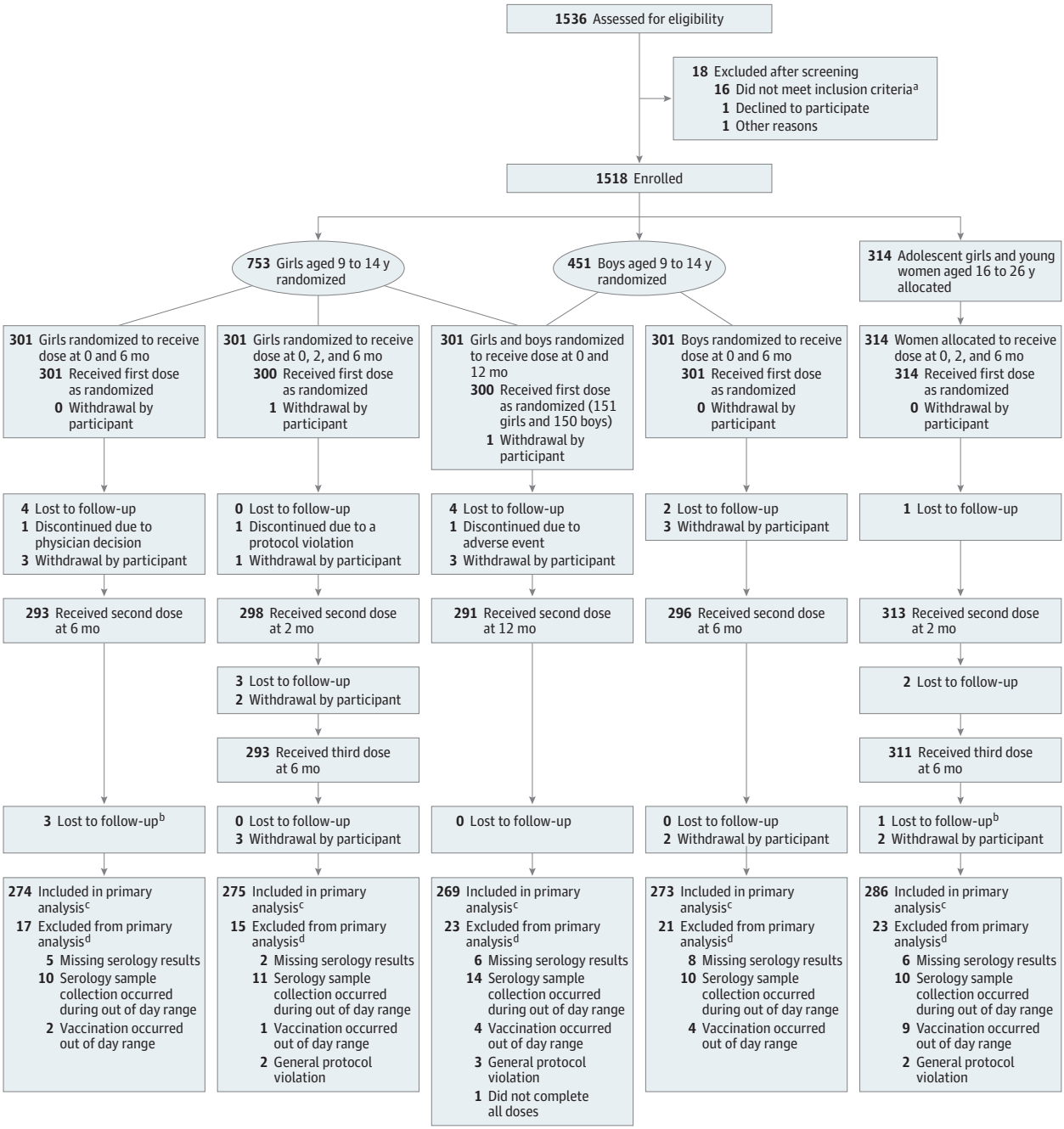
Eligible girls and boys aged 9 to 14 years had to be generally healthy and not sexually active prior to enrollment. Adolescent girls and young women aged 16 to 26 years had to be generally healthy with 4 or fewer lifetime sexual partners, without a history of abnormal Papanicolaou test results or other cervical abnormalities, and agree to use effective contraception through study month 7. Participants were required to be afebrile (oral temperature <37.8°C) for 24 hours before each vaccine injection.

Exclusion criteria included pregnancy, known allergy to any vaccine component, thrombocytopenia, prior or ongoing immunosuppression, or previous receipt of an HPV vaccine. An interactive voice response system was used to allocate study participants, balance randomization between sites, and assist with vaccine supply management at the study sites.

The 9-valent HPV vaccine (Gardasil 9, Merck & Co) was administered to 5 vaccination cohorts. The first cohort was composed of girls aged 9 to 14 years who were randomized to receive 2 doses of the HPV vaccine 6 months apart (at 0 and 6 months); the second cohort, boys aged 9 to 14 years were randomized to receive 2 doses of the HPV vaccine 6 months apart (at 0 and 6 months); the third cohort, girls and boys aged 9 to 14 years were randomized to receive 2 doses of the HPV vaccine 12 months apart (at 0 and 12 months); the fourth cohort, girls aged 9 to 14 years were randomized to receive 3 doses of the HPV vaccine (at 0, 2, and 6 months); and the fifth cohort, adolescent girls and young women aged 16 to 26 years were allocated to receive 3 doses of the HPV vaccine (at 0, 2, and 6 months) (**Figure**).

Each vaccination cohort was to enroll approximately 300 participants. Enrollment of girls and boys was stratified into

Figure. Flow Diagram for Primary Per-Protocol Immunogenicity Population Administered the 9-Valent Human Papillomavirus (HPV) Vaccine



[a] Four (aged 9-14 years) were sexually active prior to enrollment; 4 unlikely to adhere to study procedures; 3 unable to give consent or assent; 2 had a history or current evidence of medical conditions that might interfere with the results of the study; 1 was judged to be in poor physical health; 1 had a history of abnormal Papanicolaou test results; and 1 had a history of severe allergic reaction.

[b] One participant discontinued the study after providing data for the analyses.

[c] To be included in the primary per-protocol immunogenicity population, individuals were required to (1) be seronegative at day 1 for the HPV type being analyzed; (2) receive all planned doses within acceptable day ranges; (3) have a serology result after the last dose within an acceptable day range; and (4) have no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. Individuals included provided data for analysis of 1 or more HPV types.

[d] The total number of participants excluded from the primary analysis only counts a participant once. Individuals were counted once in each applicable exclusion subcategory, but a participant may appear in more than 1 subcategory. Additional data and information appear in eTable 1 in Supplement 2.

3 age strata (9-10, 11-12, and 13-14 years) of similar size. Girls were randomized in a 2:1:2 ratio within each age stratum to girls (vaccine administered at 0 and 6 months), girls and boys (vaccine administered at 0 and 12 months), and girls (vaccine administered at 0, 2, and 6 months). Boys were randomized in a 2:1 ratio within each age stratum to boys (vaccine administered at 0 and 6 months) and girls and boys (vaccine administered at 0 and 12 months).

Participants were observed for 30 minutes after each vaccine injection for any immediate reaction. Serious adverse events were to be reported irrespective of causality from day 1 (month 0) through 6 months after the last vaccination. Serious adverse events were predefined as those events that resulted in death, were deemed life-threatening, led to a persistent or significant disability, required hospitalization, or were associated with a congenital anomaly, cancer, or other important medical event. Investigators were instructed to assign causality to adverse events on the basis of exposure, time course, likely cause, and consistency with the vaccine's known safety profile (extensively described in previous trials).[14]

Outcomes

The primary end point was prespecified as the antibody response against HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 assessed just prior to the first dose and 1 month after the last dose (after dose 2 or after dose 3 depending on the assigned vaccine schedule) using a competitive Luminex immunoassay.[15] The secondary end point was seropositivity rates assessed just prior to the first dose and 1 month after the last dose of the given regimen. Seroconversion was defined as a changing serostatus from seronegative at baseline to seropositive by 4 weeks after the last vaccine dose. Serostatus cutoffs were defined as the antibody level above the assay's lower limit of quantification that reliably distinguished samples classified by clinical likelihood of HPV infection and positive or negative status using previous versions of the competitive Luminex immunoassay.

A participant with an antibody titer at or above the predetermined cutoff for a given HPV type was considered seropositive for that type. Antibody titers function as a surrogate marker for vaccine protection in children before sexual debut, although the actual minimum antibody concentration needed for prevention has not been established. Human papillomavirus seropositivity at day 1 was not a reason for exclusion from the study; however, it was a reason for exclusion from the HPV type–specific per-protocol analyses.

In the primary noninferiority analyses using the per-protocol population, antibody GMTs at 1 month after the last dose in girls and boys who received 2 doses (6 or 12 months apart) were compared with antibody GMTs at 1 month after the last dose in adolescent girls and young women who received 3 doses over 6 months. A supportive intention-to-treat analysis was conducted in all randomized participants. The prespecified secondary analyses examined noninferiority of seropositivity rates at 1 month after the last dose in girls and boys who received 2 doses vs adolescent girls and young women who received 3 doses.

Exploratory analyses were planned to summarize antibody GMTs at 1 month after the last dose in girls and boys who received 2 doses by age strata. Four hypothesis-generating post hoc analyses were performed comparing (1) antibody GMTs 6 months after the last dose in girls and boys who received 2 doses 6 months apart vs adolescent girls and young women who received 3 doses; (2) antibody GMTs 1 month after the last dose in girls and boys who received 2 doses vs girls who received 3 doses; (3) antibody GMTs 1 month after the last dose in girls who received 3 doses vs adolescent girls and young women who received 3 doses; and (4) 2-dose regimens separated by 6 or 12 months.

Statistical Analyses

As a noninferiority trial, the primary analysis used the per-protocol population. Participants were required to (1) be seronegative at day 1 for the HPV type being analyzed (for the HPV-6 and HPV-11 immunogenicity analyses, participants had to be seronegative for both HPV-6 and HPV-11); (2) receive all planned doses of the vaccine within predetermined day ranges; (3) have a serology result after the last dose within an acceptable time window; and (4) have no other protocol violations that could interfere with the evaluation of the participant's immune response to the vaccine.

Noninferiority of antibody GMTs at 1 month after the last dose in girls and boys who received 2 doses vs adolescent girls and young women who received 3 doses (primary immunogenicity hypothesis) was tested by constructing a 2-sided 95% CI for the ratio of antibody GMTs as stipulated by the trial protocol. Although 2-sided 95% CIs were prespecified by the protocol, 1-sided 97.5% CIs are presented for the primary immunogenicity hypotheses in keeping with currently accepted methods of presenting noninferiority results.

Prespecified noninferiority criteria required that the lower bound of the 2-sided 95% CI (equivalent to the lower bound of the 1-sided 97.5% CI) for the ratio of antibody GMTs in girls and boys who received 2 doses relative to antibody GMTs in adolescent girls and young women who received 3 doses to be 0.67 or greater for each of the 9 vaccine HPV types. For an individual HPV type, the 95% CI for the ratio of antibody GMTs was derived from an analysis of variance model with the log of type-specific antibody titers as the response and vaccination group as the fixed effect.

The lower bound of 0.67 represents a more conservative choice than the 0.5 limit used in the earlier bridging noninferiority study of the quadrivalent HPV vaccine.[9,16] The specific choice of the noninferiority margin was based on protective antibody levels in the pivotal efficacy trials of the quadrivalent HPV vaccine, which informed benchmarks set by Merck in conjunction with regulatory agencies for bridging studies leading to licensure.

Noninferiority of seroconversion rates at 1 month after the last dose in girls and boys given 2 doses vs adolescent girls and young women given 3 doses (secondary immunogenicity hypothesis) was tested by constructing a 2-sided 95% CI for the difference in seroconversion rates (girls, boys, or girls and boys minus adolescent girls and young

Table 1. Baseline Characteristics of Participants at Enrollment

	HPV Vaccine Administered at 0 and 6 mo in Girls Aged 9-14 y (n = 301)	HPV Vaccine Administered at 0 and 6 mo in Boys Aged 9-14 y (n = 301)	HPV Vaccine Administered at 0 and 12 mo		HPV Vaccine Administered at 0, 2, and 6 mo in Girls Aged 9-14 y (n = 301)	HPV Vaccine Administered at 0, 2, and 6 mo in Adolescent Girls and Young Women Aged 16-26 y (n = 314)
			Girls Aged 9-14 y (n = 151)	Boys Aged 9-14 y (n = 150)		
Age, mean (SD), y	11.4 (1.7)	11.5 (1.7)	11.4 (1.6)	11.4 (1.7)	11.4 (1.7)	21.0 (2.7)
Age group, y						
9-10	100 (33.2)	98 (32.6)	49 (32.5)	51 (34.0)	101 (33.6)	0
11-12	102 (33.9)	102 (33.9)	53 (35.1)	53 (35.3)	100 (33.2)	0
13-14	99 (32.9)	101 (33.6)	49 (32.5)	46 (30.7)	100 (33.2)	0
16-26	0	0	0	0	0	314 (100.0)
Weight, mean (SD), kg	44.8 (13.6)	46.4 (14.5)	46.4 (16.4)	45.1 (13.7)	44.7 (13.6)	64.1 (13.9)
BMI, mean (SD)[a]	19.7 (4.2)	19.5 (3.8)	20.2 (5.1)	19.0 (3.8)	19.6 (4.2)	23.9 (5.0)
Self-reported race						
White	160 (53.2)	211 (70.1)	88 (58.3)	102 (68.0)	154 (51.2)	213 (67.8)
Asian	64 (21.3)	30 (10.0)	27 (17.9)	19 (12.7)	63 (20.9)	45 (14.3)
Black	32 (10.6)	14 (4.7)	19 (12.6)	6 (4.0)	43 (14.3)	21 (6.7)
Multiple	32 (10.6)	34 (11.3)	13 (8.6)	19 (12.7)	31 (10.3)	22 (7.0)
American Indian or Alaska Native	13 (4.3)	12 (4.0)	4 (2.6)	4 (2.7)	10 (3.3)	8 (2.5)
Missing	0	0	0	0	0	5 (1.6)
Ethnicity						
Not Hispanic or Latino	217 (72.1)	249 (82.7)	109 (72.2)	126 (84.0)	223 (74.1)	228 (72.6)
Hispanic or Latino	68 (22.6)	46 (15.3)	37 (24.5)	21 (14.0)	64 (21.3)	81 (25.8)
Not reported	16 (5.3)	6 (2.0)	5 (3.3)	3 (2.0)	14 (4.7)	5 (1.6)
Region						
North America	83 (27.6)	85 (28.2)	38 (25.2)	39 (26.0)	60 (19.9)	70 (22.3)
Asia Pacific	79 (26.2)	39 (13.0)	36 (23.8)	22 (14.7)	81 (26.9)	63 (20.1)
Europe	56 (18.6)	132 (43.9)	32 (21.2)	70 (46.7)	66 (21.9)	114 (36.3)
Latin America	57 (18.9)	34 (11.3)	29 (19.2)	15 (10.0)	56 (18.6)	55 (17.5)
Africa	26 (8.6)	11 (3.7)	16 (10.6)	4 (2.7)	38 (12.6)	12 (3.8)

Abbreviations: BMI, body mass index; HPV, human papillomavirus.

[a] Calculated as weight in kilograms divided by height in meters squared.

women). Although 2-sided 95% CIs were again prespecified, 1-sided 97.5% CIs are presented for the secondary immunogenicity hypotheses to be consistent with currently accepted methods of presenting noninferiority results. Prespecified noninferiority criteria required that the lower bound of the 2-sided 95% CI (equivalent to the lower bound of the 1-sided 97.5% CI) for the difference in seroconversion rates exceed −5 percentage points for each HPV type. All data analyses were conducted using SAS version 9.3 (SAS Institute Inc).

To satisfy the 3 primary immunogenicity hypotheses, noninferiority criteria had to be met for all 9 HPV types; thus, no multiplicity adjustment was made to account for the multiple HPV types within each hypothesis. A closed stepwise procedure was used to control for multiplicity resulting from 3 primary hypotheses and to ensure an overall 1-sided type I error rate at the 0.025 level. Noninferiority in girls vaccinated at 0 and 6 months had to be established vs adolescent girls and young women vaccinated at 0, 2, and 6 months before noninferiority in boys vaccinated at 0 and 6 months vs adolescent girls and young women vaccinated at 0, 2, and 6 months was tested. Similarly, noninferiority in boys vaccinated at 0 and 6 months vs adolescent girls and young women vaccinated at 0, 2, and 6 months had to be established before noninferiority in girls and boys vaccinated at 0 and 12 months vs adolescent girls and young women vaccinated at 0, 2, and 6 months was tested.

With the planned sample size of approximately 300 participants per cohort, the study had greater than 99% power to establish the primary immunogenicity hypothesis at a 1-sided significance level of 0.025, assuming a true ratio of antibody GMTs of 1.2 for all 9 vaccine HPV types, an exclusion rate from the per-protocol analyses of 20% for girls and boys and 30% for adolescent girls and young women, an SD of 1.2 for the natural log-transformed titers, and a noninferiority margin with a 1.5-fold difference for the ratio of antibody GMTs.

Every participant who received at least 1 study vaccination and had follow-up data was included in the safety analysis. Because the safety profile of the 9-valent HPV vaccine has already been characterized in phase 3 clinical studies,[14] the protocol did not use vaccination report cards.

Table 2. Noninferiority Analysis of Antibody Geometric Mean Titers (GMTs) at 1 Month After Administration of the Last Dose of the 9-Valent Human Papillomavirus (HPV) Vaccine

	HPV Vaccine Administered at 0 and 6 mo in Girls Aged 9-14 y (n = 301)		HPV Vaccine Administered at 0 and 12 mo in Girls and Boys Aged 9-14 y (n = 300)		HPV Vaccine Administered at 0, 2, and 6 mo in Adolescent Girls and Women Aged 16-26 y (n = 314)		Ratio of GMT (1-sided 97.5% CI) vs Adolescent Girls and Women With HPV Vaccine Administered at 0, 2, and 6 mo[a]		
	No.	GMT (95% CI), mMU/mL	No.	GMT (95% CI), mMU/mL	No.	GMT (95% CI), mMU/mL	Girls (Vaccine at 0 and 6 mo)	Boys (Vaccine at 0 and 6 mo)	Girls and Boys (Vaccine at 0 and 12 mo)
HPV-6	258	1657.9 (1479.6-1857.6)	263	1557.4 (1391.5-1743.1)	257	2678.8 (2390.2-3002.1)	238	770.9 (684.8-867.9)	2.15 (1.83-∞)	2.02 (1.73-∞)	3.47 (2.93-∞)
HPV-11	258	1388.9 (1240.4-1555.3)	264	1423.9 (1273.2-1592.3)	257	2941.8 (2626.6-3294.9)	238	580.5 (516.0-653.0)	2.39 (2.03-∞)	2.45 (2.09-∞)	5.07 (4.32-∞)
HPV-16	272	8004.9 (7160.5-8948.8)	273	8474.8 (7582.4-9472.3)	264	14 329.3 (12 796.4-16 045.9)	249	3154.0 (2807.1-3543.7)	2.54 (2.14-∞)	2.69 (2.29-∞)	4.54 (3.84-∞)
HPV-18	272	1872.8 (1651.6-2123.6)	272	1860.9 (1641.1-2110.2)	266	2810.4 (2474.9-3191.3)	267	761.5 (670.8-864.5)	2.46 (2.05-∞)	2.44 (2.04-∞)	3.69 (3.06-∞)
HPV-31	272	1436.3 (1272.1-1621.8)	271	1498.2 (1326.5-1692.0)	268	2117.5 (1873.7-2393.1)	264	572.1 (505.8-647.2)	2.51 (2.10-∞)	2.62 (2.20-∞)	3.70 (3.08-∞)
HPV-33	273	1030.0 (920.4-1152.7)	271	1040.0 (928.9-1164.3)	269	2197.5 (1961.9-2461.3)	279	348.1 (311.5-389.1)	2.96 (2.50-∞)	2.99 (2.55-∞)	6.31 (5.36-∞)
HPV-45	274	357.6 (313.7-407.6)	273	352.3 (309.0-401.7)	268	417.7 (365.9-476.9)	280	213.6 (187.7-243.2)	1.67 (1.38-∞)	1.65 (1.37-∞)	1.96 (1.61-∞)
HPV-52	272	581.1 (521.9-647.1)	273	640.4 (575.2-713.0)	268	1123.4 (1008.1-1251.9)	271	364.2 (327.0-405.6)	1.60 (1.36-∞)	1.76 (1.51-∞)	3.08 (2.64-∞)
HPV-58	270	1251.2 (1119.6-1398.4)	270	1325.7 (1186.2-1481.6)	265	2444.6 (2185.2-2734.9)	261	491.1 (438.6-549.8)	2.55 (2.15-∞)	2.70 (2.30-∞)	4.98 (4.23-∞)

Abbreviation: mMU, milli-Merck units.

[a] Although the protocol specified that noninferiority testing would use 2-sided 95% CIs, 1-sided 97.5% CIs are displayed in keeping with the standard method of presenting noninferiority studies. The lower bound of the 1-sided 97.5% CI and the lower bound of the 2-sided 95% CI are identical. The full 2-sided 95% CIs are presented in the Gardasil 9 US product information (https://www.gardasil9.com/) and also have been posted elsewhere (https://clinicaltrials.gov).

Nonserious injection site and systemic events were not actively solicited (although investigators could report such events at their discretion). Consequently, the frequencies of nonserious adverse events reported in this study cannot be quantitatively compared with other HPV vaccine studies that used vaccination report cards.

Results

Baseline Characteristics

A total of 1536 potential participants were screened for inclusion in the study and 1518 (753 girls [mean age, 11.4 years]; 451 boys [mean age, 11.5 years]; and 314 adolescent girls and young women [mean age, 21.0 years]) were enrolled, including 1516 who received at least 1 vaccine dose (Figure). Overall, 1474 completed the study and data from 1377 (274 girls aged 9-14 years randomized to receive 2 vaccine doses 6 months apart; 273 boys aged 9-14 years randomized to receive 2 doses 6 months apart; 269 girls and boys aged 9-14 years randomized to receive 2 doses 12 months apart; 275 girls aged 9-14 years randomized to receive 3 doses over 6 months; and 286 adolescent girls and young women aged 16 to 26 years allocated to receive 3 doses over 6 months) were included in the per-protocol analyses.

Baseline characteristics of randomized participants appear in **Table 1**. The most common reasons for exclusion from the per-protocol immunogenicity analyses were seropositivity for a HPV type included in the vaccine on day 1 or a missing result for the primary end point collected 4 weeks after the last vaccination (eTable 1 in Supplement 2).

Immunogenicity

Antibody GMTs against the 9 HPV types assayed 1 month after the last dose were consistently higher in girls (vaccine doses at 0 and 6 months), boys (vaccine doses at 0 and 6 months), and girls and boys (vaccine doses at 0 and 12 months) than for adolescent girls and young women (vaccine doses at 0, 2, and 6 months) in the per-protocol population (**Table 2**). Compared with adolescent girls and young women who received 3 doses over 6 months, the 1-sided 97.5% CIs for the ratio of antibody GMTs at 1 month after the last dose across the 9 HPV vaccine subtypes ranged from 1.36 to ∞ to 2.50 to ∞ for girls who received vaccine doses at 0 and 6 months; from 1.37 to ∞ to 2.55 to ∞ for boys who received doses at 0 and 6 months; and from 1.61 to ∞ to 5.36 to ∞ for girls and boys who received doses at 0 and 12 months. Accordingly, noninferiority criteria of antibody GMTs were met for all 9 HPV types for the 27 primary comparisons (all $P < .001$). Similar results were found in supportive analyses of the intention-to-treat population (eTable 2 in Supplement 2).

More than 98% of participants in each cohort seroconverted by 1 month after the last vaccine dose to each individual HPV type in the vaccine. The lower bounds of 1-sided 97.5% CIs for the differences in seroconversion rates between girls (vaccine doses at 0 and 6 months), boys (doses at 0 and 6 months), and girls and boys (doses at 0 and 12 months) com-

Table 3. Noninferiority Analysis of Seropositivity Rates at 1 Month After Administration of the Last Dose of the 9-Valent Human Papillomavirus (HPV) Vaccine

	Anti-HPV Serum Level, mMU/mL	HPV Vaccine Administered at 0 and 6 mo in Girls Aged 9-14 y (n = 301)		HPV Vaccine Administered at 0 and 6 mo in Boys Aged 9-14 y (n = 301)		HPV Vaccine Administered at 0 and 12 mo in Girls and Boys Aged 9-14 y (n = 300)		HPV Vaccine Administered at 0, 2, and 6 mo in Adolescent Girls and Women Aged 16-26 y (n = 314)		Difference in Seroconversion Rates (1-sided 97.5% CI) vs Adolescent Girls and Women With HPV Vaccine Administered at 0, 2, and 6 mo[a]		
		No.	Seroconversion, % (95% CI)[b]	No.	Seroconversion, % (95% CI)[b]	No.	Seroconversion, % (95% CI)[b]	No.	Seroconversion, % (95% CI)[b]	Girls (Vaccine at 0 and 6 mo)	Boys (Vaccine at 0 and 6 mo)	Girls and Boys (Vaccine at 0 and 12 mo)
HPV-6	≥30	258	99.6 (97.9 to 100)	263	100 (98.6 to 100)	257	100 (98.6 to 100)	238	99.6 (97.7 to 100)	0 (−1.8 to 100)	0.4 (−1.0 to 100)	0.4 (−1.1 to 100)
HPV-11	16	258	100 (98.6 to 100)	264	100 (98.6 to 100)	257	100 (98.6 to 100)	238	99.6 (97.7 to 100)	0.4 (−1.1 to 100)	0.4 (−1.0 to 100)	0.4 (−1.1 to 100)
HPV-16	20	272	100 (98.7 to 100)	273	100 (98.7 to 100)	264	100 (98.6 to 100)	249	99.6 (97.8 to 100)	0.4 (−1.0 to 100)	0.4 (−1.0 to 100)	0.4 (−1.0 to 100)
HPV-18	24	272	100 (98.7 to 100)	272	100 (98.7 to 100)	266	100 (98.6 to 100)	267	98.5 (96.2 to 99.6)	1.5 (0.1 to 100)	1.5 (0.1 to 100)	1.5 (0.1 to 100)
HPV-31	10	272	99.6 (98.0 to 100)	271	100 (98.6 to 100)	268	100 (98.6 to 100)	264	99.6 (97.9 to 100)	0 (−1.7 to 100)	0.4 (−1.0 to 100)	0.4 (−1.0 to 100)
HPV-33	8	273	99.6 (98.0 to 100)	271	100 (98.6 to 100)	269	100 (98.6 to 100)	279	99.6 (98.0 to 100)	0 (−1.7 to 100)	0.4 (−1.0 to 100)	0.4 (−1.1 to 100)
HPV-45	8	274	99.3 (97.4 to 99.9)	273	99.3 (97.4 to 99.9)	268	100 (98.6 to 100)	280	97.9 (95.4 to 99.2)	1.4 (−0.7 to 100)	1.4 (−0.7 to 100)	2.1 (0.7 to 100)
HPV-52	8	272	99.6 (98.0 to 100)	273	100 (98.7 to 100)	268	100 (98.6 to 100)	271	99.6 (98.0 to 100)	0 (−1.7 to 100)	0.4 (−1.0 to 100)	0.4 (−1.0 to 100)
HPV-58	8	270	100 (98.6 to 100)	270	100 (98.6 to 100)	265	100 (98.6 to 100)	261	99.6 (97.9 to 100)	0.4 (−1.0 to 100)	0.4 (−1.0 to 100)	0.4 (−1.1 to 100)

Abbreviation: mMU, milli-Merck units.

[a] Although the protocol specified that noninferiority testing would use 2-sided 95% CIs, 1-sided 97.5% CIs are displayed in keeping with the standard method of presenting noninferiority studies. The lower bound of the 1-sided 97.5% CI and the lower bound of the 2-sided 95% CI are identical. The full 2-sided 95% CIs have been posted elsewhere (https://clinicaltrials.gov).

[b] Represents the proportion of participants with anti-HPV serum level.

pared with adolescent girls and young women (vaccine doses at 0, 2, and 6 months) were less than −5 percentage points for all comparisons (**Table 3**). Thus, the noninferiority criteria for seroconversion rates were met for all 9 HPV types for the 27 secondary comparisons (all $P < .001$).

In a planned exploratory, hypothesis-generating analysis of antibody GMTs by age strata among girls and boys receiving a 2-dose regimen (eTable 3 in Supplement 2), antibody GMTs for each age stratum of girls and boys receiving 2 doses on a 6- or 12-month schedule were higher than in adolescent girls and young women given 3 doses over 6 months.

Post hoc hypothesis-generating analyses at 1 month after the last dose showed that the 2-dose regimen given at 0 and 6 months in girls aged 9 to 14 years resulted in higher antibody GMTs against 5 HPV types (HPV-6, HPV-11, HPV-16, HPV-33, HPV-58) and lower antibody GMTs against 4 HPV types (HPV-18, HPV-31, HPV-45, HPV-52) than the 3-dose regimen given at 0, 2, and 6 months in girls aged 9 to 14 years. The 2-dose regimen given at 0 and 12 months to girls aged 9 to 14 years resulted in higher antibody GMTs against 8 HPV types (HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-52, HPV-58) and lower antibody GMTs against 1 HPV type (HPV-45) than the 3-dose regimen given at 0, 2, and 6 months in girls (**Table 4**). Similar relative results for antibody GMTs also were seen for boys after 2 doses compared with girls after 3 doses (eTable 4 in Supplement 2).

A post hoc analysis was performed to assess the persistence of antibody responses at 6 months after the last dose in the vaccine groups receiving 2 or 3 doses on a 6-month schedule. Although antibody GMTs declined in all 4 cohorts (girls, vaccine doses at 0 and 6 months; boys, doses at 0 and 6 months; girls and boys, doses at 0 and 12 months; adolescent girls and young women, doses at 0, 2, and 6 months) over the 5-month period from study month 7 to study month 12, the ratio of antibody GMTs for responses after 2 doses in girls and boys relative to 3 doses in adolescent girls and young women were maintained above the noninferiority threshold (eTable 5 in Supplement 2). Another post hoc analysis of girls aged 9 to 14 years receiving doses at 0, 2, and 6 months showed that antibody GMTs against HPV types in the vaccine were higher in girls than in adolescent girls and young women aged 16 to 26 years (eTable 6 in Supplement 2).

In a hypothesis-generating analysis contrasting 2 doses separated by 6 or 12 months, antibody GMTs were higher in the cohort of girls and boys given doses at 0 and 12 months than in either the cohort of girls or cohort of boys given doses at 0 and 6 months with nonoverlapping 2-sided 95% CIs for all HPV types except HPV-45 (Table 2).

Safety and Tolerability

Twenty-two participants experienced serious adverse events (eTable 7 in Supplement 2), none of which were considered related to the vaccine. One participant (a 9-year-old girl) discontinued the study because of a vaccine-related adverse event of transient urticaria 1 day after the first dose of vaccine, which fully resolved. There were no deaths during the course of the study.

Table 4. Post Hoc Analysis of Antibody Geometric Mean Titers (GMTs) at 1 Month After Administration of the Last Dose of the 9-Valent Human Papillomavirus (HPV) Vaccine

	HPV Vaccine Administered at 0 and 6 mo in Girls Aged 9-14 y (n = 301)		HPV Vaccine Administered at 0 and 12 mo in Girls Aged 9-14 y (n = 151)		HPV Vaccine Administered at 0, 2, and 6 mo in Girls Aged 9-14 y (n = 300)		Ratio of GMT (95% CI) vs Girls With HPV Vaccine Administered at 0, 2, and 6 mo	
	No.	GMT (95% CI), mMU/mL	No.	GMT (95% CI), mMU/mL	No.	GMT (95% CI), mMU/mL	Girls (Vaccine at 0 and 6 mo)	Girls (Vaccine at 0 and 12 mo)
HPV-6	258	1657.9 (1479.6-1857.6)	123	2685.7 (2274.6-3171.2)	254	1496.1 (1332.7-1679.5)	1.11 (0.94-1.30)	1.80 (1.44-2.23)
HPV-11	258	1388.9 (1240.4-1555.3)	123	2915.9 (2475.1-3435.1)	254	1306.3 (1165.5-1464.1)	1.06 (0.90-1.25)	2.23 (1.82-2.74)
HPV-16	272	8004.9 (7160.5-8948.8)	129	13 828.1 (11 780.6-16 231.5)	269	6996.0 (6261.1-7817.0)	1.14 (0.98-1.34)	1.98 (1.62-2.41)
HPV-18	272	1872.8 (1651.6-2123.6)	129	2696.0 (2252.4-3227.0)	270	2049.3 (1809.8-2320.4)	0.91 (0.77-1.09)	1.32 (1.05-1.65)
HPV-31	272	1436.3 (1272.1-1621.8)	132	2086.4 (1761.7-2471.1)	271	1748.3 (1553.6-1967.5)	0.82 (0.69-0.97)	1.19 (0.96-1.48)
HPV-33	273	1030.0 (920.4-1152.7)	132	2037.4 (1737.6-2389.0)	275	796.4 (713.3-889.3)	1.29 (1.10-1.52)	2.56 (2.10-3.11)
HPV-45	274	357.6 (313.7-407.6)	132	439.6 (366.0-528.0)	275	661.7 (582.8-751.2)	0.54 (0.45-0.65)	0.66 (0.53-0.84)
HPV-52	272	581.1 (521.9-647.1)	131	1028.2 (885.0-1194.7)	275	909.9 (820.4-1009.1)	0.64 (0.55-0.75)	1.13 (0.93-1.37)
HPV-58	270	1251.2 (1119.6-1398.4)	129	2244.7 (1919.2-2625.3)	273	1229.3 (1103.8-1369.1)	1.02 (0.87-1.20)	1.83 (1.49-2.23)

Abbreviation: mMU, milli-Merck units.

Discussion

In an international immunogenicity trial of the 9-valent HPV vaccine, HPV type-specific antibody responses in girls and boys aged 9 to 14 years after 2 doses separated by 6 or 12 months were noninferior to responses in adolescent girls and young women aged 16 to 26 years after the standard 3-dose series. Quantitative antibody responses to HPV vaccines tend to be higher in children than in adults, as previously shown in studies assessing a 3-dose schedule.[17,18] In this study, an exploratory analysis found that antibody GMTs at 1 month after the last dose were higher in each subgroup of girls and boys vaccinated with 2 doses when categorized by age strata (9-10 years, 11-12 years, and 13-14 years) than in adolescent girls and young women after 3 doses for all 9 HPV types. These observations suggest that the overall results of the primary immunogenicity analyses may be applicable across the entire studied age range of girls and boys.

In exploratory analyses, antibody GMTs at 1 month after the last dose were lower for some HPV types in girls who received a 2-dose series compared with girls who received a 3-dose series. Previous studies of 2-dose regimens of the bivalent or quadrivalent vaccines had also reported lower antibody responses with 2 doses for some HPV vaccine types (HPV-16 for the bivalent vaccine and HPV-18 for the quadrivalent vaccine).[9,10] Vaccine-mediated protection against HPV infection is thought to be primarily mediated through neutralizing antibodies.[19] High seroconversion rates have consistently occurred after HPV vaccination but the minimum protective titer has not been established.

The relevant objective of this study was to demonstrate that 2 doses given to boys and girls aged 9 to 14 years led to protective antibody levels as operationally quantified by efficacy trials, and was not to show which age group and dosing regimen achieved the highest antibody levels. The 2-dose regimens were limited to girls and boys in this study to take advantage of the recognized higher immunogenicity in the younger age cohort. Without direct evidence of vaccine efficacy in girls, the clinical significance of these differences in immunogenicity is unknown.

Dosing interval appears to be an important determinant of immunogenicity. In studies of 3-dose regimens of the quadrivalent HPV vaccine, a longer interval preceding the third dose (ie, third dose at month 12 instead of at month 6) resulted in higher antibody responses after the third dose.[20] Likewise, a longer interval between the first 2 doses (ie, 12 months vs 3 or 6 months) resulted in higher antibody responses after the second dose.[21-23]

Vaccination with a 2-dose regimen separated by short intervals is likely to be less immunogenic than separation by longer intervals. In the current study, HPV antibody responses were generally higher in girls and boys who received 2 doses at a 12-month interval than in girls and boys who received 2 doses 6 months apart. These results allow for some flexibility in the spacing of the second dose.

The European Medicines Agency approved the 2-dose regimen of the 9-valent HPV vaccine in April 2016 for young

adolescents aged 9 to 14 years,[24] recommending that the second dose be administered 5 to 13 months after the first dose. Similarly, the World Health Organization recommended administration of 2 doses separated by 6 months or longer, without specifying a maximum interval.[13] In this regard, postlicensure observational data indicate that administering the second dose earlier than 5 months after the initial dose may be associated with reduced effectiveness.[25,26]

This study provides a broad evaluation of the immunogenicity of 2-dose schedules of the 9-valent HPV vaccine (including a direct comparison of 2 alternative schedules in both girls and boys); however, there are several limitations. First, because children are typically not exposed to HPV prior to adolescence, efficacy of prophylactic HPV vaccines cannot be directly assessed in this population. Thus, the primary objective was to demonstrate noninferior immunogenicity compared with a group in whom efficacy had been established. Second, although this approach has been widely adopted by regulators, there are no universally accepted noninferiority criteria. Nonetheless, it is reassuring that antibody responses in girls and boys who received 2 doses were consistently and substantially greater than the protective responses seen in adolescent girls and young women who received 3 doses.

Third, effectiveness and antibody responses over time were not evaluated. The ratio of antibody GMTs comparing 2-dose with 3-dose regimens for the bivalent and quadrivalent vaccines can vary over time.[9,27] Observational studies suggest that administration of less than 3 doses may be associated with reduced effectiveness, although prevalent HPV infection and noncompletion of the vaccination schedule may itself be associated with higher-risk behavior and compliant participants may therefore be at lower risk of HPV exposure.[25,26,28-34] Duration of protection is important both from clinical and public health standpoints.[35] Evaluation of antibody persistence is ongoing and assessment of the duration of protection is planned. The 2-dose schedule has not been tested in persons aged 15 years or older.

In many countries, HPV vaccination rates remain suboptimal.[36] Using an effective 2-dose regimen entailing fewer visits could improve adherence to HPV vaccination programs.[35] Coadministration of the 9-valent HPV vaccine with diphtheria, tetanus, pertussis, polio, and meningococcal vaccines could also be completed at the same visit, which has been demonstrated in clinical studies.[37,38] Based on health economics modeling, use of a 2-dose vaccination schedule could potentially reduce the total costs of HPV vaccination.[13,39]

Conclusions

Among girls and boys aged 9 to 14 years receiving 2-dose regimens of a 9-valent HPV vaccine separated by 6 or 12 months, immunogenicity 4 weeks after the last dose was noninferior to a 3-dose regimen in a cohort of adolescent girls and young women. Further research is needed to assess persistence of antibody responses and effects on clinical outcomes.

ARTICLE INFORMATION

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