Ten-Year Follow-up of 9-Valent Human Papillomavirus Vaccine: Immunogenicity, Effectiveness, and Safety

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abstract

BACKGROUND AND OBJECTIVES: The 9-valent human papillomavirus (9vHPV) vaccine Phase III immunogenicity study in 9- to 15-year-old boys and girls was extended to assess immunogenicity and effectiveness through 10 years after the last vaccine dose (NCT00943722).

METHODS: Boys ($n = 301$) and girls ($n = 971$) who received three 9vHPV vaccine doses in the base study (day 1, months 2 and 6) enrolled in the extension. Serum was collected through month 126 for antibody assessments by competitive Luminex immunoassay and immunoglobulin G-Luminex immunoassay. For effectiveness analysis starting at age 16 years, genital swabs were collected (to assess HPV DNA by polymerase chain reaction) and external genital examinations conducted every 6 months. Primary analyses were conducted in per-protocol populations.

RESULTS: Geometric mean antibody titers peaked around month 7, decreased sharply between months 7 and 12, then gradually through month 126. Seropositivity rates remained ≥81% by competitive Luminex immunoassay and ≥95% by immunoglobin G-Luminex immunoassay at month 126 for each 9vHPV vaccine type. After up to 11.0 (median 10.0) years of follow-up postdose 3, there were no cases of HPV6/11/16/18/31/33/45/52/58-related high-grade intraepithelial neoplasia or condyloma in males or females. Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in males and females were low (54.6 and 52.4 per 10000 person-years, respectively) and within ranges expected in vaccinated cohorts, based on previous human papillomavirus vaccine efficacy trials.

CONCLUSIONS: The 9vHPV vaccine demonstrated sustained immunogenicity and effectiveness through ∼10 years post 3 doses of 9vHPV vaccination of boys and girls aged 9 to 15 years.

WHAT'S KNOWN ON THIS SUBJECT: Efficacy of 9vHPV vaccine against HPV6/11/16/18/31/33/45/52/58-related diseases was established in females aged 16 to 26 years and inferred in 9- to 15-year-old boys and girls, based on immunogenicity. Immunogenicity and effectiveness through 8 years in 9 to 15-year-olds was demonstrated.

WHAT THIS STUDY ADDS: Immunogenicity, effectiveness, and safety were demonstrated through 10 years postvaccination. Rates of persistent infection and disease related to vaccine-targeted HPV types were within expected ranges, compared with vaccinated cohorts of similar age in previous HPV vaccine efficacy studies.

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The 9-valent human papillomavirus (9vHPV) vaccine (initially licensed in 2014 and registered in more than 80 countries[1]) targets human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58, which cause ~90% of cervical cancers and HPV-related vulvar, vaginal, anal, and oropharyngeal cancers,[2] as well as HPV types 6 and 11, which cause ~90% of cases of genital warts and recurrent respiratory papillomatosis.[3,4] Efficacy of the 9vHPV vaccine was demonstrated in a pivotal study, V503-001, in young women aged 16 to 26 years.[5–7] Efficacy in girls and boys aged 9 to 15 years was inferred from noninferior antibody responses versus young women in Study V503-002.[8] Other licensed vaccines include 2 quadrivalent HPV (qHPV; types 6, 11, 16, and 18) vaccines initially licensed in 2006[1] and 2022,[9] and 3 bivalent HPV (types 16 and 18) vaccines initially licensed in 2007,[1] 2019,[10] and 2022.[11]

HPV infection may be acquired soon after sexual debut.[12] HPV vaccination should therefore target individuals before first sexual intercourse for maximal benefit. Since the risk of HPV infection is lifelong, HPV vaccines should confer durable protection. Accordingly, the World Health Organization recommends the inclusion of long-term follow-up (LTFU) of efficacy, safety, and immunogenicity in the development of prophylactic HPV vaccines.[13] Clinical studies demonstrated immunogenicity and effectiveness of the qHPV vaccine and immunogenicity of the AS04-adjuvanted bivalent vaccine through 10 years post vaccination.[14,15]

An extension of Study V503-002 was implemented to evaluate the long-term immunogenicity, safety, and effectiveness of 9vHPV vaccine through 10 years after vaccination. Results from an interim analysis with up to 8 years of follow-up have been encouraging.[16] Here, we report the final 10-year data of this long-term follow-up study.

METHODS

Study Design and Participants

The base study (NCT00943722)[8,17] enrolled girls and boys aged 9 to 15 years and young women aged 16 to 26 years to receive 3 doses of the 9vHPV vaccine (day 1, month 2, month 6). Girls and boys were followed for safety and immunogenicity through month 36, whereas the young women completed study participation at month 12.[8]

Girls and boys who received 3 doses of 9vHPV vaccine in the base study were eligible for the LTFU study to evaluate immunogenicity, effectiveness, and safety through month 126 (10 years postdose 3). Of the 72 sites that participated in the base study, 32 sites were unable to commit to an additional 7.5 years of follow-up. As such, the LTFU study was conducted at 40 sites across 13 countries (Belgium, Brazil, Colombia, Costa Rica, Peru, Poland, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, and the United States). No other HPV vaccine was administered during LTFU.

The study was conducted in accordance with the principles of Good Clinical Practice and received appropriate institutional review board and regulatory approval. All participants (or their parents or legal guardians for minors) provided written informed consent at the start of the base study and for the LTFU study; participants coming of legal age were consented again per local regulations.

Measures were put in place to minimize the potential effects of the coronavirus disease 2019 pandemic on the execution of the study. Compliance with relevant guidelines and continuous coordination with the study sites mitigated the impact of the pandemic on study implementation.

Endpoints and Follow-up

The primary objective of the LTFU study was to evaluate anti-HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses through 10 years postdose 3. Serologic responses were assessed at day 1 and month 7 for all participants and months 12, 24, 36, 66, 90, and 126 in a subset of participants consisting of all boys and a random sample of ~600 girls (random selection was made before the unblinding of the database of the base study, as previously reported[8,16]) using the 9-valent competitive Luminex immunoassay (cLIA)[18,19] and the HPV-9 IgG Luminex immunoassay (IgG-LIA)[19,20] as the primary and secondary immunoassay, respectively. Although the same term (milli-Merck units [mMU]/mL) is used for the unit of measurement in the cLIA and IgG LIA assays, the "HPV-9 cLIA mMU/mL" and the "HPV-9 IgG mMU/mL" are different units of measurement and cannot be directly compared.

Secondary objectives were to estimate the long-term effectiveness of the vaccine based on the incidence of the composite endpoint of HPV6/11/16/18/31/33/45/52/58-related persistent infection (≥6 months duration ±1 month visit window) and disease. In female participants, disease included cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), genital warts (condyloma acuminatum), and cervical, vaginal, and vulvar cancer. In male participants, disease included penile intraepithelial neoplasia (PIN), genital warts, and penile, perineal, and perianal cancers. In participants aged ≥16 years, visits for effectiveness occurred every 6 months, including collection of sexual history, genital examination, and genital clinical specimen collection (Supplemental Table 4).[16] A consensus diagnosis by the HPV Vaccine Program Pathology Panel was used for clinical disease efficacy endpoints; the relationship to a given HPV type was determined based on polymerase chain reaction (PCR) detection in an adjacent section from the same tissue block. Endpoints of HPV-related persistent infection were defined as PCR positivity for the same HPV type in genital swabs or tissue specimens collected at consecutive visits at least 6 months (±1 month visit windows) apart; at least 2 and

3 positive specimens were required to define a case of 6-month and 12-month persistent infection, respectively.

Safety assessments during LTFU included reporting of all vaccine-related serious adverse events (SAEs) and deaths. Pregnancies were followed to outcome.

Statistical Analysis

Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population, consisting of participants who were seronegative (by cLIA) for the appropriate HPV type(s) at day 1 (or seronegative for both HPV6/11 for analyses of HPV6- and HPV11-related endpoints), received all 3 vaccinations within prespecified day ranges, had a month 7 serology result within 21 to 49 days postdose 3, and had no other protocol violations that could interfere with evaluation of immune response. Geometric mean titers (GMTs) and seropositivity rates were summarized with their associated 95% confidence intervals (CI)s for each time point.

Effectiveness analysis was in the per-protocol effectiveness (PPE) population, consisting of participants who were seronegative (by cLIA) for the appropriate HPV type(s) at the time of 9vHPV vaccine dose 1 (or seronegative for both HPV6 and HPV11 for analyses of HPV6- and HPV11-related endpoints), received all 3 doses of 9vHPV vaccine within 1 year, and had no other protocol violations that could interfere with evaluation of vaccine effectiveness. Supportive analyses were performed in the HPV-naïve, type-specific (HN-TS) population, consisting of participants who received at least 1 vaccination of 9vHPV vaccine and were seronegative by cLIA to the specific HPV type at the time of dose 1 of 9vHPV vaccine (seronegative to both types 6 and 11 in analysis of HPV6- and HPV11-related endpoints). Incidence rates (cases per 10 000 person-years) of persistent infection and disease endpoints are provided through end of the study. Nominal 95% CI estimates of the incidence rates were calculated based on the Poisson distribution.

Safety was summarized for all participants who received at least 1 study vaccination and had any follow-up data.

There was no formal hypothesis testing during the LTFU study. The sample size was based on the number of base study participants who continued into LTFU.

RESULTS

Study Participants

This study was conducted from August 27, 2009 (first participant visit in the base study) through April 22, 2021 (last participant, last visit in the LTFU study). Of 2553 boys and girls who received 3 doses in the base study,[8] 1272 consented to participate and 922 (72.5%) completed the study (Fig 1). The most common reasons for discontinuation from LTFU were participant withdrawal or loss to follow-up. As previously described,[16] baseline characteristics (collected before the first vaccine dose) of participants who enrolled in the LTFU study (Table 1) were generally similar to those previously reported for the overall population of boys and girls enrolled in the base study.[8]

Immunogenicity

Across 9vHPV vaccine HPV types, anti-HPV cLIA GMTs peaked around month 7, decreased most sharply between months 7 and 12, then decreased gradually thereafter through month 126 (Fig 2; Supplemental Tables 5 and 6). This trend was consistent with observations in young women through month 60 in the 9vHPV vaccine pivotal efficacy study[5] (Fig 2). A similar trend in GMTs over time was observed using the HPV-9 IgG-LIA (Supplemental Tables 7 and 8). GMTs by cLIA or IgG-LIA were generally similar in female and male participants (Supplemental Tables 6 and 8). Anti-HPV GMTs were generally higher for those enrolled in the base study at age 9 to 12 years versus those enrolled at age 13 to 15 years (Supplemental Tables 5 and 7).

Overall, 99.6% to 100% of participants were seropositive by cLIA at month 7, and 81.3% to 97.7% remained seropositive at month 126, depending on the HPV type (Supplemental Tables 9 and 10). Based on the more sensitive HPV-9 IgG-LIA, 94.9% to 100% of participants were seropositive at month 126 (Supplemental Tables 11 and 12).

Effectiveness

Participants were followed for effectiveness up to 11.0 years postdose 3 (median 10.0 years). Females were followed up to 11.0 years postdose 3 (median 10.0 years); males were followed up to 10.6 years postdose 3 (median 9.9 years). All had reached 16 years of age by the month 90 visit and most participants (>90%) provided samples for evaluation of effectiveness during the LTFU (Supplemental Table 13).

Among females, the incidence in PPE analyses of the composite endpoint of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection and disease was 52.4 per 10 000 person-years (persistent infection: 52.4 per 10 000 person-years; disease: 2.2 per 10 000 person-years; Table 2). There were no cases of high-grade CIN and no cases of VIN and VaIN related to vaccine-targeted HPV types. One case of cervical intraepithelial neoplasia grade 1 (CIN1) tested positive for HPV16, HPV39, and HPV59 by PCR at month 84 (Supplemental Appendix 1); cervical cytology results were negative at subsequent visits.

Among males, the incidence in PPE analyses of the composite endpoint of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection and disease was 54.6 per 10 000 person-years (persistent infection: 54.6 per 10 000 person-years; disease: 0 per 10 000 person-years; Table 2). There were no cases of disease related to vaccine-targeted HPV types.

Results were similar when effectiveness was analyzed in the HN-TS population (Supplemental Table 14). There were

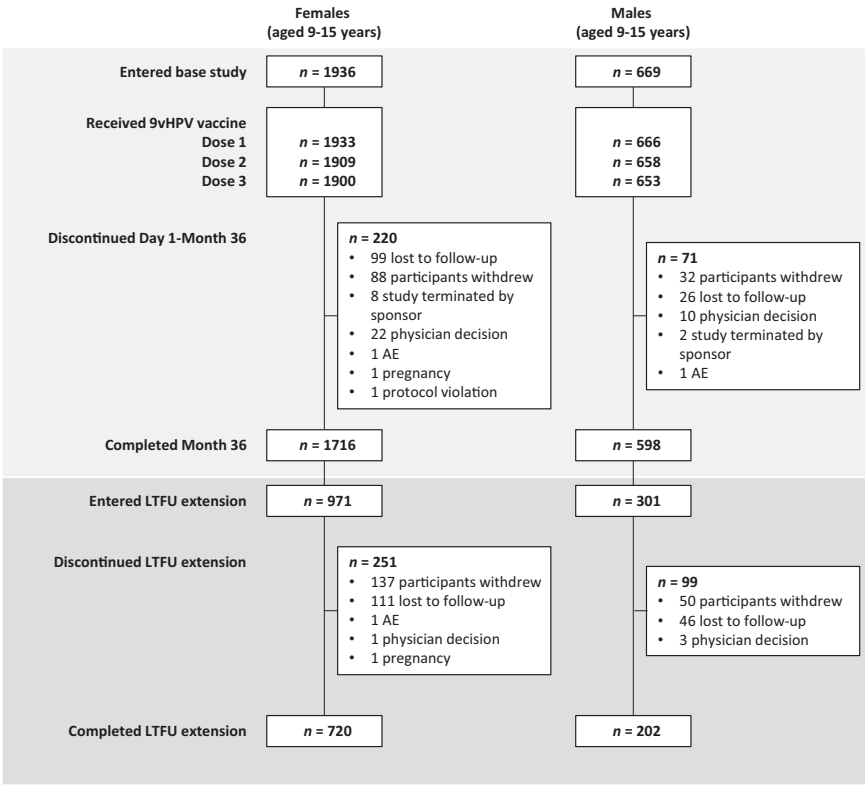


FIGURE 1
Participant disposition in the base study and LFTU. AE, adverse event.

no additional cases of disease endpoints in females or males in the HN-TS population.

The incidence rates of persistent infection and disease endpoints in the LTFU study, including composite endpoints of HPV6/11/16/18- and HPV31/33/45/52/58-related persistent infection (Fig 3A), endpoints of persistent infection related to each HPV type (Fig 3B), and disease endpoints related to vaccine HPV types, including CIN, any grade; CIN grade 2 (CIN2) or worse (Fig 3C); and external genital lesions in females (Fig 3D) and males (Fig 3E) were within ranges expected in vaccinated cohorts based on previous studies of the 9vHPV and qHPV vaccines.

Persistent infection and disease that were attributable to nonvaccine HPV types continued to accumulate during the LTFU study in the PPE population (Table 3). The incidence rate of HPV35/39/51/56/59-related 6-month persistent infection was 927.4 and 261.5 per 10 000 person-years in female participants and in male participants, respectively. Among females, the incidence rate of HPV35/39/51/56/59-related disease was 68.8 per 10 000 person-years. No cases of HPV35/39/51/56/59-related disease were observed in male participants.

Females and males in the PPE population acquired new sexual partners at a rate of 0.76 and 1.12 per person-year of follow-up, respectively (Supplemental Table 15). The incidence of *Chlamydia* was 4.0 and 2.3 per 100 person-years among females and males, respectively, and incidence of gonorrhea was 0.9 and 0.7, respectively. As shown in Supplemental Table 15, females in this study acquired new sexual partners at slightly higher rates and had similar or higher rates of *Chlamydia* and gonorrhea compared with young women who participated in previous HPV vaccine efficacy trials.[5,21] Males acquired new sexual partners at similar rates as in a prior qHPV vaccine efficacy trial in young men.[22]

Safety

No vaccine-related SAEs were reported during LTFU through 10 years postvaccination. One participant died during LTFU because of an SAE of disseminated tuberculosis with time of onset 8.6 years postdose 3 (not considered vaccine-related). Pregnancy outcomes are described in Supplemental Appendix 2 and Supplemental Table 16.

DISCUSSION

These data demonstrate long-term immunogenicity, effectiveness, and safety of the 9vHPV vaccine, 10 years after its administration. These end-of-study results expand on findings from the previous 8-year interim analysis[16] by providing further evidence on the long-term immunogenicity, effectiveness, and safety of the 9vHPV vaccine, as well as additional analyses including long-term immunogenicity stratified by

TABLE 1 Baseline Characteristics of LTFU Participants		
	Female ($N = 971$)	Male ($N = 301$)
Age		
9 to 12 y, *n* (%)	653 (67.3)	207 (68.8)
13 to 15 y, *n* (%)	318 (32.7)	94 (31.2)
Mean (SD), years	11.6 (1.9)	11.5 (1.8)
Race, *n* (%)		
American Indian or Alaska Native	2 (0.2)	1 (0.3)
Asian	222 (22.9)	74 (24.6)
Black or African American	129 (13.3)	31 (10.3)
Multiple	204 (21.0)	114 (37.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	3 (1.0)
White	414 (42.6)	78 (25.9)
Ethnicity		
Hispanic or Latino	372 (38.3)	140 (46.5)
Not Hispanic or Latino	599 (61.7)	161 (53.5)
BMI, mean (SD) kg/m^2	19.8 (4.1)[a]	19.6 (4.0)
Region		
Africa	79 (8.1)	28 (9.3)
Asia-Pacific	222 (22.9)	74 (24.6)
Europe	256 (26.4)	27 (9.0)
Latin America	297 (30.6)	122 (40.5)
North America	117 (12.0)	50 (16.6)

Baseline refers to before vaccine dose 1.
[a] $n = 970$.
BMI, body mass index.
SD, standard deviation.

age, incidence of disease endpoints, and of persistent infection caused by individual HPV types in this study versus previous efficacy trials of qHPV and 9vHPV vaccines, and pregnancy outcomes.

The 9vHPV vaccine elicited sustained antibody responses to the 9 vaccine-targeted HPV types through 10 years postdose 3 in girls and boys 9 to 15 years of age. GMTs peaked at month 7, decreased sharply through month 12, and slowly thereafter. The vast majority of participants remained seropositive for each vaccine-targeted HPV type through month 126.

There were no cases of high-grade cervical, vulvar, or vaginal intraepithelial neoplasia in female participants, of high-grade penile, perineal, or perianal intraepithelial neoplasia in male participants, or of genital warts in all participants related to vaccine-targeted HPV types through end of the LTFU. The single case of low-grade intraepithelial neoplasia related to a 9vHPV vaccine type (a CIN1 associated with HPV16, HPV39, and HPV59) was likely caused by HPV39 and/or HPV59, given the detection of persistent infection with these types, and is not considered a breakthrough case since these 2 types are not covered by the 9vHPV vaccine.

In the absence of a control group, interpretation of effectiveness data in this study is based on comparisons with multiregional HPV vaccine clinical trials, including a Phase II efficacy study of the qHPV vaccine in women aged 16 to 23 years,[21] the FUTURE I pivotal efficacy study of the qHPV vaccine in women aged 16 to 24 years,[23] the pivotal efficacy study of the qHPV vaccine in men aged 16 to 26 years,[22] and the pivotal 9vHPV vaccine efficacy, immunogenicity, and safety study in women aged 16 to 26 years.[5] The incidence rates of 6-month persistent infection and disease observed in this study were consistent with incidence rates reported in 9vHPV and qHPV vaccine recipients in prior efficacy studies of the 9vHPV and qHPV vaccines conducted in individuals who were approximately the same age as those in the LTFU study and lower than reported rates in the control arms of those studies. Taken together, the results indicate high vaccine effectiveness in male and female participants in this study.

The low incidence rates of infection and disease related to vaccine HPV types observed in this study are unlikely to be the result of lack of exposure to HPV through sexual activity. Participants continued to accrue infections and disease related to HPV types not covered by the vaccine during LTFU. The incidence of HPV35/39/51/56/59-related 6-month persistent infection was similar to that in the pivotal efficacy study of 9vHPV vaccine in young women (~800 per 10 000 person-years; O.B., A.L., unpublished observations). Moreover, participants acquired new sexual partners during LTFU at rates similar to or higher than in other HPV vaccine clinical trials.[5,21,22] Other non-HPV-related sexually transmitted diseases (*Chlamydia* and gonorrhea) were also detected at rates consistent with sexual exposure observed in previous trials.[5,21,22]

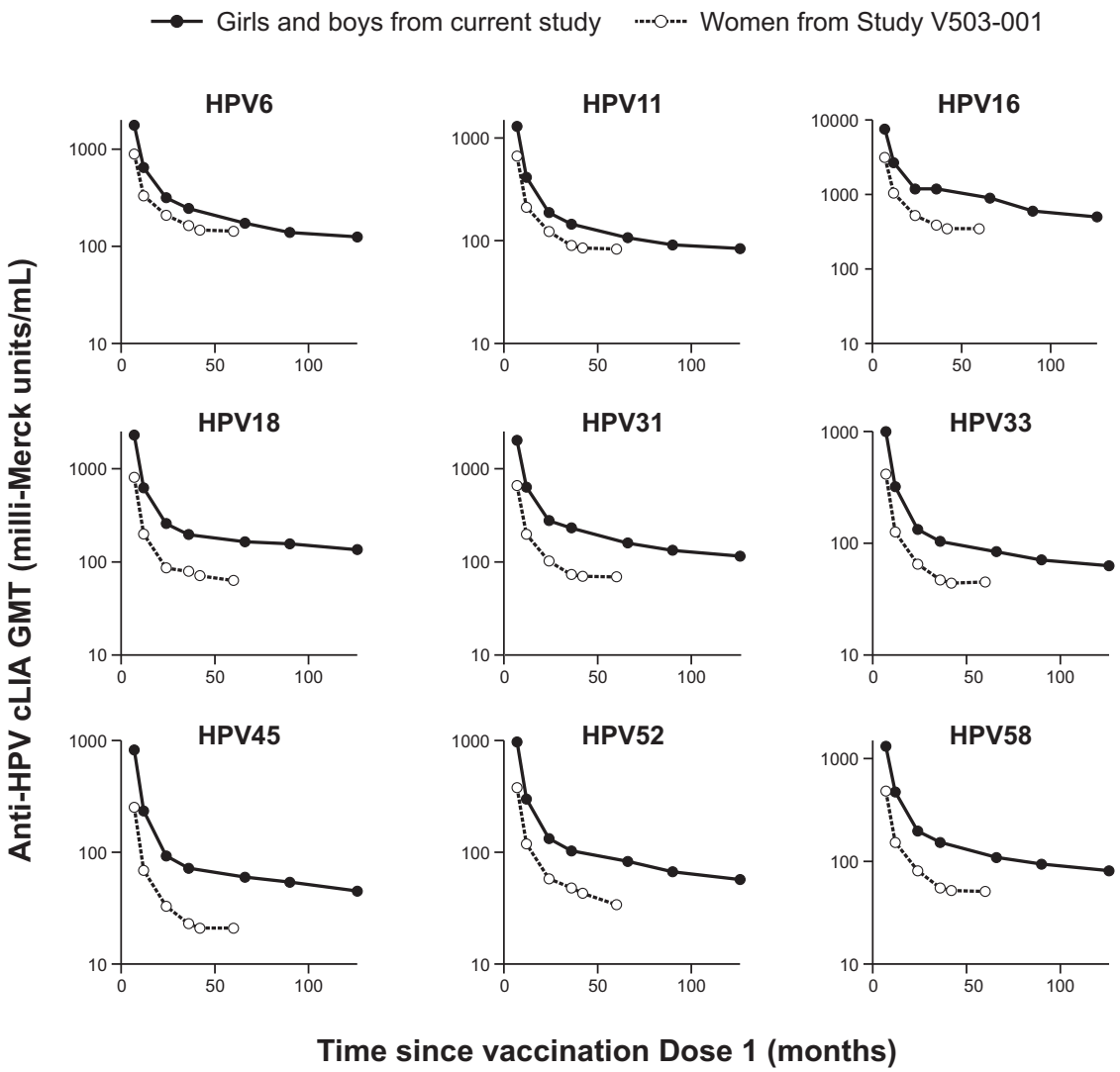


FIGURE 2

Anti-HPV cLIA GMTs through 10 years post vaccination in girls and boys aged 9 to 15 years from the 9vHPV vaccine LTFU (Study V503-002-20) and women aged 16 to 26 years from Study V503-001.[5]

No vaccine-related SAEs were observed during LTFU. One participant died; the event was not considered vaccine related. The proportion of participants who discontinued from the study between month 42 and month 126 (27.5%, or ~4% per year) was comparable to that observed in the pivotal 9vHPV vaccine efficacy study[5] and previous qHPV vaccine efficacy studies. Because of the long duration of follow-up, discontinuations relating to the changing life stages of the participants who entered the study as young adolescents were expected (eg, for school, jobs, or family endeavors). Indeed, most discontinuations during LTFU were because of loss to follow-up or participant decision.

This study has many strengths. It used the same rigorous assessment of study endpoints as used in the pivotal efficacy studies of the qHPV and 9vHPV vaccines, and LTFU effectiveness studies of the qHPV vaccine.[15,24,25] The results of prior 9vHPV and qHPV vaccine studies could therefore be used as benchmarks to interpret the results of the current study. Participants were evaluated for effectiveness after reaching age 16 years, which is similar to the age of participants enrolled in the prior efficacy studies of qHPV and 9vHPV vaccines,[5,21–23,26] allowing results to be interpreted in the context of prior placebo-controlled efficacy studies. The study included a diverse population across 13 countries in 5 continents, supporting the generalizability of these findings.

The study also has some limitations. Since the study did not include a control group, the incidences of persistent infection and disease endpoints were interpreted in the context of incidences of the same endpoints in the vaccinated and control arms of previous efficacy studies of qHPV and 9vHPV vaccine. Even though it involved cross-study comparisons, this approach was justified

TABLE 2 Incidence of HPV6/11/16/18/31/33/45/52/58-related Persistent Infection and Disease Endpoints in Female and Male LTFU Participants (PPE population)

	Female (N = 971)			Male (N = 301)		
	Cases/n	Person-years Follow-up[a]	Rate per 10 000 Person-years (95% CI)	Cases/n	Person-years Follow-up[a]	Rate per 10 000 Person-years (95% CI)
HPV6/11/16/18/31/33/45/52/58-related 6-mo persistent infection[b] or disease[c]	24/872	4579.6	52.4 (33.6–78.0)	7/261	1282.7	54.6 (21.9–112.4)
HPV6/11/16/18/31/33/45/52/58-related 6-mo persistent infection[b]	24/872	4579.6	52.4 (33.6–78.0)	7/261	1282.7	54.6 (21.9–112.4)
HPV6/11/16/18-related	22/870	4580.4	48.0 (30.1–72.7)	1/261	1296.1	7.7 (0.2–43.0)
HPV6-related	4/847	4520.4	8.8 (2.4–22.7)	0/255	1273.4	0.0 (0.0–29.0)
HPV11-related	0/847	4530.1	0.0 (0.0–8.1)	1/255	1270.9	7.9 (0.2–43.8)
HPV16-related	17/860	4541.3	37.4 (21.8–59.9)	0/260	1293.0	0.0 (0.0–28.5)
HPV18-related	1/867	4627.2	2.2 (0.1–12.0)	0/259	1285.9	0.0 (0.0–28.7)
HPV31/33/45/52/58-related	2/872	4649.5	4.3 (0.5–15.5)	6/261	1285.2	46.7 (17.1–101.6)
HPV31-related	0/855	4657.1	0.0 (0.0–8.1)	2/259	1287.6	15.5 (1.9–56.1)
HPV33-related	1/866	4625.7	2.2 (0.1–12.0)	0/259	1294.0	0.0 (0.0–28.5)
HPV45-related	0/871	4652.5	0.0 (0.0–7.9)	1/261	1292.6	7.7 (0.2–43.1)
HPV52-related	0/870	4645.5	0.0 (0.0–7.9)	4/261	1286.8	31.1 (8.5–79.6)
HPV58-related	1/863	4611.5	2.2 (0.1–12.1)	0/259	1293.2	0.0 (0.0–28.5)
HPV6/11/16/18/31/33/45/52/58-related 12-mo persistent infection[d]	9/872	4621.1	19.5 (8.9–37.0)	2/261	1294.2	15.5 (1.9–55.8)
HPV6/11/16/18-related	8/870	4619.9	17.3 (7.5–34.1)	0/261	1298.6	0.0 (0.0–28.4)
HPV6-related	2/847	4524.4	4.4 (0.5–16.0)	0/255	1273.4	0.0 (0.0–29.0)
HPV11-related	0/847	4530.1	0.0 (0.0–8.1)	0/255	1273.4	0.0 (0.0–29.0)
HPV16-related	5/860	4576.8	10.9 (3.5–25.5)	0/260	1293.0	0.0 (0.0–28.5)
HPV18-related	1/867	4627.2	2.2 (0.1–12.0)	0/259	1285.9	0.0 (0.0–28.7)
HPV31/33/45/52/58-related	1/872	4651.4	2.1 (0.1–12.0)	2/261	1294.2	15.5 (1.9–55.8)
HPV31-related	0/855	4567.1	0.0 (0.0–8.1)	0/259	1289.2	0.0 (0.0–28.6)
HPV33-related	1/866	4625.7	2.2 (0.1–12.0)	0/259	1294.0	0.0 (0.0–28.5)
HPV45-related	0/871	4652.5	0.0 (0.0–7.9)	0/261	1298.6	0.0 (0.0–28.4)
HPV52-related	0/870	4645.5	0.0 (0.0–7.9)	2/261	1294.2	15.5 (1.9–55.8)
HPV58-related	0/863	4613.5	0.0 (0.0–8.0)	0/259	1293.2	0.0 (0.0–28.5)
HPV6/11/16/18/31/33/45/52/58-related disease[c]	1/866	4576.1	2.2 (0.1–12.2)	0/261	1278.6	0.0 (0.0–28.9)
CIN1[f]	1/866[e]	4573.9	2.2 (0.1–12.2)	—	—	—
CIN2 or CIN3[f]	0/866	4577.5	0.0 (0.0–8.1)	—	—	—
AIS[f]	0/866	4577.5	0.0 (0.0–8.1)	—	—	—
Cervical cancer[f]	0/866	4577.5	0.0 (0.0–8.1)	—	—	—
Condyloma[f,g]	0/866	4579.6	0.0 (0.0–8.1)	0/261	1278.6	0.0 (0.0–28.9)
VIN1 or worse[f]	0/866	4579.6	0.0 (0.0–8.1)	—	—	—
VaIN1 or worse[f]	0/866	4579.6	0.0 (0.0–8.1)	—	—	—
PIN1 or worse[g]	—	—	—	0/261	1278.6	0.0 (0.0–28.9)

—, not applicable; AIS, adenocarcinoma in situ; CIN3, cervical intraepithelial neoplasia grade 3; N, number of participants who received at least 1 vaccination of 9vHPV vaccine and consented to LTFU; n, number of participants contributing to the analysis; PIN1, penile intraepithelial neoplasia grade 1; VaIN1, vaginal intraepithelial neoplasia grade 1; VIN1, vulvar intraepithelial neoplasia grade 1.

[a] For each participant, person-years of follow-up was calculated starting from the beginning of the LTFU study (ie, month 42 visit) or the date when the participant reached age 16 y, whichever came later.

[b] A case of 6-month persistent infection is a participant who is positive to ≥1 common gene for the same HPV type in the HPV6/11/16/18/31/33/45/52/58 PCR assay in 2 or more cervicovaginal or external genital swab, biopsy, or definitive therapy samples obtained at 2 or more consecutive visits at least 6 mo (±1 mo) apart.

[c] In females, disease includes condyloma, CIN, AIS, VIN, VaIN, and cervical, vulvar, or vaginal cancer; in males, this includes condyloma, PIN, and penile, perineal, or perianal cancer.

[d] A case of 12-month persistent infection is a participant who is positive to ≥1 common gene for the same HPV type in the HPV6/11/16/18/31/33/45/52/58 PCR assay in 3 or more cervicovaginal or external genital swab, biopsy, or definitive therapy samples obtained at 3 or more consecutive visits at least 6 mo (±1 mo) apart.

[e] HPV16-related CIN1.

[f] In female participants.

[g] In male participants.

because all the studies considered had similar eligibility criteria, used the same definition for the efficacy endpoints, and conducted endpoint assessment using the same laboratory assays and the same procedures and pathology panel for endpoint adjudication, which minimized the risk of bias. Overall, the demonstration of sustained

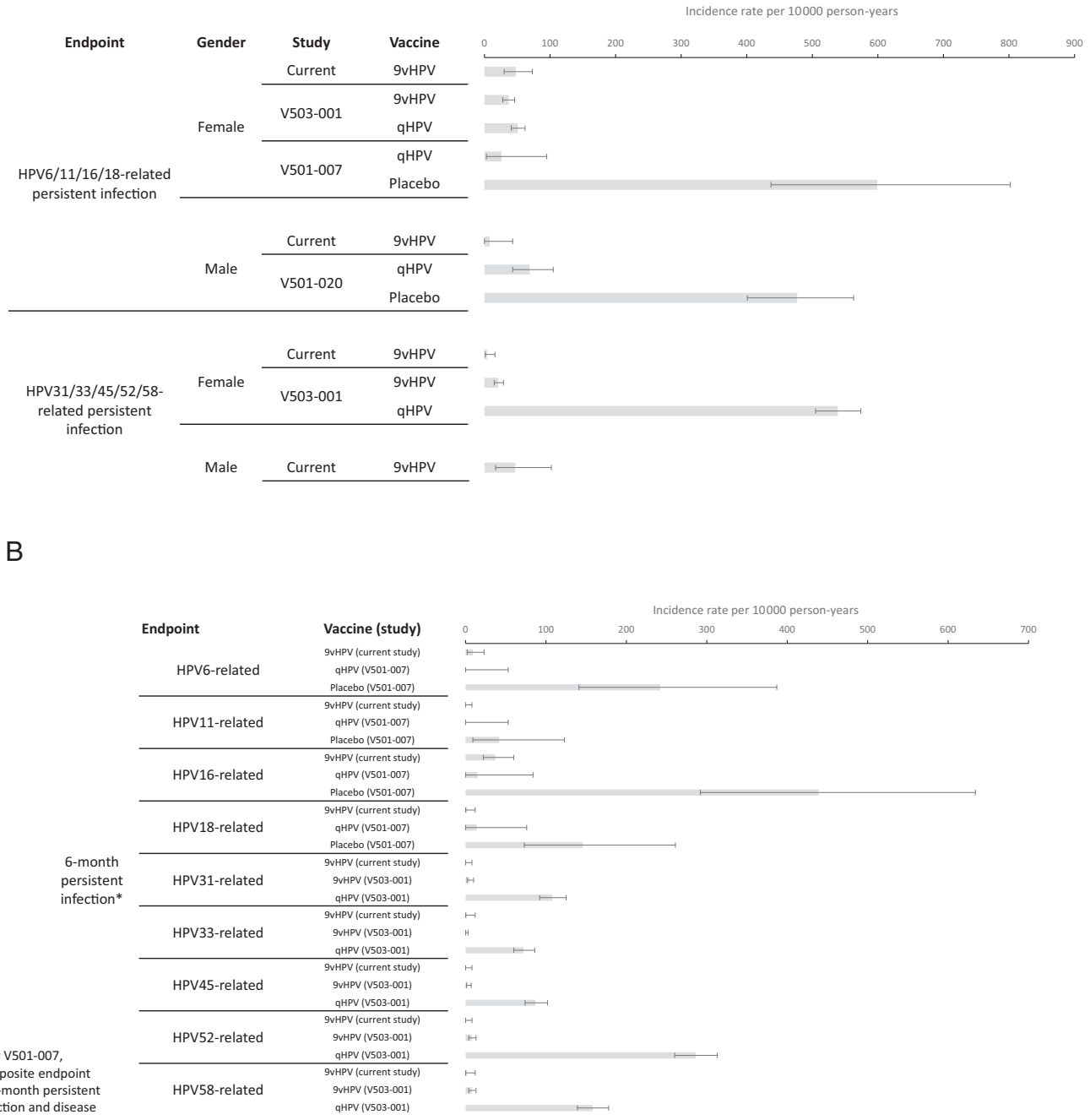
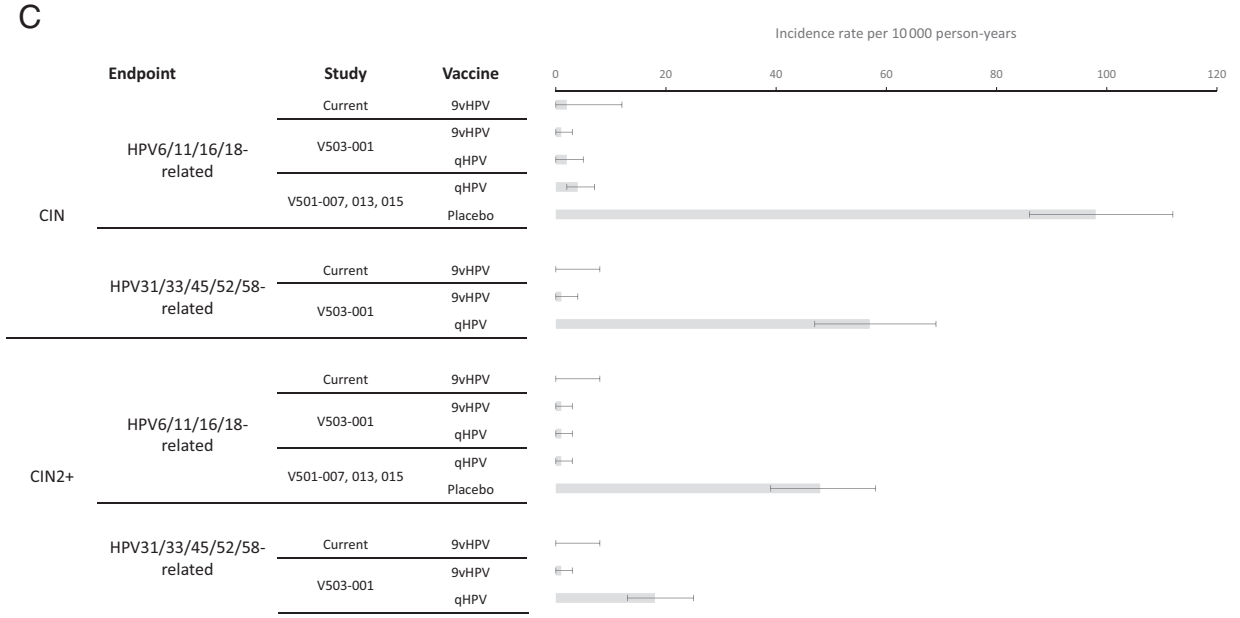


FIGURE 3

Incidence rates of vaccine HPV-type-related endpoints in qHPV and 9vHPV vaccine trials. A, Combined incidence of persistent infection related to HPV6/11/16/18 and HPV31/33/45/52/58 in female and male participants in the present study and prior efficacy studies of 9vHPV and qHPV vaccines. Error bars show 95% CI. Study V503-001: NCT00543543[5]; Study V501-007: NCT00365716[21]; Study V501-020 NCT00090285.[22] B, Incidence of persistent infection related to individual vaccine-targeted HPV types in the present study and prior efficacy studies of 9vHPV and qHPV vaccines. Error bars show 95% CI. Study V503-001: NCT00543543[5]; Study V501-007: NCT00365716.[21] C, Incidence of cervical dysplasia related to HPV6/11/16/18 and HPV31/33/45/52/58 in the present study and prior efficacy studies of 9vHPV and qHPV vaccines. Error bars show 95% CI. Study V503-001: NCT00543543[5]; Study V501-007: NCT00365716[43]; Study V501-013: NCT00092521[23]; Study V501-015: NCT00092534.[44] D, Incidence of external genital lesions and condyloma in females related to HPV6/11/16/18 and HPV31/33/45/52/58 in the present study, and prior efficacy studies of 9vHPV and qHPV vaccines. Error bars show 95% CI. Study V503-001: NCT00543543[5]; Study V501-007: NCT00365716[43]; Study V501-013: NCT00092521[23]; Study V501-015: NCT00092534.[44] E, Incidence of external genital lesions and condyloma in males related to HPV6/11/16/18 in the present study and Study V501-020. Error bars show 95% CI. Study V501-020: NCT00090285.[22]

C



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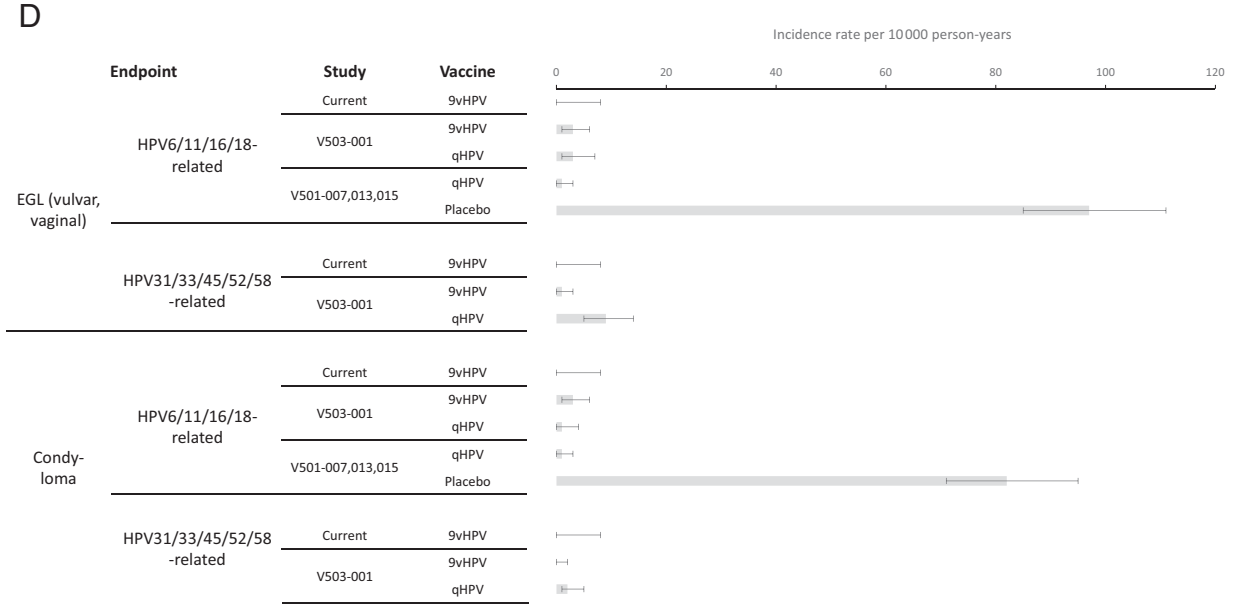

E

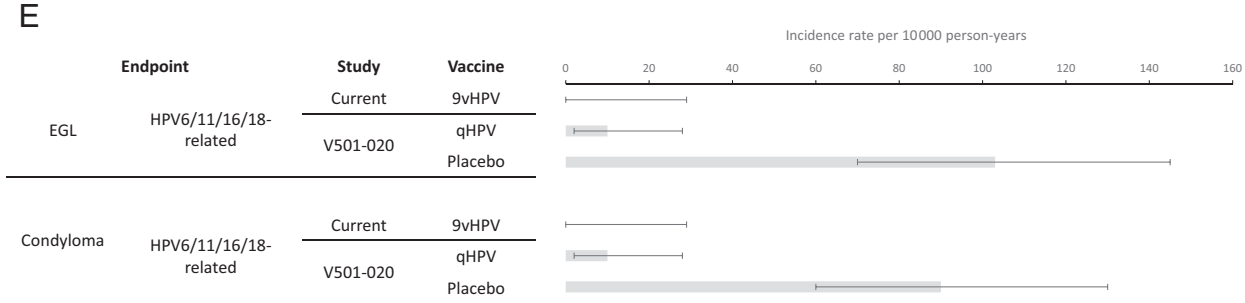

FIGURE 3
Continued

TABLE 3 Incidence of HPV35/39/51/56/59-related Persistent Infection and Disease Endpoints in Female and Male LTFU Participants (PPE population)

	Female (N = 971)			Male (N = 301)		
	Cases/n	Person-years Follow-up[b]	Rate per 10 000 Person-years (95% CI)	Cases/n	Person-years Follow-up[b]	Rate per 10 000 Person-years (95% CI)
HPV35/39/51/56/59-related[a] 6-mo persistent infection[c] or disease[d]	305/807	3287.7	927.7 (826.5–1037.9)	30/246	1147.3	261.5 (176.4–373.3)
HPV35/39/51/56/59-related 6-mo persistent infection[c]	305/807	3288.6	927.4 (826.3–1037.6)	30/246	1147.3	261.5 (176.4–373.3)
HPV35-related	20/807	4266.8	46.9 (28.6–72.4)	3/246	1227.2	24.4 (5.0–71.4)
HPV39-related	102/807	3984.4	256.0 (208.7–310.8)	6/246	1224.4	49.0 (18.0–106.7)
HPV51-related	134/807	3908.8	342.8 (287.2–406.0)	11/246	1212.3	90.7 (45.3–162.4)
HPV56-related	173/807	3755.6	460.6 (394.6–534.6)	14/246	1183.4	118.3 (64.7–198.5)
HPV59-related	98/807	4023.6	243.6 (197.7–296.8)	4/246	1221.9	32.7 (8.9–83.8)
HPV35/39/51/56/59-related 12-mo persistent infection[e]	208/807	3605.4	576.9 (501.2–660.9)	14/246	1186.1	118.0 (64.5–198.0)
HPV35-related	13/807	4282.3	30.4 (16.2–51.9)	2/246	1228.9	16.3 (2.0–58.8)
HPV39-related	61/807	4100.5	148.8 (113.8–191.1)	3/246	1229.6	24.4 (5.0–71.3)
HPV51-related	65/807	4126.0	157.5 (121.6–200.8)	3/246	1227.0	24.4 (5.0–71.5)
HPV56-related	103/807	3973.6	259.2 (211.6–314.4)	8/246	1205.0	66.4 (28.7–130.8)
HPV59-related	53/807	4155.0	127.6 (95.5–166.8)	2/246	1227.6	16.3 (2.0–58.9)
HPV35/39/51/56/59-related disease[d]	29/802	4216.7	68.8 (46.1–98.8)	0/246	1215.5	0.0 (0.0–30.3)
CIN1[f]	24/802	4226.1	56.8 (36.4–84.5)	—	—	—
CIN2 or CIN3[f]	5/802	4264.5	11.7 (3.8–27.4)	—	—	—
AIS[f]	0/802	4268.6	0.0 (0.0–8.6)	—	—	—
Cervical cancer[f]	0/802	4268.6	0.0 (0.0–8.6)	—	—	—
Condyloma[f,g]	1/802	4269.3	2.3 (0.1–13.1)	0/246	1215.5	0.0 (0.0–30.3)
VIN1 or worse[f]	1/802	4265.4	2.3 (0.1–13.1)	—	—	—
VaIN1 or worse[f]	1/802	4265.4	2.3 (0.1–13.1)	—	—	—
PIN1 or worse[g]	—	—	—	0/246	1215.5	0.0 (0.0–30.3)

—, not applicable; AIS, adenocarcinoma in situ; CIN3, cervical intraepithelial neoplasia grade 3; N, number of participants who received at least 1 vaccination of 9vHPV vaccine and consented to LTFU; n, number of participants contributing to the analysis; PIN1, penile intraepithelial neoplasia grade 1; VaIN1, vaginal intraepithelial neoplasia grade 1; VIN1, vulvar intraepithelial neoplasia grade 1.

[a] Baseline HPV-naïve population with respect to HPV types 35/39/51/56/59 cannot be defined in this study because of the absence of baseline sero- and PCR-status with respect to these nonvaccine HPV types. As such, a baseline HPV-naïve population with respect to these HPV types is approximated by the population of participants who were naïve for all of HPV types 6/11/16/18/31/33/45/52/58. The PPE population for the nonvaccine HPV types 35/39/51/56/59 is comprised of participants who were PPE-eligible for all of HPV types 6/11/16/18/31/33/45/52/58.

[b] For each participant, person-years of follow-up was calculated starting from the beginning of the LTFU study (ie, month 42 visit) or the date when the participant reached age 16 y, whichever came later.

[c] A case of 6-mo persistent infection is a participant who is PCR-positive to ≥1 common gene for the same HPV type in 2 or more cervicovaginal or external genital swab, biopsy, or definitive therapy samples obtained at 2 or more consecutive visits at least 6 mo (±1 mo) apart.

[d] In females, disease includes condyloma, CIN, AIS, VIN, VaIN, and cervical, vulvar, or vaginal cancer; in males, this includes condyloma, PIN, and penile, perineal, or perianal cancer.

[e] A case of 12-mo persistent infection is a participant who is PCR-positive to ≥1 common gene for the same HPV type in 2 or more cervicovaginal or external genital swab, biopsy, or definitive therapy samples obtained at 3 or more consecutive visits at least 6 mo (±1 mo) apart.

[f] In female participants.

[g] In male participants.

effectiveness is robust given that no disease cases caused by vaccine-targeted HPV types were observed, the rates of persistent infection caused by vaccine-targeted HPV types were consistent with rates observed in vaccinated cohorts in prior efficacy trials of 9vHPV and qHPV vaccines, and the evidence of continued sexual activity and exposure to nonvaccine HPV types during LTFU. This study used a 3-dose vaccination regimen. Two-dose HPV vaccination regimens, which may be easier to implement and more adaptable to vaccination schedules worldwide, are widely licensed and recommended for individuals aged 9 to 14 years.[27] In prior clinical studies, anti-HPV GMTs at 1 month after the last dose in girls aged 9 to 13 years who received 2 doses of qHPV vaccine[28–30] and girls and boys aged 9 to 14 years who received 2 doses of the 9vHPV vaccine[31,32] were noninferior to those in women aged 16 to 26 years who received 3 doses of the same vaccine. Moreover, antibody responses to 2-dose regimens have been observed to persist through 10 years for the qHPV vaccine[30] and 3 years for the 9vHPV vaccine,[32] and the noninferiority criterion compared with women aged 16 to 26 years remained verified for the entire duration of follow-up.[28,30,32] Long-term protection in girls and boys who received 2 doses can be inferred based on the demonstration of long-term effectiveness of qHPV and 9vHPV vaccine in women aged 16 to 26 years.[24,33] As previously reported, girls and boys receiving

2 doses of HPV vaccine 12 months apart generally had higher or similar GMT trends, and girls and boys receiving 2 doses 6 months apart had similar or lower GMT trends compared with girls receiving 3 doses.[30,32] Overall, effectiveness and immunogenicity results from this and other long-term studies of 3-dose regimens of qHPV and 9vHPV vaccines in adolescents and young adults[15,24,33] provide benchmarks to infer that antibody responses elicited by 2-dose regimens also provide long-term protection.

CONCLUSIONS

After the introduction of HPV vaccines, real-world studies have demonstrated decreases in prevalence of vaccine HPV types as well as reduced rates of high-grade cervical lesions[34–36] and invasive cervical cancer[37–41] in vaccinated populations. Accumulated safety data from large postmarketing surveillance studies and epidemiologic studies have been consistent with the safety profile in clinical trials.[42] These postlicensure results, together with the results from LTFU extensions of clinical trials including the study described herein, continue to support the favorable benefit-risk profile of HPV vaccination.

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ABBREVIATIONS

9vHPV: 9-valent human papillomavirus
CIN: cervical intraepithelial neoplasia
CIN1: cervical intraepithelial neoplasia grade 1
CIN2: cervical intraepithelial neoplasia grade 2
cLIA: competitive Luminex immunoassay
GMT: geometric mean titers
HN-TS: HPV-naïve, type-specific
HPV: human papillomavirus
IgG-LIA: IgG Luminex immunoassay
LTFU: long-term follow-up
mMU: milli-Merck units
PCR: polymerase chain reaction
PIN: penile intraepithelial neoplasia
PIN1: penile intraepithelial neoplasia grade 1
PPE: per-protocol effectiveness
PPI: per-protocol immunogenicity
qHPV: quadrivalent HPV
SAE: serious adverse event
VaIN: vaginal intraepithelial neoplasia
VaIN1: vaginal intraepithelial neoplasia grade 1
VIN: vulvar intraepithelial neoplasia
VIN1: vulvar intraepithelial neoplasia grade 1

interpretation of data; and all authors critically reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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

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Data Sharing Statement: Deidentified individual participant data will not be made available.

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