**OBJECTIVES:** We describe the final 10-year data for the long-term follow-up study of the 4-valent human papillomavirus (4vHPV) vaccine in preadolescents and adolescents.

**METHODS:** In the base study (V501-018), 1661 sexually inactive boys and girls received the 4vHPV vaccine (early vaccination group [EVG], managed for 9.9 years) or a placebo at day 1, month 2, and month 6. Thereafter, at month 30, the placebo group (catch-up vaccination group [CVG], managed for 7.4 years) received the 4vHPV vaccine by using the same dosing schedule. Long-term anti-HPV type 6, 11, 16, and 18 immune responses were assessed. Effectiveness was estimated by calculating the incidence rate of the primary endpoints (HPV types 6, 11, 16, and 18–related disease or persistent infection).

**RESULTS:** For HPV types 6, 11, and 16, 89% to 96% of subjects remained seropositive through 10-years postvaccination. The preadolescents had 38% to 65% higher geometric mean titers at month 7, which remained 16% to 42% higher at 10 years compared with adolescents. No cases of HPV type 6, 11, 16, and 18–related diseases were observed. Ten subjects had a persistent infection of ≥6 months duration with vaccine-type HPV and 2 subjects had persistent infection for ≥12 months. No new serious adverse events were reported through 10 years.

**CONCLUSIONS:** A 3-dose regimen of the 4vHPV vaccine was immunogenic, clinically effective, and generally well tolerated in preadolescents and adolescents during 10 years of follow-up. These long-term findings support efforts to vaccinate this population against HPV before exposure.

**WHAT'S KNOWN ON THIS SUBJECT:** The 4-valent human papillomavirus (4vHPV) vaccine is clinically effective, immunogenic, and well-tolerated in preadolescents and adolescents. As a prophylactic vaccine administered before sexual debut, long-term persistence of efficacy and immunogenicity is desired.

**WHAT THIS STUDY ADDS:** This is the longest follow-up study of the 4vHPV vaccine to date. These 10-year follow-up data of the 4vHPV vaccine support greater, widespread implementation of HPV vaccination in preadolescents and adolescents.
Ten years have passed since the licensure of Gardasil (4-valent human papillomavirus [4vHPV] [types 6, 11, 16, and 18] vaccine, recombinant [Merck & Company Inc; Kenilworth, NJ]) in the United States. This prophylactic vaccine prevents cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts caused by HPV types 6 and 11, and precancerous cervical, vulvar, vaginal, and anal lesions caused by HPV types 6, 11, 16, and 18. Although approved for both boys and girls who are 9 to 26 years old, initiating the vaccination series before exposure to HPV is important. Earlier vaccination produces more robust antibody responses, and the impact of early vaccination (in grades 8 and 9; at ~13 years old) in reducing cervical dysplasia and genital warts is already evident ~4 years later. When administered between 11 and 12 years old, the HPV vaccination series can be initiated along with the meningococcal and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, absorbed vaccines. However, the vaccine must enable a sustained immune response and long-term effectiveness to protect individuals because HPV acquisition risks are greater later in life.

Given the long latency between the acquisition of HPV and the development of precancer and cancer, a long-term follow-up (LTFU) program was established to monitor vaccine immunogenicity, effectiveness, and safety in participants of the 4vHPV vaccine clinical studies. This was particularly important for studies in preadolescents and adolescents, in whom the vaccine was administered before the average age of sexual debut (and potential HPV exposure) and several years before the typical diagnosis of cervical and genital precancers and cancers. LTFU studies are critical to understanding the potential real-world impact of HPV vaccination.

Clinical follow-up studies of 4 and 6 years in young and mid-adult women (15–26 years old, [Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II] and 24–45 years old [FUTURE III]) have demonstrated durable antibody responses, long-term safety, and sustained effectiveness against the development of cervical and/or genital precancers and cancers.

Durable immunity and safety through 8 years postvaccination have also been documented for adolescents. In addition to follow-up for cervical and genital precancers and cancers, this younger population has also been assessed for HPV infection of the cervix and genital tract as a measure of vaccine effectiveness. The data for up to 8 years of follow-up have been reassuring, and to date, there has been no indication that a booster dose for the 4vHPV vaccine will be required among vaccinated individuals.

To understand the extended durability of the 4vHPV vaccine, we determined the immunogenicity, effectiveness, and safety of the 4vHPV vaccine after 10 years of follow-up in the preadolescent and adolescent population. Favorable evidence-based findings should provide additional reassurance for widespread early vaccination.

**METHODS**

**Base Study**

The base study V501-018 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and immunogenicity of the 4vHPV vaccine (types 6, 11, 16, and 18) among 9- to 15-year-old boys and girls, as previously described.

Subjects were randomly assigned in a 2:1 ratio to receive 3 intramuscular injections of either the 4vHPV vaccine (early vaccination group [EVG]) or a placebo at months 0, 2, and 6. At the end of the base study (month 30), the placebo recipients were offered the 4vHPV (at months 30, 32, and 36; catch-up vaccination group [CVG]). An institutional review board for each clinical site approved the study protocol. At enrollment, informed consent was obtained from each participant and his or her legal guardian.

**LTFU Study**

The LTFU study was conducted at 34 sites across 9 countries spanning 4 continents. All subjects who received the 4vHPV vaccine during or at the end of the base study were offered participation in the LTFU, and separate consent was required for participation. The LTFU study extended the follow-up period to 10 years. No study vaccinations were provided within the context of this LTFU study. There was no placebo group in the LTFU study because after the 4vHPV vaccine became licensed, it was deemed to be unethical to not offer the vaccine to LTFU participants.

**Immunogenicity**

The immunogenicity end points in the LTFU were serum antibody geometric mean titers (GMTs) and percent seropositivity to HPV types 6, 11, 16, and 18. Immune responses were measured by 2 separate immunoassays developed in house and used across the 4vHPV development program. The competitive Luminex immunoassay (cLIA) was used in the base and LTFU studies and the total immunoglobulin G (IgG) Luminex immunoassay (LIA) was added for the LTFU only, as previously described.

Seropositivity by the cLIA to vaccine-HPV types 6, 11, 16, and 18 was defined as cLIA titers (mU/mL) of ≥20, 16, 20, and 24, respectively.

**Effectiveness**

Because there were no placebo groups, vaccine efficacy
measurements could not be assessed. Instead, the effectiveness of vaccination with the 4vHPV vaccine was assessed by calculating the incidence of disease end points (EVG and CVG cohorts). These rates were compared with the observed incidence rates in previous efficacy studies within the 4vHPV vaccine program at Merck & Company Inc. The base study evaluated immunogenicity only. Effectiveness was assessed only in the follow-up period. Analyses for effectiveness included assessment for genital warts and cervical and genital precancers and cancers as well as persistent infection. Anal and oropharyngeal end points were not included. Because cervical lesions may take longer to manifest in a young population, 4vHPV vaccine type (6, 11, 16, and 18) persistent infection (defined by the detection of HPV by polymerase chain reaction [PCR] in serial sampling over a specified duration) was assessed. Effectiveness sampling started at 3.5 years (month 42) with follow-up visits occurring every 6 months thereafter.6,8,12 The disease effectiveness end points were adjudicated by the HPV Vaccine Program Pathology Panel using the same procedures as in previous studies of the 4vHPV vaccine in female and male subjects aged 16 to 26 years.6,7,13

Safety
Deaths and serious adverse events deemed by the study investigators to be related to the vaccine or procedure were captured for all subjects in the LTFU study.

Statistical Analysis
The primary approach to the analysis of immunogenicity and effectiveness was per-protocol conducted among subjects who received all 3 doses of the vaccine and were seronegative for all 4 vaccine HPV types before vaccination (day 1 for the EVG and month 30 for the CVG) and had at least 1 follow-up visit with PCR data collected during the LTFU study. An additional criterion of not having a sexual debut until after receiving the third dose of the 4vHPV vaccine (as defined by the subject using a personal report) was added. Sexual activity was defined as having had vaginal and/or anal intercourse and/or oral sex and/or genital-to-genital contact.

Immunogenicity in this population was summarized at 3 time points to include follow-up data through 6 years (month 72), 8 years (month 96), and 10 years (month 120). Anti-HPV responses to each of the 4 vaccine HPV types (6, 11, 16, and 18) were summarized by sex (male or female) and age at enrollment as GMTs and seropositivity rates with associated 95% confidence intervals (CIs). Effectiveness was summarized separately for girls and boys at 10 years, and the cumulative and current incidence rates for effectiveness end points were computed along with the associated 95% CIs. Effectiveness against nonvaccine types was assessed in a population that included subjects who were ≥16 years of age, received at least 1 dose of the 4vHPV vaccine, and had at least 1 follow-up visit. These subjects, who might have been seropositive at enrollment or might have had positive results for the quadrivalent HPV vaccine types (6, 11, 16, and 18) on PCR assay, represented the general population of boys and girls. Summaries were provided by vaccination group, sex (male or female), and age group. These are observational data that describe trends in the vaccinated population.

RESULTS

Subject Disposition
A total of 1245 (EVG, n = 821; CVG, n = 424) subjects were enrolled in the LTFU extension. Of these subjects, 803 (~65% [803 of 1245]) completed 10 years of follow-up postvaccination (EVG, n = 528; CVG, n = 275), as shown in Fig 1. Of subjects, 1134 (~91%); EVG, n = 799; CVG, n = 335) had at least 1 immunogenicity follow-up, and 681 subjects (~55%; EVG, n = 451; CVG, n = 230) had at least 1 follow-up visit with effectiveness data. The median follow-up time postvaccination was 9.9 years for the EVG and 7.4 years for the CVG. Effectiveness, which was only measured after age 16 years or the start of sexual activity, was assessed for 5.5 years in both the EVG and CVG. Characteristics of study subjects at the time of vaccination have been described previously.8 Subjects in the CVG who were older at the time of vaccination compared with subjects in the EVG (14.5 vs 11.9 years, respectively) were also more likely to be seropositive for vaccine-type HPV at the time of vaccination (15.9% vs 1.7%, respectively).

Immunogenicity
The anti-HPV type 6, 11, 16, and 18 responses (GMTs and seropositivity) measured by the cLIA assay over time for all subjects in the EVG and CVG are summarized in Fig 2 and Supplemental Table 5. In the per-protocol populations of both cohorts, the antibody responses peaked at month 7 then plateaued and persisted over the 10 years of follow-up. The proportion of subjects who remained seropositive at the end of the study remained high. Both the GMTs and percent seropositivity remained similar between month 96 and 120 (Supplemental Table 5).

Given the importance of vaccinating subjects before sexual debut and potential HPV exposure, the durability of the immune response was compared between the younger (preadolescents, 9–12 years old) and older (adolescents, 13–16 years old) subgroups of the cohort. The preadolescents had 38% to 65% higher GMTs of the 4vHPV vaccine types (6, 11, 16, and 18) at month 7, which remained 16% to 42%
higher at 10 years compared with the adolescents. When comparing the corresponding proportion of subjects who were seropositive between preadolescents and adolescents, there were no differences at month 7 and small differences at 10 years (Supplemental Table 5). Overall GMTs of HPV 6, 11, 16, and 18 were similar between girls and boys both at month 7 and at 10 years. However, comparing the 2 age groups among girls, the preadolescents had 63% to 93% higher GMTs compared with adolescents at month 7, and this difference persisted to 10 years (54%–73% higher GMTs among preadolescents versus adolescents). This early difference was also noted among boys at month 7 (15%–44% higher GMTs among the preadolescents versus adolescents); however, it did not persist to 10 years.

The kinetics of the immune response as well as the proportion of subjects who remained seropositive were comparable between the HPV cLIA and IgG LIA assays for HPV 6, 11, and 16. For HPV types 6, 11, and 16, 89% to 96% of subjects remained seropositive through 10 years postvaccination. For HPV 18, a much higher percentage of subjects remained seropositive by total IgG LIA at 10 years compared with the cLIA assay, as shown in Table 1.

Effectiveness

Given the young age of the population vaccinated, vaccine efficacy was not assessed in the preadolescents versus adolescents; however, it did not persist to 10 years. The kinetics of the immune response as well as the proportion of subjects who remained seropositive were comparable between the HPV cLIA and IgG LIA assays for HPV 6, 11, and 16. For HPV types 6, 11, and 16, 89% to 96% of subjects remained seropositive through 10 years postvaccination. For HPV 18, a much higher percentage of subjects remained seropositive by total IgG LIA at 10 years compared with the cLIA assay, as shown in Table 1.

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HPV-16 in a female subject, and 1 was related to HPV-6 in a male subject. To evaluate the entire spectrum of HPV in adolescents, infection and disease because of high-risk HPV types not contained in the vaccine were also assessed. As shown in Table 3, among girls, nonvaccine HPV types led to 151 cases of 6-month persistent infection and/or disease (EVG, 90 cases; CVG, 61 cases). Among boys in the same group, 53 cases of nonvaccine HPV type–related 6-month persistent infection (EVG, 34 cases; CVG, 19 cases) were observed, but no external genital lesion (EGLs) were reported.

This study reported similar rates of sexual activity compared with young adults in other studies in the 4vHPV vaccine clinical development program. The rates of new sexual partner acquisition were higher among boys as compared with girls. Among boys, the rate of acquisition of new partners was similar between the EVG and CVG, whereas among girls, the rate of acquisition of new partners was higher in the CVG. Sexually transmitted diseases were

### TABLE 1 Percent Seropositivity to HPV Types 6, 11, 16, and 18 in Male and Female Subjects After 10 Years by Using the cLIA and the IgG LIA Assays in the EVG Per-Protocol Population

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>% Seropositivity (95% CI)</th>
<th>% Seropositivity (95% CI)</th>
<th>% Seropositivity (95% CI)</th>
<th>% Seropositivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–HPV-6</td>
<td>91.0 (88.4–94.4)</td>
<td>86.6 (80.9–91.2)</td>
<td>94.5 (90.7–97.0)</td>
<td>91.3 (86.4–94.8)</td>
</tr>
<tr>
<td>Anti–HPV-11</td>
<td>90.1 (85.4–93.7)</td>
<td>87.2 (81.5–91.6)</td>
<td>91.1 (86.7–94.4)</td>
<td>89.7 (84.6–93.6)</td>
</tr>
<tr>
<td>Anti–HPV-16</td>
<td>97.7 (94.7–99.3)</td>
<td>94.1 (89.6–97.0)</td>
<td>98.7 (96.3–99.7)</td>
<td>97.4 (94.1–99.2)</td>
</tr>
<tr>
<td>Anti–HPV-18</td>
<td>61.4 (54.6–67.8)</td>
<td>59.6 (52.2–66.7)</td>
<td>78.5 (72.2–83.6)</td>
<td>77.0 (70.5–82.7)</td>
</tr>
</tbody>
</table>

The indicated time point of 10 years is relative to the day of injection of dose 1 of the 4vHPV vaccine.

### FIGURE 2

Long-term (10-year) anti-HPV cLIA GMTs among male and female subjects (9–15 years old) in the EVG, per-protocol immunogenicity population.
also evaluated as a marker of sexual activity. The overall rate of *Chlamydia* was 2.7 to 3.2 per 100 person-years, and the overall rate of gonorrhea was 0.4 to 0.6 per 100 person-years. The incidence of *Chlamydia* and gonorrhea was similar between boys and girls and among subjects in the EVG and CVG.

The incidence of low-grade abnormalities in cervical cytology among adolescent girls was slightly higher than corresponding incidences in other age groups (Table 4). However, similar incidence rates of high-grade cervical cytology abnormalities were observed.

### Safety

The administration of the 4vHPV vaccine to preadolescent and adolescent girls and boys was generally safe and well tolerated through 10 years postvaccination. No new safety events were reported beyond published data at the 8-year (month 96) interval.  

### Discussion

These end-of-study data demonstrate the long-term immunogenicity, effectiveness, and safety of the 4vHPV vaccine 10 years after its administration to preadolescents and adolescents. Importantly, the highest anti-HPV antibody titers were observed in subjects who received the vaccine at a younger age (9–12 years). These findings justify efforts to vaccinate subjects at the earliest opportunity. Moreover, by vaccinating preadolescents before exposure to HPV, the full potential of the vaccine is more likely to be realized. Certainly, older adolescents and adults who have not been previously vaccinated should receive the HPV vaccine, but greater efforts must be exerted to ensure that the majority of preadolescents are successfully vaccinated.

Our data demonstrated a sustained maintenance of seropositive status

### Table 2: Incidence of HPV Types 6, 11, 16, and 18–Related CIN (Girls), EGLs, or Persistent Infection in Male and Female Subjects Vaccinated With the 4vHPV Vaccine in the Per-Protocol Efficacy Population

<table>
<thead>
<tr>
<th></th>
<th>EVG Girls (N=614)</th>
<th>CVG Girls (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate per 100 Person-years</td>
</tr>
<tr>
<td>HPV types 6,11,16</td>
<td>257 3 0.3 94 1 0.3</td>
<td></td>
</tr>
<tr>
<td>HPV 6 related</td>
<td>254 0 0 89 0 0</td>
<td></td>
</tr>
<tr>
<td>HPV 11 related</td>
<td>254 0 0 89 0 0</td>
<td></td>
</tr>
<tr>
<td>HPV 16 related</td>
<td>254 3 0.3 87 1 0.3</td>
<td></td>
</tr>
<tr>
<td>HPV 18 related</td>
<td>254 0 0 91 0 0</td>
<td></td>
</tr>
<tr>
<td>CIN</td>
<td>227 0 0 83 0 0</td>
<td></td>
</tr>
<tr>
<td>EGL</td>
<td>259 0 0 96 0 0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: The Incidence of Nonvaccine HPV Type–Related Persistent Infection, CIN, or EGLs Among Girls and Boys in the FAS Population

<table>
<thead>
<tr>
<th></th>
<th>EVG Girls (FAS) N = 614</th>
<th>CVG Girls (FAS) N = 262</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate per 100 Person-years</td>
</tr>
<tr>
<td>HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 related persistent infection</td>
<td>90 9.8 (7.4–11.5)</td>
<td>61 14.5 (11.1–18.8)</td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>17 1.6 (0.8–2.6)</td>
<td>13 2.4 (1.3–4.1)</td>
</tr>
<tr>
<td>CIN 1</td>
<td>17 1.6 (0.8–2.6)</td>
<td>13 2.4 (1.3–4.1)</td>
</tr>
<tr>
<td>CIN 2</td>
<td>2 0.2 (0.0–0.7)</td>
<td>2 0.4 (0.0–1.3)</td>
</tr>
<tr>
<td>CIN 3</td>
<td>1 0.1 (0.0–0.5)</td>
<td>0 0.0 (0.0–0.7)</td>
</tr>
<tr>
<td>EGL</td>
<td>2 0.2 (0.0–0.6)</td>
<td>1 0.2 (0.0–0.9)</td>
</tr>
<tr>
<td>Condyloma (vulvar or vaginal)</td>
<td>1 0.1 (0.0–0.4)</td>
<td>0 0.0 (0.0–0.6)</td>
</tr>
<tr>
<td>VIN 1 or VaIN 1</td>
<td>1 0.1 (0.0–0.4)</td>
<td>1 0.2 (0.0–0.9)</td>
</tr>
<tr>
<td>VIN 2/3 or VaIN 2/3 or worse</td>
<td>0 0.0 (0.0–0.3)</td>
<td>0 0.0 (0.0–0.6)</td>
</tr>
</tbody>
</table>

### Table 4: Vaccine Breakthrough Rates and Cervical Abnormalities in the FAS Population

<table>
<thead>
<tr>
<th></th>
<th>EVG Boys (FAS) N = 565</th>
<th>CVG Boys (FAS) N = 220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate per 100 Person-years</td>
</tr>
<tr>
<td>HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 related persistent infection</td>
<td>34 4.8 (3.5–6.7)</td>
<td>19 5.3 (3.1–8.1)</td>
</tr>
<tr>
<td>EGL</td>
<td>0 0.0 (0.0–0.5)</td>
<td>0 0.0 (0.0–0.9)</td>
</tr>
</tbody>
</table>
for vaccine recipients to HPV types 6, 11, and 16, thus providing evidence for durable immune responses. Fewer subjects remained seropositive for HPV-18; however, the clinical relevance of this difference is not clearly understood in the absence of an immune correlate of protection. The subjects determined to be seronegative to the 4vHPV vaccine types (6, 11, 16, and 18) at 10 years postvaccination continued to be protected from vaccine-type HPV-related cervical and genital lesions, suggesting a role of immune memory in vaccine protection.\textsuperscript{14}

The 4vHPV vaccine was extremely effective in preventing HPV-related cervical and genital neoplasia for 10 years after vaccination, with no cases of HPV-related disease being detected in the study. The clinical significance is notable because none of the subjects who were vaccinated as preadolescents or adolescents developed genital warts or low-grade or high-grade cervical, vaginal, vulvar, or other genital cancer precursors caused by any of the 4v HPV vaccine types (6, 11, 16, and 18) during the 10 years of observation. Thus, the 4vHPV vaccine was highly effective in preventing HPV vaccine–related cancer precursor lesions.

Additionally, the rates of sexual activity and HPV exposure were similar to those seen in previous 4vHPV vaccine clinical programs, thus indicating that the reductions in vaccine-type HPV infection and disease are not a result of decreased sexual activity and overall HPV exposure among adolescents in the LTFU study. If health care providers improve the rate of HPV vaccination, most aggressive types of cervical and genital neoplasia can be prevented.

The incidence of persistent infection with vaccine-type HPV (6, 11, 16, and 18) was also managed as a secondary end point of the LTFU study. Here, we report 4 cases of HPV-16–related persistent infection (6 months’ duration) in girls and 6 cases of HPV type 6- and 16-related persistent infection (6 months’ duration) in boys. Detection rates of persistent infection were similar in this population to what was observed in vaccinated young adult women (ages 16–23 years at vaccination) and men (ages 16–26 years at vaccination).\textsuperscript{13,15} In all 10 cases of persistent infection, vaccine-type HPV (6, 11, 16, and 18) was detected concurrently with 1 or more nonvaccine HPV types, and the detection of the nonvaccine-type HPV persisted longer than the detection of vaccine-type HPV. In contrast, persistent infection and disease continued to occur because of nonvaccine HPV types, supporting continued HPV exposure and infection in the population.

As is typical with the young population, a high incidence of low-grade abnormalities in cervical cytology was observed in this study.\textsuperscript{16} A high rate of new partner acquisition and HPV infection in adolescents may explain the increased detection of these abnormalities in adolescents at a time when they are not routinely screened. However, these findings demonstrate the vulnerability and potentially serious risks adolescents face even at an early age. In addition, the detection of lower genital tract abnormalities at this young age underscores the importance of early HPV vaccination of all preadolescents and adolescents.

The limitations of this LTFU study are inherent to the study design. We were not able to manage an unvaccinated group because base study placebo recipients were designed to be offered vaccination once the efficacy, immunogenicity, and safety of the 4vHPV vaccine were established in this population and the vaccine was licensed. Additionally, not all of the subjects

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**TABLE 4 Incidence of Cervical Cytology Abnormalities in Girls Vaccinated With the 4vHPV Vaccine**

<table>
<thead>
<tr>
<th>Protocol 018 LTFU Study</th>
<th>Protocol 007, 013, 015\textsuperscript{a}</th>
<th>Protocol 019\textsuperscript{a} Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100 Person-years (95% CI)</td>
<td>Rate per 100 Person-years (95% CI)</td>
<td>Rate per 100 Person-years (95% CI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASCUS HR-HPV–positive, LSIL, or worse</th>
<th>ASCUS HR-HPV–positive</th>
<th>LSIL</th>
<th>ASC-H</th>
<th>HSIL</th>
<th>AGC</th>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVG (N = 614)</td>
<td>10.4 (8.2–13.1)</td>
<td>17.6</td>
<td>13.3–22.8</td>
<td>10.6</td>
<td>10.2–11.0</td>
<td>4.2 (3.7–4.7)</td>
<td></td>
</tr>
<tr>
<td>CVG (N = 262)</td>
<td>4.5 (3.2–6.2)</td>
<td>7.1</td>
<td>4.8–10.2</td>
<td>2.8</td>
<td>2.8–3.1</td>
<td>2.0 (1.7–2.4)</td>
<td></td>
</tr>
<tr>
<td>N = 9075</td>
<td>7.9 (6.0–10.2)</td>
<td>13.3</td>
<td>8.7–17.7</td>
<td>8.2</td>
<td>7.9–8.8</td>
<td>2.8 (2.4–3.3)</td>
<td></td>
</tr>
<tr>
<td>N = 1910</td>
<td>0.3 (0.1–0.9)</td>
<td>0.2</td>
<td>0.0–1.2</td>
<td>0.6</td>
<td>0.5–0.7</td>
<td>0.2 (0.1–0.3)</td>
<td></td>
</tr>
<tr>
<td>AGC</td>
<td>0.1 (0.0–0.6)</td>
<td>0.0</td>
<td>0.0–0.8</td>
<td>0.5</td>
<td>0.4–0.8</td>
<td>0.2 (0.1–0.3)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.0 (0.0–0.4)</td>
<td>0.0</td>
<td>0.0–0.8</td>
<td>&lt;0.1</td>
<td>0.0–0.1</td>
<td>&lt;0.1 (0.0–0.1)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0.0 (0.0–0.4)</td>
<td>0.0</td>
<td>0.0–0.8</td>
<td>0.0</td>
<td>0.0–0.1</td>
<td>0.0 (0.0–0.1)</td>
<td></td>
</tr>
</tbody>
</table>
who participated in the base study chose to continue to the LTFU. The mobility of the age group (for school, jobs, etc) as well as the addition of genital examinations to assess efficacy (which were not present in the base study) decreased subject participation in the LTFU. Finally, this study was not designed to manage oropharyngeal and anal disease end points.

Our long-term study findings support the durability of immunogenicity, protection, and safety of HPV vaccines and should help to dismiss any lingering doubts about the safety and durability of HPV vaccine-induced protection. Although the 4vHPV vaccine was effective in preventing HPV types 16- and 18-induced infections and lesions, some vaccinated subjects subsequently developed infections and lesions caused by high-risk HPV types not contained in the vaccine. A 9-valent HPV (9vHPV) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine (Gardasil 9; Merck & Company Inc, Kenilworth, NJ) is now available to provide protection against the HPV types already covered by the 4vHPV vaccine (types 6, 11, 16, and 18) and the next 5 most common oncogenic types associated with cervical cancer worldwide (types 31, 33, 45, 52, 58). In a clinical trial conducted in women 16 to 26 years of age (Protocol V503-001, NCT00543543), the 9vHPV vaccine effectively prevented infection and disease caused by HPV types 31, 33, 45, 52, and 58 as well as noninferior immunity to the 4vHPV vaccine for HPV types 6, 11, 16, and 18. The 10-year effectiveness and immunogenicity follow-up data on the 9vHPV vaccine will not be available for some years. Therefore, LTFU data from the 4vHPV vaccine should be translatable to the 9vHPV vaccine and are the closest it comes to estimating the long-term effectiveness of both the 4vHPV and 9vHPV vaccines. Continued evidence on the long-term effectiveness, immunogenicity, and safety of the 4vHPV vaccine should support efforts to achieve HPV vaccination coverage comparable to those now seen with other pediatric vaccines.

CONCLUSIONS
The 4vHPV vaccine continues to be highly effective, immunogenic, and safe in adolescent and preadolescent subjects after 10 years.

ACKNOWLEDGMENTS
We are indebted to all the participants and their caregivers involved with this study. We thank Ms Karyn Davis of Merck & Company for her editorial assistance.

ABBREVIATIONS

- 4vHPV: 4-valent human papillomavirus
- 9vHPV: 9-valent human papillomavirus
- CI: confidence interval
- cLIA: competitive Luminex immunoassay
- CVG: catch-up vaccination group
- EGL: external genital lesion
- EVG: early vaccination group
- GMT: geometric mean titer
- IgG: immunoglobulin G
- LIA: Luminex immunoassay
- LTFU: long-term follow-up
- PCR: polymerase chain reaction

REFERENCES


4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years
Daron G. Ferris, Rudiwilai Samakoses, Stanley L. Block, Eduardo Lazcano-Ponce, Jaime Alberto Restrepo, Jesper Mehlsen, Archana Chatterjee, Ole-Erik Iversen, Amita Joshi, Jian-Li Chu, Andrea Likos Krick, Alfred Saah and Rituparna Das

Pediatrics 2017;140;
DOI: 10.1542/peds.2016-3947 originally published online November 22, 2017;

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