Long-term Study of a Quadrivalent Human Papillomavirus Vaccine

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KEY WORDS: quadrivalent HPV vaccine, safety, effectiveness, immunogenicity, adolescents, anogenital cancer, genital warts, immunogenicity

ABBREVIATIONS
AE—adverse event
CDC—Centers for Disease Control and Prevention
cLIA—competitive Luminex immunoassay
CVG—Catch-Up Vaccination Group
EVG—Early Vaccination Group
HPV—human papillomavirus
HPV4—human papillomavirus (types 6, 11 16, 18) recombinant vaccine
ITT—intention to treat

Dr Ferris enrolled patients and contributed to data collection for the study and drafted the initial manuscript; Drs. Samakoses, Block, Lazzcano-Ponce, Restrepo, Reisinger, Mehlisen, Chatterjee, and Iversen enrolled patients and contributed to data collection for the study and reviewed and revised the manuscript; Mr Sausser and Dr Saah conceptualized and designed the study and reviewed and revised the manuscript; Dr Shou performed the statistical analyses and critically reviewed the manuscript; Dr Sings analyzed and interpreted the data and drafted the original manuscript; and all authors approved the data and drafted the final manuscript as submitted.

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abstract

BACKGROUND: We present a long-term safety, immunogenicity, and effectiveness study of a quadrivalent human papillomavirus (HPV4) vaccine.

METHODS: Sexually naive boys and girls aged 9 to 15 years (N = 1781) were assigned (2:1) to receive HPV4 vaccine or saline placebo at day 1 and months 2 and 6. At month 30, the placebo group (n = 482) received HPV4 vaccine following the same regimen and both cohorts were followed through month 96. Subjects ≥16 years were eligible for effectiveness evaluations. The primary objective was to evaluate the long-term anti-HPV6/11/16/18 serological levels. The secondary objective was to estimate vaccine effectiveness against HPV6/11/16/18-related persistent infection or disease.

RESULTS: For each of the HPV4 vaccine types, vaccination-induced anti-HPV response persisted through month 96. Among 429 subjects who received HPV4 vaccine at a mean age of 12, none developed HPV6/11/16/18-related disease or persistent infection of ≥12 months’ duration. Acquisition of new sexual partners (among those ≥16 years) was ~1 per year. Subjects receiving HPV4 vaccine at month 30 (mean age 15 years) had a similar baseline rate of seropositivity to ≥1 of the 4 HPV types to those vaccinated at day 1 (mean age 12 years; 1.9% [9 of 474] vs 1.7% [20 of 1157]); however, 4 of the 9 subjects vaccinated at the later age were seropositive to 3 vaccine types, indicating previous HPV exposure. No new significant serious adverse events were observed for 8 years postvaccination in both genders.

CONCLUSIONS: When administered to adolescents, the HPV4 vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years. Pediatrics 2014;134:e657–e665

WHAT’S KNOWN ON THIS SUBJECT: The short-term immunogenicity and safety of a HPV4 vaccine have been previously evaluated in preadolescents and adolescents. To date, no long-term studies of the safety, effectiveness, and immunogenicity of the HPV4 vaccine have been reported in this age group.

WHAT THIS STUDY ADDS: The HPV4 vaccine administered to adolescents demonstrated durability in clinically effective protection and sustained antibody titers over 8 years. These data, along with extensive postapproval safety surveillance data, should help reinforce national recommendations for HPV vaccination of preadolescents and adolescents.
The quadrivalent HPV6/11/16/18 L1 viruslike particle vaccine (HPV4) was launched in 2006 to substantially reduce the burden associated with HPV-related neoplasias of the anogenital tract. The results from a series of large randomized controlled trials in >17,500 young women aged 16 to 26 years conducted across 4 continents showed that the vaccine was highly effective in preventing cervical, vaginal, and vulvar neoplasias and anogenital condylomata in women who were naive to the respective HPV type at enrollment. In support of a gender-neutral vaccination program, excellent HPV4 vaccine efficacy has been demonstrated for the prevention of external genital and anal lesions in heterosexual and homosexual men. Multiple studies of HPV4 vaccine immunogenicity across the 9- to 45-year-old age range have revealed robust antibody responses for all 4 HPV types. Evidence of a HPV4 vaccine anamnestic response and immune memory have also been observed.

In 2 separate meta-analyses of 5 clinical trials of the HPV4 vaccine, vaccination was generally well tolerated with no apparent adverse health impact after completion of the vaccination regimen. National adverse event (AE) surveillance systems have also monitored HPV4 vaccine safety postapproval. A review of the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System data for the HPV4 vaccine during the first 2.5 years after implementation showed most reported AE rates were no greater than background rates associated with other vaccines. Several years later, in a study of >600,000 HPV4 vaccine doses analyzed using the CDC Vaccine Safety Datalink, no statistically significant increased risk for any of the prespecified AEs were observed. However, the authors concluded that further study of a possible association with venous thromboembolism after vaccination was warranted. As of 2013, the Australian Therapeutic Goods Administration Database of Adverse Events Notifications reported only mild AEs previously recognized as routinely associated with the HPV4 vaccine. Hence, in the 7 years of independent postlicensure vaccine safety monitoring and evaluation, no serious safety concerns have been identified.

Despite ample evidence of the safety, immunogenicity, and efficacy of the HPV4 vaccine from numerous large randomized controlled trials, national AE surveillance systems, and recent population-based documentation of the positive impact of vaccination, questions remain regarding the duration of vaccine effectiveness. The vaccine needs to show sustained immunity after vaccination of the primary target population of preadolescents. The possible need for an additional booster dose depends on whether loss of protection is observed over the next 5 to 10 years after vaccination. Additional long-term safety data would also help to clarify lingering unverified concerns about HPV vaccination. Although vaccine uptake in several countries has been widespread, undocumented concerns have unfortunately fostered a negative impact on vaccination rates in many other locations worldwide. Suboptimal HPV4 vaccine uptake has drawn the attention and concern from organizations such as the CDC, which acknowledged earlier this year that HPV vaccines are safe, effective, and grossly underutilized. Further dissemination of data demonstrating long-term safety and effectiveness could reduce reluctance to vaccination and improve uptake.

The short-term immunogenicity and safety of the HPV4 vaccine has been previously established in preadolescent and adolescent children. To date, no long-term studies of the safety, durability, immunogenicity, and effectiveness of the HPV4 vaccine in boys and girls aged 9 to 15 years have been reported. To address these questions, we present a long-term follow-up study through 8 years postvaccination in boys and girls who received HPV4 vaccine between the ages of 9 and 15 years.

**METHODS**

**Objectives**

The lack of a placebo arm in the long-term follow-up study made vaccine efficacy hypothesis testing unavailable. The primary objective was to evaluate the anti-HPV6/11/16, and 18 serological levels after administration of a 3-dose regimen of HPV4 vaccine as measured at months 72, 96, and 126. The secondary objective was to estimate the long-term effectiveness of the HPV4 vaccine with respect to the combined incidence of HPV6/11/16 and 18-related persistent infection and disease. The safety objective was to describe the incidence of serious AEs and deaths deemed to be vaccine- or procedure-related.

**Baseline Study**

Protocol V501-018 was a randomized, double-blind, placebo-controlled study to assess the safety and immunogenicity of the HPV4 vaccine among 9- to 15-year-old boys and girls over a 1-year period after the third dose, as previously described. An Institutional Review Board for each clinical site approved the study protocol. At enrollment, written consent was obtained from each participant and his or her legal guardian. Subjects were randomized in a 2:1 ratio within study centers to receive 3 intramuscular injections of either HPV4 vaccine or non–aluminum-containing placebo at months 0, 2, and 6. The data for the prespecified primary endpoints for the base study were described by Reisinger et al in 2007.

**Long-term Follow-up Study**

The follow-up study was designed to evaluate the long-term immunogenicity, effectiveness, and safety of the HPV4 vaccine (Fig 1). The cohort who received HPV4 vaccine at months 0, 2, and 6 in the
base study are referred to as the Early Vaccination Group (EVG) and the cohort who received placebo in the base study and who later received a 3-dose regimen of HPV4 vaccine starting at month 30 are referred to as the Catch-up Vaccination Group (CVG). All subjects who received 3 doses of HPV4 vaccine and consented to participate in the extension were eligible. The protocol (see Supplemental Information) stated an interim analysis would be conducted at months 72 and 96 relative to month 0 of the base study. Here we present the month 96 interim analysis.

Annual serum samples were collected and a brief physical examination was conducted at each scheduled visit until the subject reached 16 years of age. Starting at age 16 years, visits were scheduled twice yearly and included the collection of sexual history, serological specimens, and genital clinical specimens (if agreed to), consistent with previous efficacy studies of the HPV4 vaccine in male and female subjects aged 16 to 26 and as described in the study protocol.1–3,21

Effectiveness Endpoints and Analysis Populations

Analyses for effectiveness began at month 42, with follow-up visits occurring every 6 months thereafter (Fig 1). Disease was defined as a tissue sample diagnosed by a 4-member pathology panel as cervical intraepithelial neoplasia, adenocarcinoma in situ, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, genital condyloma, cervical/vaginal/vulvar cancer, penile intraepithelial neoplasia, or penile/perineal/perianal cancer with HPV6/11/16 or 18 DNA detected in tissue from the same lesion, as previously described in previous studies of the HPV4 vaccine in female and male subjects aged 16 to 26.14–7 Persistent infection was defined as detection of the same HPV type in genital swabs at ≥2 consecutive visits spaced ≥4 months apart (prespecified endpoint) or ≥12 months apart (post hoc analysis) or the presence of disease associated with the relevant type with DNA for that same type found in the swab at the visit directly before or after the biopsy.

The effectiveness analyses for the EVG and CVG were assessed in an intention-to-treat (ITT) population, which included subjects who were ≥16 years of age, received at least 1 dose of HPV4 vaccine, and had at least 1 follow-up visit. In the effectiveness analyses (presented in Table 3 later in the article), a subject is counted only once for each endpoint (ie, once in each row), but a subject may have developed >1 endpoint during the trial (ie, a subject may appear in >1 row). For example, a female may have developed HPV16-related persistent infection and HPV16-related CIN1. Overall she would be counted as a case once each for (1) HPV6/11/16 or 18-related persistent infection or disease, (2) HPV16-related persistent infection, and (3) HPV6/11/16 or 18-related cervical disease.

Immunogenicity Endpoints and Analysis Populations

Previous studies of the HPV4 vaccine in women aged 16 to 26 years have shown important differences in the serologic assays used to assess anti-HPV6/11/16 and 18 responses.21 Differences in seropositivity status have been observed between the standard competitive Luminex immunoassay (cLIA) that was used in the clinical trials of the HPV4 vaccine,22 and a new total immunoglobulin (Ig)G assay that was developed as a research assay to evaluate preclinical multivalent HPV vaccine formulations.23 These differences are attributed to the measurement parameters and sensitivity of the individual immunoassays.21 Whereas the cLIA measures a single neutralizing epitope that is a subset of the total immune response to HPV vaccination, the total IgG assay is a less restricted, sensitive
assay that measures a broader subset of the total immune response to vaccination. Therefore, antibodies to HPV6/11/16 and 18 were measured using both the cLIA and the IgG assay. The immune response to vaccination was assessed in the per-protocol immunogenicity population as previously described, with an additional criteria of not yet having sexual debut until after receiving the third dose of HPV4 vaccine. Subjects must have also had at least 1 follow-up visit after dose 3. Reasons for exclusion from the per-protocol immunogenicity population are shown in Supplemental Table 5.

Safety endpoints and analysis populations

The safety objective was to describe the incidence of deaths and serious AEs deemed by the study investigators to be vaccine- or procedure-related for all subjects in the long-term follow-up study who received at least 1 dose of the HPV4 vaccine.

RESULTS

Among the 1781 subjects who received HPV4 vaccine (N = 1179) or placebo (N = 597) during the baseline study, 1661 (1179 vaccine [EVG] and 482 placebo [CVG]) participated in the long-term follow-up study. Table 1 displays the baseline characteristics of these subjects at the time of the first dose of HPV4 vaccine. As expected, the mean age of the CVG group was 3 years older than the EVG (15 vs 12 years). In both groups, approximately half were female. Although subjects were supposed to be sexually naive at the time of enrollment in the base study, prevaccination anti-HPV titers above the seropositivity cutoff for a given HPV type indicated likely previous exposure to that type in 20 (1.7%) subjects in the EVG. The seropositivity rate in the CVG as measured at month 30 immediately before receiving the first dose of HPV4 vaccine was similar at 1.9% (9 of 474); however, 4 of the 9 subjects were seropositive to 3 vaccine types. This was attributable to the older age of CVG group and the higher likelihood of having been exposed to HPV before receiving the first dose of HPV4 vaccine at a mean age of 15 years rather than at 12 years of age.

Immunogenicity

A total of 1116 subjects (95%) in the EVG had follow-up for immunogenicity with a median (mean) follow-up time of 6.5 (5.2) years postdose 3. The median (mean) follow-up time postdose 3 for the CVG was 4.7 (3.5) years, thus the following analyses focus on the EVG. For each of the HPV4 vaccine types for both genders, the vaccination-induced anti-HPV response persisted through month 96; however, for both boys and girls, geometric mean titers (GMTs) at month 96 were 11- to 34-fold lower than the GMTs observed at month 7 (Table 2).

As shown in Fig 2, the seroconversion status differed between the total IgG and cLIA assays. Because the cLIA measures a much more restricted subset of the immune response, the reported seropositivity results were different at month 96, particularly for HPV18. In the cLIA assay, the proportion of subjects with detectable anti-HPV6/11/16 and 18 antibody levels (both genders combined) at month 96 were 88.4%, 89.1%, 96.8%, and 64.1%, respectively, whereas the corresponding seropositivity rates for the total IgG assay were 94.3%, 89.4%, 99.5%, and 88.8%, respectively.

Indicators of Sexual Activity

During the long-term follow-up study, among subjects ≥16 years of age, the rate of acquisition of new partners among male subjects tended to be higher than that for their female counterparts (Table 3). In the EVG and CVG groups, male subjects acquired ∼1.2 new partners per year, and female subjects acquired 0.7 and 0.9 new partners per year, respectively. The 3% to 4% incidence of Chlamydia and gonorrhea was similar between the EVG and CVG groups and between male and female subjects within the EVG and CVG groups (Table 3).

### Table 1: Baseline Characteristics of Subjects at the Time They Received the First Dose of HPV4 Vaccine

<table>
<thead>
<tr>
<th></th>
<th>EVG (n = 1179)</th>
<th>CVG (n = 482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>614 (52.1)</td>
<td>262 (54.4)</td>
</tr>
<tr>
<td>Male</td>
<td>565 (47.9)</td>
<td>220 (45.6)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.9 (1.9)</td>
<td>14.5 (1.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12 (9 to 16)</td>
<td>15 (11 to 18)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>143 (12.1)</td>
<td>60 (12.4)</td>
</tr>
<tr>
<td>Europe</td>
<td>317 (26.9)</td>
<td>128 (28.6)</td>
</tr>
<tr>
<td>Latin America</td>
<td>210 (17.8)</td>
<td>104 (21.6)</td>
</tr>
<tr>
<td>Nordic</td>
<td>23 (2.0)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>North America</td>
<td>486 (41.2)</td>
<td>179 (37.1)</td>
</tr>
<tr>
<td>HPV serostatus, m/n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive to HPV6/11/16</td>
<td>20/1157 (1.7)</td>
<td>9/474 (1.9)</td>
</tr>
<tr>
<td>or 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive to HPV6</td>
<td>8/1155 (0.7)</td>
<td>7/474 (1.5)</td>
</tr>
<tr>
<td>Positive to HPV11</td>
<td>1/1155 (0.1)</td>
<td>3/474 (0.6)</td>
</tr>
<tr>
<td>Positive to HPV16</td>
<td>8/1154 (0.7)</td>
<td>5/474 (1.1)</td>
</tr>
<tr>
<td>Positive to HPV18</td>
<td>3/1156 (0.3)</td>
<td>2/474 (0.4)</td>
</tr>
<tr>
<td>Positive to exactly 1 type</td>
<td>20/1157 (1.7)</td>
<td>5/474 (1.1)</td>
</tr>
<tr>
<td>Positive to exactly 2 types</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive to exactly 3 types</td>
<td>0</td>
<td>4/474 (0.8)</td>
</tr>
<tr>
<td>Positive to exactly 4 types</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

m/n, number of subjects with serology data for the indicated type/number of subjects with the indicated characteristic.
TABLE 2 Summary of Anti-HPV cLIA Geometric Mean Titers (mMU/mL) Among Male and Female Subjects in the Long-term Follow-up Study (Per-Protocol Immunogenicity Populations)

<table>
<thead>
<tr>
<th>Time</th>
<th>Female Subjects</th>
<th>Male Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>GMT</td>
</tr>
<tr>
<td>A. HPV6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>535</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Month 7</td>
<td>501</td>
<td>893.9</td>
</tr>
<tr>
<td>Month 18</td>
<td>491</td>
<td>213.9</td>
</tr>
<tr>
<td>LTFU study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 42</td>
<td>302</td>
<td>122.6</td>
</tr>
<tr>
<td>Month 60</td>
<td>227</td>
<td>112.7</td>
</tr>
<tr>
<td>Month 72</td>
<td>256</td>
<td>123.5</td>
</tr>
<tr>
<td>Month 84</td>
<td>268</td>
<td>89.8</td>
</tr>
<tr>
<td>Month 96</td>
<td>242</td>
<td>77.7</td>
</tr>
<tr>
<td>B. HPV11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>535</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Month 7</td>
<td>501</td>
<td>1356.8</td>
</tr>
<tr>
<td>Month 18</td>
<td>491</td>
<td>304.1</td>
</tr>
<tr>
<td>LTFU study</td>
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<td></td>
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<tr>
<td>Month 42</td>
<td>302</td>
<td>140.3</td>
</tr>
<tr>
<td>Month 60</td>
<td>227</td>
<td>125.8</td>
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<tr>
<td>Month 72</td>
<td>258</td>
<td>140.8</td>
</tr>
<tr>
<td>Month 84</td>
<td>268</td>
<td>89.0</td>
</tr>
<tr>
<td>Month 96</td>
<td>242</td>
<td>72.7</td>
</tr>
<tr>
<td>C. HPV16</td>
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</tr>
<tr>
<td>Base study</td>
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<tr>
<td>Day 1</td>
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<tr>
<td>Month 7</td>
<td>497</td>
<td>4992.2</td>
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<tr>
<td>Month 18</td>
<td>487</td>
<td>1258.8</td>
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<tr>
<td>LTFU study</td>
<td></td>
<td></td>
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<tr>
<td>Month 42</td>
<td>298</td>
<td>597.1</td>
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<tr>
<td>Month 60</td>
<td>225</td>
<td>464.7</td>
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<td>Month 72</td>
<td>257</td>
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<tr>
<td>Month 84</td>
<td>267</td>
<td>401.4</td>
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<tr>
<td>Month 96</td>
<td>240</td>
<td>335.0</td>
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<td>D. HPV18</td>
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<tr>
<td>Day 1</td>
<td>537</td>
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<tr>
<td>Month 7</td>
<td>503</td>
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<td>268</td>
<td>45.4</td>
</tr>
<tr>
<td>Month 96</td>
<td>241</td>
<td>41.8</td>
</tr>
</tbody>
</table>

CI, confidence interval; GMT, geometric mean titer; LTFU, long-term follow-up; mMU, milli Merck units.

Effectiveness

Figure 2 shows the number of subjects with a follow-up visit to assess vaccine effectiveness between months 42 and 96. The median (mean) follow-up time to assess vaccine effectiveness for persistent infection and disease was similar for both groups: 4.1 (3.8) years in the EVG and 3.9 (3.6) years in the CVG because this evaluation began when the subject reached 16 years of age in both groups.

E VG

Among female subjects (n = 256), no cases of HPV6/11/16- or 18-related persistent infection or 4 cases of HPV 18-related persistent infection were detected (Table 4). The 4 cases of HPV18-related persistent infection were persistent infections of ≥12 months duration (data not shown).

Among male subjects (n = 173), no cases of HPV6/11/16- or 18-related disease and 2 cases of persistent infection of ≥4 months’ duration (1 HPV6-related and 1 HPV16-related) were seen (Table 4). As with female subjects, the incidence of persistent infection was comparable to that observed among vaccine recipients in a previous efficacy trial in male subjects aged 16 to 26 years (Fig 3), and the 2 cases of persistent infection were of <12 months’ duration.

C V G

In the ITT analyses for the CVG among female subjects, 2 cases of HPV16-related persistent infection and 4 cases of HPV 18-related persistent infection were detected (Table 4). The 4 cases of HPV18-related persistent infection were persistent infections of ≥12 months’ duration. In the CVG, there was also 1 case CIN1 related to HPV18. Four of these 6 subjects who developed a case of persistent infection or disease were also diagnosed with Chlamydia or gonorrhea during the study. Among male subjects, no cases of disease and 1 case of HPV6-related persistent infection of <12 months’ duration was observed. This subject was also diagnosed with Chlamydia during the follow-up period. All of these subjects (both male and female) were seronegative to all 4 vaccine types at day 1 (ie, before vaccination), except for 1 female who developed a case of HPV16-related persistent infection, who was seropositive to HPV6 at day 1.

Safety

Three serious AEs occurred during the long-term follow-up study: a fatal road
traffic accident (EVG; 4.7 years postdose 3), 1 case of tonic-clonic movements of 3 minutes’ duration postphlebotomy (EVG; 7 years postdose 3), and 1 case of cranial nerve VII paralysis of 2.7 weeks’ duration (CVG, 131 days postdose 3). The latter case was determined by the investigator to be vaccine-related. The subject with cranial nerve paralysis was treated with prednisolone; vitamins B1, B6, and B12; and omeprazole and fully recovered. No significant pregnancy-related adverse outcome trends were observed. Of the 67 and 37 pregnancies with a known outcome reported in the EVG and CVG groups, 48 (72%) and 26 (70%) were live births. Of the live births in the EVG and CVE, 45 (94%) and 24 (92%) had a normal infant outcome. Only 3 births reported a congenital anomaly (2 cases of trisomy 21 [EVG] and 1 case of unilateral choanal atresia [CVG]). The duration of time from the subject’s last vaccination with HPV4 to conception was ∼15 months, 61 months, and 28 months, respectively.

Discussion
This is the first study to present detailed long-term immunogenicity, effectiveness, and safety data for the HPV4 vaccine from a closely monitored group of preadolescents (the intended primary targeted population). Three doses of HPV4 vaccine provided high protection against disease and persistent infection. The only cases of persistent HPV infection and the sole case of CIN1 were seen in the CVG (ITT analysis) who were fully vaccinated 3 years later than the EVG. With ∼5 years of follow-up postdose 3, no cases of HPV6/11/16/18-related anogenital disease were detected among female or male subjects in the per-protocol effectiveness population. On the basis of previous placebo-controlled trials, some disease cases would have been expected during this interval in unvaccinated subjects (Fig 3).1–4 The observed acquisition of ∼1 new sexual partner per year and an incidence of Chlamydia and gonorrhea being on the order of 3% to 4% in both genders indicate the emerging risks encountered by these young individuals. High uptake of HPV vaccination, preferably before sexual debut and HPV acquisition, is paramount to reduce the risk of HPV-related cancers in large populations.

According to the CDC, for each year the 3-dose HPV vaccine series coverage remains near the current level of 33% instead of achieving the Healthy People 2020 goal of 80% coverage, an additional 4400 women will be diagnosed annually with cervical cancer along with 1400 cervical cancer–attributable deaths.20 In addition, many more individuals will experience the morbidity and significant anxiety associated with the diagnosis and treatment of HPV-induced premalignant diseases. Long-term HPV vaccine effectiveness and safety data, such as that provided by our study, should help to reassure health providers, patients, and families, and ultimately improve vaccine acceptance and compliance. These data also reinforce existing national vaccine recommendations.

Table 3: Incidence of New Sexual Partners and Chlamydia or Gonorrhea Among Male and Female Subjects, ITT Populations

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVG</th>
<th>CVG</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>No. of Cases</td>
<td>Rate a</td>
</tr>
<tr>
<td>New partners since sexual debut</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male subjects</td>
<td>226</td>
<td>976</td>
</tr>
<tr>
<td>Females</td>
<td>263</td>
<td>645</td>
</tr>
<tr>
<td>Chlamydia or gonorrhea—male subjects</td>
<td>273</td>
<td>26</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>273</td>
<td>20</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>264</td>
<td>7</td>
</tr>
<tr>
<td>Chlamydia or gonorrhea—female subjects</td>
<td>356</td>
<td>44</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>356</td>
<td>42</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>350</td>
<td>8</td>
</tr>
</tbody>
</table>

CI, confidence interval; n, number of subjects with at least one follow-up visit for effectiveness.

a Incidence rate per 100 person-year-at-risk.
Long-term antibody persistence was observed for HPV6, 11, and 16 for each gender and each age group, and the vast majority (86%–100%) of subjects remained seropositive through 8 years. Reduced anti-HPV18 titers have been reported for women aged 16 to 26 compared with the other 3 antibody titers as measured by the cLIA.21 In our study, a 27- to 34-fold decline in GMTs occurred by month 96, relative to month 7 (ie, 1 month postdose 3). In addition, only 64.1% of subjects were seropositive to HPV18 at month 96. However, when a total IgG assay was compared with the cLIA, antibodies to other HPV18 neutralizing epitopes were detected, resulting in a higher seropositivity rate. The particular neutralizing epitope and relevant mAb selected for the HPV18 cLIA (18.J4) was selected for its analytical specificity. Although it can distinguish between HPV18 antibody response and other HPV types that are phylogenetically related to HPV18 (such as HPV45), it is not detecting all of the HPV18 neutralizing antibodies.24 The IgG assay data corroborate the already documented sustained HPV4 vaccine effectiveness against HPV18-related anogenital disease.24 Yet no immune correlate of protection nor antibody threshold that correlates with protection against HPV infection or disease has been established.

### TABLE 4 Vaccine Effectiveness in Preventing HPV6/11/16/18-Related Persistent Infection or Disease, ITT Populations

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVG</th>
<th>CVG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV6/11/16 or 18-related persistent infection or disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>256</td>
<td>126</td>
</tr>
<tr>
<td>No. of cases</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Rate a</td>
<td>0.3</td>
<td>1.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–1.1</td>
<td>0.7–4.0</td>
</tr>
<tr>
<td>HPV6-related</td>
<td>256</td>
<td>126</td>
</tr>
<tr>
<td>HPV11-related</td>
<td>256</td>
<td>126</td>
</tr>
<tr>
<td>HPV16-related</td>
<td>256</td>
<td>126</td>
</tr>
<tr>
<td>HPV18-related</td>
<td>256</td>
<td>126</td>
</tr>
<tr>
<td>HPV6/11/16 or 18-related persistent infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td>No. of cases</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Rate a</td>
<td>0.3</td>
<td>2.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–1.2</td>
<td>0.7–4.4</td>
</tr>
<tr>
<td>HPV6-related</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td>HPV11-related</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td>HPV16-related</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td>HPV18-related</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td>HPV6/11/16 or 18-related cervical disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>206</td>
<td>107</td>
</tr>
<tr>
<td>No. of cases</td>
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<td>1</td>
</tr>
<tr>
<td>Rate a</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–1.1</td>
<td>0.4–1.9</td>
</tr>
<tr>
<td>HPV6/11/16 or 18-related genital warts or vulvar/vaginal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>206</td>
<td>121</td>
</tr>
<tr>
<td>No. of cases</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Rate a</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–1.1</td>
<td>0.4–3.5</td>
</tr>
</tbody>
</table>

CI, confidence interval; n, number of subjects with at least 1 follow-up visit for effectiveness. A subject is counted only once within each applicable row but may appear in more than 1 row.

* Number of subjects with an endpoint per 100 person-years-at-risk.

* The single case of cervical disease was HPV18-related CIN1.
Our study is accompanied by some limitations. The lack of a control group did not allow for a direct measurement of vaccine efficacy. However, given the known attributes of the HPV4 vaccine, failure to subsequently administer the vaccine to the later control group would have been considered unethical. Some attrition was also observed, which is not uncommon in long-term follow-up trials. This is particularly true for adolescents faced with a required first-time genital examination. Only ~25% of original enrollees continued into the effectiveness portion of the study. The relatively small number of participants also precludes the ability to detect rare and serious adverse events. These data complement the large population-based evaluations of the HPV4 vaccine. Recent data from the CDC showed a 56% decline in HPV vaccine type infections in teenage girls since the introduction of the HPV vaccine.14 In Australia a significant decline in high-grade lesions in young women has been seen since the introduction of the HPV vaccine.15,16 The rate of genital warts in young women has also decreased in Australia by 93% since the introduction of the nationwide HPV vaccination program.17,18 Marked reductions in HPV prevalence and/or genital warts have also been observed in the United States, Sweden, and Denmark.14,25–28 Six years after licensure of the quadrivalent HPV vaccine in Denmark, a reduced risk of cervical lesions has also been observed at the population level.29

CONCLUSIONS
The HPV4 vaccine administered to preadolescents and adolescents demonstrated durability in clinically effective protection and sustained antibody titers over 8 years. No new significant serious AEs were observed for 8 years after vaccination in both genders. These long-term follow-up data, along with other extensive postapproval safety surveillance data, should help to encourage practitioners and reinforce national recommendations for HPV vaccination of all preadolescents and young adolescents.

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REFERENCES
young Australians following the national HPV vaccination program. BMC Infect Dis. 2013;13:140


(Continued from first page)

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