Efficacy of Human Papillomavirus-16 Vaccine to Prevent Cervical Intraepithelial Neoplasia
A Randomized Controlled Trial

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OBJECTIVE: Human papillomavirus (HPV) virus-like particle (VLP) vaccines have demonstrated effectiveness in preventing persistent HPV infections. Whether protection lasts longer than 18 months and, thus, impacts rates of cervical intraepithelial neoplasia (CIN) 2–3 has not yet been established. We present results from an HPV16 L1 VLP vaccine trial through 48 months.

METHODS: A total of 2,391 women, aged 16–23 years, participated in a randomized, double-blind, placebo-controlled trial. Either 40 μg HPV16 L1 VLP vaccine or placebo was given intramuscularly at day 1, month 2, and month 6. Genital samples for HPV16 DNA and Pap tests were obtained at day 1, month 7, and then 6-monthly through month 48. Colposcopy and cervical biopsies were performed if clinically indicated and at study exit. Serum HPV16 antibody titer was measured by radioimmunoassay.

RESULTS: Among 750 placebo recipients in the per protocol population, 12 women developed HPV16-related CIN2–3 (6 CIN2 and 6 CIN3). Among 755 vaccine recipients, there were no cases (vaccine efficacy 100%, 95% confidence interval [CI] 65–100%). There were 111 cases of persistent HPV16 infection in placebo recipients and 7 cases in vaccine recipients (vaccine efficacy 94%, 95% CI 88–98%). After immunization, HPV16 serum antibody geometric mean titers peaked at month 7 (1,519 milli-Merck units [mMU]/mL), declined through month 18 (202 mMU/mL), and remained relatively stable between month 30 and month 48 (128–150 mMU/mL).

CONCLUSION: The vaccine HPV16 L1 VLP provides high-level protection against persistent HPV16 infection and HPV16-related CIN2–3 for at least 3.5 years after immunization. Administration of L1 VLP vaccines targeting HPV16 is likely to reduce risk for cervical cancer. (Obstet Gynecol 2006;107:18–27)

LEVEL OF EVIDENCE: I

Over 40 genital human papillomavirus (HPV) types have been identified. Of these, HPV16 is responsible for approximately half of all cervical cancers worldwide.1 Pap testing has reduced cervical cancer rates, but this undertaking is costly. Evaluation of abnormal Pap tests and treatment of precancerous cervical intraepithelial neoplasia (CIN) lesions has an estimated cost of $3.6 billion annually in the United States.2 Despite this effort, over 10,000 new cervical cancers were reported in the United States in 2004.3

Prophylactic vaccines targeting common HPV types, including HPV16, hold promise as effective tools for cervical cancer prevention. The evaluation of

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such vaccines with regard to cervical cancer rates is complicated by the long interval between initial infection and development of cancer. Large-scale studies of these vaccines are using intermediate virologic and clinical end points to estimate impact on cervical cancer rates.

Persistent HPV infections are necessary for development of CIN 2–3, the precursor lesion of cervical cancer. Analysis of a randomized placebo-controlled trial of the prophylactic HPV16 L1 virus-like particle (VLP) vaccine showed that vaccination prevented persistent HPV16 infections during an average 1.5 years of follow-up. A bivalent HPV16 and 18 VLP vaccine was also effective in preventing persistent HPV16 and 18 infections during a similar follow-up interval. However, because the median duration of HPV infection is approximately 8–12 months, persistent infections with short-term follow-up may be difficult to distinguish from routine resolution of viral disease. The U.S. Food and Drug Administration Vaccines Advisory Committee recommended using CIN 2–3 as a surrogate marker for cervical cancer in HPV vaccine trials because this lesion is the immediate precursor to cervical cancer. This report includes HPV vaccine trials because this lesion is the immediate precursor to cervical cancer. This report includes HPV vaccine trials because this lesion is the immediate precursor to cervical cancer.

MATERIALS AND METHODS

The HPV16 L1 virus-like particle vaccine (Merck Research Laboratories, West Point, PA) consists of highly purified virus-like particles of the L1 capsid polypeptide of HPV16. The HPV16 L1 polypeptide is expressed in a yeast host (Saccharomyces cerevisiae). Virus-like particles are isolated to achieve more than 97% purity and adsorbed onto amorphous aluminum hydroxyphosphate sulfate adjuvant without preservative. The HPV16 vaccine used in this study contained 40 μg of HPV16 L1 virus-like particle formulated on 225 μg of aluminum adjuvant in a total carrier volume of 0.5 mL. The placebo contained 225 μg of aluminum adjuvant in a total carrier volume of 0.5 mL. Vaccine and placebo were visually indistinguishable.

Between October 1998 and November 1999, 2,391 women from 16 centers in the United States were recruited by advertising on college campuses and surrounding communities. Women 16–23 years of age, not pregnant, reporting no prior abnormal Pap tests and a lifetime history of 0–5 male sex partners were eligible for study participation. Virgins were enrolled if they were seeking contraception. The institutional review board at each clinical site approved the study protocol, and at the enrollment visit, women provided written informed consent. Study participants’ race/ethnicity data were collected to evaluate their association with vaccine immunogenicity. They were asked to classify themselves into one of 5 categories: White, Black, Hispanic, Asian, Native American, or Other (specified).

Study participants were randomized in a 1:1 ratio within study centers to receive 3 intramuscular injections of either HPV16 vaccine or placebo at day 1, month 2, and month 6. Permuted blocks were used to ensure that roughly equal numbers of subjects at each site received vaccine and placebo. Allocation sequence was generated by computer. Allocation numbers were assigned at each site. Participants and study staff were blinded to the group assignments. Participants were observed for 20–30 minutes after each vaccination, and they recorded body temperature for 5 days after each injection. All adverse experiences were collected by diary for 14 days after each vaccination. In addition, at months 2, 6, and 7, participants were questioned by their study clinician about possible adverse experiences.

At enrollment, women underwent a gynecologic examination, including collection of cervical samples for thin-layer Pap testing (ThinPrep, Cytyc, Boxborough, MA). Cervical swab, external genital swab, and cervicovaginal lavage specimens were obtained for HPV16 DNA testing. Testing for chlamydia and gonorrhea was performed. Wet mount for bacterial vaginosis and trichomonas was performed. Serum samples were obtained for HPV16 antibody titers. Follow-up visits were scheduled for 1 month after the third vaccination (month 7), 6 months after the third vaccination (month 12), and 6-monthly until month 48. During these visits, women underwent examination with specimen collection for Pap and HPV DNA. Human papillomavirus 16 serum antibody testing was performed at enrollment and months 7, 12, 18, 30, 42, and 48. Funds were made available to pay for travel if participants relocated before completing month 48 visit. Human papillomavirus 16 DNA test results were not used for clinical management.

The protocol required that women with Pap test results showing high-grade squamous intraepithelial lesions (HSIL) or repeated tests showing low-grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASC-US) be referred...
for colposcopy. However, some women with a single abnormal Pap test were referred for colposcopy more often than required by the protocol because of local standards of care. All women underwent a colposcopic examination at the month 48 visit.

All women with colposcopic abnormalities underwent biopsy. For each area of abnormality, 2 adjacent biopsies were obtained. The first specimen, taken from the most concerning area seen at colposcopy, was sent for pathologic diagnosis. The second specimen was placed in Specimen Transport Medium (Digene, Gaithersburg, MD) and submitted for HPV typing by polymerase chain reaction (PCR). Also, after cervical biopsy, a cervical swab for HPV16 DNA was obtained from the biopsy site. Women with CIN 2–3 biopsy results, determined at study-designated pathology labs, were referred for therapy. Loop electrical excision procedure (LEEP) was performed as a study procedure. At the clinician’s discretion, women were referred for conization, cryotherapy, or laser therapy as indicated. At the time of therapy, biopsy specimens were obtained from areas of most severe abnormality before treatment.

Cervical samples for Pap testing were prepared based on manufacturer’s specifications, screened by cytotechnologists, and reviewed by pathologists at study-designated cytology laboratories. Cellular changes were classified according to the Bethesda 1991 system.8

Cervical biopsy specimens were fixed in 10% zinc formalin and paraffin-embedded. Hematoxylin and eosin-stained slides were prepared and reviewed by study-designated pathology labs. Clinical management was based on these results. Afterward, an independent masked group of 4 pathologists (Pathology Panel) reviewed the same slides without knowledge of other clinical or laboratory data. The Pathology Panel results were used for case definitions in the analysis.

Cervical swabs, external genital swabs, cervicovaginal lavages, and biopsy specimens were prepared for PCR using a QIAamp DNA Blood kit (QIAGEN, Inc, Valencia, CA). DNA was analyzed by qualitative PCR using HPV16 type-specific and gene-specific primers based on the HPV 16 L1, E6, and E7 genes as described.9 Beta-globin PCR assay was performed to verify that the purified samples contained DNA of sufficient quantity and quality for PCR amplification. Polymerase chain reaction products were dot-blotted, hybridized to the corresponding 32P-labeled β-globin or HPV16 gene-specific oligonucleotide, and visualized by autoradiography. Appropriate negative and positive controls were run with each assay. Any specimen that tested positive for at least 2 of the 3 genes was considered positive. Any specimen testing positive for only 1 gene was considered positive if, upon retesting for all 3 genes, it was positive for 2 or 3 genes or for the same single gene. Laboratory validation studies rigorously evaluated assay sensitivity against known copy number type- and gene-specific plasmids. This validation showed that the assay had a greater than 95% probability of detecting at least 13 copies per sample. Assay validation showed that the 95% upper confidence bounds for false negativity and false positivity of a sample were 0.7% and 0.8%, respectively. Multiplex PCR assay was used for some samples to increase output. Human papillomavirus 16 type-specific and gene-specific primer pairs were used to simultaneously amplify portions of the HPV16 L1, E6, and E7 genes. All PCR assays were performed at Merck Research Laboratories, West Point, Pennsylvania.

A competitive radioimmunoassay developed by Merck Research Laboratories was used to quantitate serum titers of HPV16 antibodies.10 Quantitation was by standard curve, corrected for dilution, and reported in arbitrary units (milli-Merck units or mMU/mL). A fixed cutoff of 5.9 mMU/mL (derived by repeatedly testing a panel of positive and negative samples against the standard curve) was used to determine the HPV16 serologic status of participants. Results below the cutoff were reported as seronegative. At enrollment, serum from all subjects was also evaluated by an HPV16 enzyme-linked immunosorbent assay (ELISA).11

Human papillomavirus 16–related CIN cases were defined based on the following criteria: 1) histology result of CIN 1, 2, or 3 by pathology panel review, 2) adjacent tissue biopsy or swab from biopsy site positive for HPV16 DNA, and 3) genital samples from one visit immediately before or after the biopsy was positive for HPV16 DNA. All 3 criteria were required to identify each case. Persistent HPV infections were defined by positive HPV16 DNA results on 2 or more consecutive visits at least 4 months apart. Although follow-up study visits were scheduled every 6 months, intervals for return ranged between 4 and 8 months. In addition, women who had a single visit positive for HPV16 DNA at their last visit of record were included in the case definition for persistent HPV infection.

This study used a fixed-number-of-events design, whereby at least 31 cases of persistent HPV-16 infection were required for the study to show a statistically significant reduction in the primary end point (of persistent HPV16 infection) with a power of at least 90%, assuming that the true vaccine efficacy was at
least 75%. A one-sided test of vaccine efficacy \((H_0: \text{VE} = 0 \text{ versus } H_1: \text{VE} > 0)\), defined as \(\text{VE} = (1 - \text{RR}) \times 100\%\), where RR is the relative risk of persistent HPV16 infection in the vaccine group compared with placebo, was conducted using an exact conditional procedure.\(^4\) On August 31, 2001, we observed the prescribed number of infection cases for the primary analysis. The analysis of data suggested that additional follow-up of subjects (through 48 months after enrollment for all subjects) would likely yield enough CIN cases to allow for evaluation of this clinically relevant end point. Criteria for vaccine efficacy calculations remain the same as reported previously.\(^1^2\)

Probability value was computed only for the primary statistical test comparing vaccine and placebo with regard to persistent HPV16 infection. For all other end points, comparison of placebo and vaccine group was done through 95% confidence intervals of vaccine efficacy estimates. Statistically significant was generally used to characterize the result of a vaccine-to-placebo group comparison where the 95% confidence interval (CI) of the vaccine efficacy estimate excluded 0%, and the lower limit of the 95% CI was greater than 0%. Not statistically significant was generally used to characterize the result of a vaccine-to-placebo group comparison where the 95% CI of the vaccine efficacy estimate included 0%, and the lower limit of the 95% CI of vaccine efficacy was less than 0%.

The per-protocol analysis of efficacy included only participants who tested seronegative for HPV16 at the first study visit, tested negative for HPV16 DNA at all visits between day 1 and month 7 inclusive, and completed the entire 3 dose vaccine series. Women who engaged in sexual intercourse within 48 hours of either the first or month 7 visit, received nonstudy vaccine, received immunosuppressive agents or immune globulin, enrolled in another study of an investigational agent, or had a month 7 visit outside the range (14–72 days after the third vaccinations) were also excluded from the per-protocol analysis. For this analysis, cases were counted starting after month 7.

Two additional populations were examined to provide more generalizable estimates of vaccine efficacy. A modified intention-to-treat population (MITT)-1 analysis included participants who received at least one vaccination, were HPV16 seronegative, and HPV16 DNA–negative at day 1. Analysis of MITT-1 included all protocol violators. The MITT-2 population included all MITT-1 subjects as well as subjects who tested positive for HPV16 infection at enrollment. For both MITT analyses, cases were counted beginning at 30 days after day 1.

For both the per-protocol and MITT populations, vaccine efficacy was defined as the percentage reduction in risk of infection/disease in the vaccinated group relative to the risk of infection/disease in the placebo group. A participant lost to follow-up before becoming an end-point case was censored at the date of the last follow-up visit with HPV 16 DNA evaluation.

For cases of persistent HPV16 infection, the median duration of the infection was defined as the number of days, divided by 30, between the date of the first study visit at which the persistent HPV16 infection was detected and the date of the last HPV16-positive visit. All participants positive for HPV16 DNA at the last visit before being lost to follow-up were censored at that visit for the median duration calculation.

**RESULTS**

The study participant flow diagram shows women included in our per-protocol analysis population as well as less restrictive MITT populations (Fig. 1). Of 2,391 women randomized into the study who received at least 1 vaccination, 360 (15.1%) discontinued participation by month 7 for the following reasons: 9 clinical adverse events, 189 lost to follow-up, 33 pregnancy, 35 protocol deviations, and 94 consent withdrawal. Within each study discontinuation category, the vaccine and placebo groups were generally comparable with respect to the proportion of women who discontinued participation by month 7. Over all categories, slightly more vaccine recipients failed to complete the 7-month vaccination period compared with placebo.

There was no significant difference in losses in the vaccine versus placebo groups. Of the 2,391 women who began the vaccination series, 835/1,193 (70%) vaccine and 836/1,198 (70%) placebo recipients completed their month 48 visit. The primary reason for loss to follow-up was “discontinuation of study” or “withdrew consent.” Other reasons included 11 moves, 3 protocol deviations, 1 pregnancy, and 34 other reasons.

Demographic characteristics at enrollment were balanced among the vaccination groups (Table 1). Tolerability data were essentially unchanged from those previously reported.\(^4\)

In the per-protocol population, administration of the 3-dose regimen of HPV 16 L1 VLP vaccine resulted in a 94% reduction in the incidence of persistent HPV16 infection (Table 2). Vaccine efficacy was 100% for preventing HPV16-related CIN
Among placebo recipients there were 14 subjects with HPV16-related CIN1 and 12 subjects with HPV16-related CIN2 or worse. One woman had CIN2 at one visit and then had CIN3 at a subsequent visit (Table 3). All 24 women with HPV16-related CIN were identified within 3 years of first detection of HPV16 infection (Fig. 2). For cases of persistent HPV16 infection in the placebo group, the median duration of infection was 20.7 months (95% CI 12.1, with no upper bound because longer durations were censored.

The vaccine was 100% efficacious with regard to confirmed persistent HPV16 infections, defined as 2 consecutive HPV16 DNA–positive tests collected 4 or more months apart (Table 2). However, the a priori case definition of persistent infection also included women who were positive at their last visit of record without observed persistence. There were 7 such cases in the vaccine group and 19 in the placebo group. Of note, a total of 32 women tested HPV16 DNA–positive at a single visit before the last visit of record; of these, 16 were among vaccine recipients and 16 were among placebo recipients.

In the MITT-1 cohort (baseline HPV16-naïve population who received at least one dose of vaccine/placebo), HPV16-related CIN developed in 32/166 (19.3%) women with persistent HPV16 infection. All of these cases occurred in the placebo group (Table 3). Similarly, observed efficacy remained high (83%) for prevention of HPV16-related CIN in the MITT-2 population (all women who received at least one dose of vaccine/placebo, regardless of baseline HPV16 status).
In the per-protocol efficacy cohort, administration of the HPV16 L1 VLP vaccine resulted in a 52% reduction in the overall incidence of CIN2–3 and a 30% reduction in the overall incidence of CIN1 caused by any HPV type (Table 4). These reductions did not reach statistical significance. When we examined the effect of vaccine on abnormal Pap rates (data not shown), we observed no statistically significant difference in the incidence of abnormal Pap tests, (ie, ASC-US or more severe), among placebo and vaccine recipients. However, although the number of cases was small, fewer vaccine recipients developed HSIL compared with placebo recipients (1.1 versus 1.5 cases per 100 person-years, respectively).

High anti-HPV16 geometric mean titers were observed after completion of the 3-dose vaccination regimen. Geometric mean titers waned over time, but at month 48, they exceeded geometric mean titers in placebo-recipient women who were anti-HPV16 seropositive at the day 1 visit (Fig. 3).

Although the study was designed to evaluate the prophylactic efficacy of the HPV16 L1 VLP vaccine, the design did allow for a preliminary evaluation of the impact of vaccination on women who already had HPV16 infection at enrollment. To evaluate the possible therapeutic effect of the vaccine on subjects who already had evidence of prior HPV16 infection, we examined a subset of the MITT-2 population. Fifty-one women who received placebo and 47 who received vaccine were HPV16 DNA–positive but HPV16-seronegative at their first visit. In this small cohort, 4 cases of HPV16-related CIN2–3 were detected in the placebo group, but zero in the vaccine group. Cases were counted beginning after day 1. We did not see any benefit in vaccination for women who were HPV16 DNA–positive but seropositive at their first visit. There were 2 cases of HPV16-related CIN2–3 in 42 placebo recipients, but 5 cases in the 44 vaccine recipients. There was no statistically significant difference between the HPV16 L1 VLP vaccine group and the placebo group with respect to the rate of clearance of HPV16 DNA (data not shown).

**DISCUSSION**

These results confirm that an HPV16 L1 VLP vaccine is not only effective for preventing persistent HPV16 infection, but also for preventing HPV16-related CIN2–3. Cervical intraepithelial neoplasia 2–3 is considered a precursor to cervical cancer and is treated with excisional or ablative therapy. Three reports have shown that L1 VLP vaccines are highly efficacious against persistent viral infections, but none had follow-up of sufficient duration to evaluate the effect on the clinical outcome CIN2–3. In our per-protocol population, the vaccine provided 100% protection against HPV16-related CIN2–3.

Ideally, a prophylactic HPV vaccine would be given to children before natural exposure with the onset of sexual activity. The MITT-1 population, which included women who were HPV16-naïve at day 1 and who received at least one vaccine dose (MITT 1), may more closely estimate vaccine effectiveness in an HPV16-naïve population such as preadolescent children. In this MITT-1 cohort, the observed vaccine efficacy with regard to HPV16-related CIN remained 100% (Table 3). If long-term effectiveness is established, consideration could be given to administering the vaccine at a very early age, with other childhood immunizations, to protect girls who experience exposure to...
HPV before the average age of coitarche (eg, sexual abuse, fomite, or digital transmission).

There will be a need to vaccinate many young women whose current HPV status is unknown because the value of testing for specific HPV types, either by DNA or serological methods, is limited.

### Table 3. Analysis of Efficacy for HPV16-Related CIN*

<table>
<thead>
<tr>
<th></th>
<th>HPV16 L1 VLP Vaccine</th>
<th>Placebo (N = 1,198)</th>
<th>Observed Efficacy (%)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td></td>
<td>(N = 1,193)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-protocol population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent HPV16 infection</td>
<td>755</td>
<td>0.3</td>
<td>750</td>
<td>4.9</td>
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<tr>
<td>With HPV16-related CIN</td>
<td>755</td>
<td>0.0</td>
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<td>HPV16 DNA detected at last visit before loss to follow-up</td>
<td>755</td>
<td>0.0</td>
<td>750</td>
<td>0.8</td>
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<tr>
<td>HPV16 DNA detection at &gt; 2 consecutive visits &gt; 4 months apart</td>
<td>755</td>
<td>0.0</td>
<td>750</td>
<td>4.1</td>
</tr>
<tr>
<td>HPV16 DNA detection at &gt; 1 visit</td>
<td>755</td>
<td>0.9</td>
<td>750</td>
<td>5.8</td>
</tr>
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</table>

HPV, human papillomavirus; VLP, virus-like particle; N, number of participants randomized to the respective vaccination group who received at least 1 injection; n, number of participants who had at least one follow-up visit; CI, confidence interval.

* A participant may be counted in more than one row if she developed more than one CIN endpoint, but a participant is only counted once within a row.

† Infection rate per 100 person-years at risk.

‡ Includes one woman with HPV16 DNA detected at 2 visits that were not consecutive.
available. Such testing would only detect current genital HPV DNA and would give no indication of past infection. Estimates of vaccine effectiveness under these conditions are likely to change over time as the prevalence of natural HPV16 infections wanes. Thus, until a time when community prevalence of HPV16 infection is reduced significantly, our MITT-2 analysis may reflect the effectiveness in a population of young sexually active women seeking routine contraception or gynecologic care. Our data suggest that, even under these less than optimal circumstances, effectiveness remained high at 83% for HPV16-related CIN.

Additionally, as new vaccines are developed that immunize against multiple HPV types, identifying women with specific HPV types will be less and less important. Even if a young woman has been exposed to one HPV type included in the vaccine, she may still benefit from protection against disease from other HPV types.

Although this study was not designed to evaluate the possible therapeutic effect of women who have evidence of HPV16 infection before vaccination, we found that among the subcohort of women who were HPV16 DNA-positive at enrollment but anti-HPV16-seronegative, those who received vaccine were less likely to develop subsequent HPV16-related CIN2–3 than those who received placebo injections. We did not see any benefit for women who were already seropositive at enrollment. Despite small numbers, this trend suggests that there may be some benefit to vaccination for women who have more recent infections or are early in the natural history of the disease. Results of larger ongoing clinical trials may provide more information on whether women who have been previously infected with HPV16 will benefit from vaccination.

The natural history of HPV16 infection was well illustrated in the placebo group (Fig. 2). Although progression from CIN2–3 to invasive cervical cancer is believed to occur over many years, it is clear from our cohort that histologic changes become apparent quickly after HPV16 infection. In all but one case, CIN was identified 6–12 months after the detection of HPV16 DNA. The median time to clearance of persistent infections (20.7 months) was similar to that in previously published reports.

In earlier observational studies, HPV16 DNA was detected in 26.6% of women who had HPV-positive low-grade cytologic abnormalities and 45% of women with biopsy-confirmed CIN2–3. Administration of HPV16 vaccine in the study resulted in reductions in the overall rate of CIN1 lesions by 31% and CIN2 or worse lesions by 52% (Table 4). These reductions were consistent with the proportion of these lesions caused by HPV16.

Overall, the observed efficacy for preventing persistent HPV infection (94%) was slightly lower than the 100% reported in the interim analysis report. Seven HPV16 L1 VLP vaccine recipients and 19 placebo recipients had a single HPV16-positive test result on their last visit of record without observed persistence and were counted as persistent cases by a priori definition. Single positive HPV16 test results at the last visit were likely to be caused by a combination of transient infection, contamination, and early persistent infections. Because no follow-up HPV results were available, they were all counted as cases of persistent infection.

We also found 16 women with positive HPV16 DNA tests at a single visit during the study in each of
the vaccine and placebo groups. These single positive visits do not appear to be laboratory artifact because 46 of 47 positive specimens were positive by at least 2 of 3 genes. Only one specimen was positive due to a single gene. The cases were not clustered at any particular recruitment site or from any particular specimen type. Also, these sporadic cases did not cluster at the end of the study, implying that there was no decrease in protection from vaccine over time. When we compared single positive infections with HPV16 antibody titers, we found that all subjects in the vaccine group sero-converted and that single positive results were not associated with low titers. These data suggest that transient HPV infections may occur even with vaccination. Only 2 vaccine recipients had a low antibody titer (below the level of detection) at a follow-up visit.

Our study showed that HPV16 L1 VLP vaccine provided protection against persistent HPV16 infections for an average of 3.5 years after vaccination. Previous studies indicate that young women are likely to have multiple HPV exposures from coitarche through their reproductive years. Therefore, establishing the durability of protection for longer periods of time is essential. More importantly, the HPV16 L1 VLP vaccine provided 100% protection against development of HPV16-related precursors, CIN2–3, in the MITT-1 population (baseline HPV16-naïve women who received at least one dose of vaccine/placebo) during the average 3.5 years follow-up. These results demonstrate that HPV VLP vaccines have the potential to significantly reduce the incidence of cervical cancer worldwide.

REFERENCES


Table 4. Analysis of Efficacy for CIN Due to Any HPV Type

<table>
<thead>
<tr>
<th>Per protocol</th>
<th>HPV16 L1 VLP Vaccine (N = 1,193)</th>
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<th>Observed Efficacy (%)</th>
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<tr>
<td>n</td>
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<td>544</td>
<td>7</td>
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</tr>
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</table>

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VLP, virus-like particle; N, number of participants randomized to the respective vaccination group who received at least 1 injection; n, number of participants who had at least one follow-up visit; CI, confidence interval.

* A participant may be counted in more than one row if she developed more than one CIN endpoint, but a participant is only counted once within a row.

† Infection rate per 100 person-years at risk.


APPENDIX

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