

ORIGINAL ARTICLE

Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases

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ABSTRACT

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BACKGROUND

A phase 3 trial was conducted to evaluate the efficacy of a prophylactic quadrivalent vaccine in preventing anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18.

METHODS

In this randomized, placebo-controlled, double-blind trial involving 5455 women between the ages of 16 and 24 years, we assigned 2723 women to receive vaccine and 2732 to receive placebo at day 1, month 2, and month 6. The coprimary composite end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18. Data for the primary analysis were collected for a per-protocol susceptible population of women who had no virologic evidence of HPV type 6, 11, 16, or 18 through 1 month after administration of the third dose.

RESULTS

The women were followed for an average of 3 years after administration of the first dose. In the per-protocol population, those followed for vulvar, vaginal, or perianal disease included 2261 women (83%) in the vaccine group and 2279 (83%) in the placebo group. Those followed for cervical disease included 2241 women (82%) in the vaccine group and 2258 (83%) in the placebo group. Vaccine efficacy was 100% for each of the coprimary end points. In an intention-to-treat analysis, including those with prevalent infection or disease caused by vaccine-type and non-vaccine-type HPV, vaccination reduced the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% confidence interval [CI], 15 to 49), and the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI, 8 to 31).

CONCLUSIONS

The quadrivalent vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women. (ClinicalTrials.gov number, NCT00092521.)

ANOGENITAL INFECTION WITH THE HUMAN papillomavirus (HPV) can cause warts, intraepithelial neoplasia, and invasive cancers.¹⁻⁶ The majority of HPV-associated diseases are caused by HPV types 6, 11, 16, and 18. HPV types 6 (HPV-6) and 11 (HPV-11) cause most anogenital warts, a portion of the cases of low-grade neoplasia,^{5,7-10} and recurrent respiratory papillomatosis, a rare but potentially life-threatening disease.¹¹⁻¹³ HPV type 16 (HPV-16) is the most common cause of invasive cancers of the cervix and other anogenital cancers associated with HPV.^{4,6,14-19} HPV type 18 (HPV-18), the second most common cause of cervical cancer, is detected even more frequently in adenocarcinoma, the incidence of which is increasing.^{18,20,21} The precursor lesion of adenocarcinoma is difficult to detect on routine Papanicolaou testing or colposcopy.^{21,22} A phase 3 trial of the efficacy and safety of a quadrivalent HPV vaccine (targeting HPV-6, HPV-11, HPV-16, and HPV-18) was designed to include an intensive schedule of visits and aggressive regimens to identify cases of genital disease associated with HPV in the study population.

METHODS

STUDY DESIGN

The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I study is an ongoing, double-blind, placebo-controlled, randomized trial sponsored by Merck; the study was designed and managed and the results were analyzed by the sponsor in conjunction with external academic investigators and an external data and safety monitoring board. From January 2002 through March 2003, 6463 women underwent screening for eligibility; of these, we enrolled a total of 5455 (84%) subjects between the ages of 16 and 24 years at 62 study sites in 16 countries. The institutional review board at each site approved the protocol. Written informed consent was obtained from each subject. The study population was drawn primarily from communities near universities. Healthy women who were not pregnant and had no history of genital warts or abnormal results on cervical cytologic testing and had a lifetime number of no more than four sex partners were eligible. The women were required to use effective contraception during the vaccination period (day 1 through month 7) of the study.

The sponsor collated the data and monitored

the conduct of the study. The cutoff date for this manuscript was June 15, 2006. The sponsor and the academic authors proposed the statistical analyses, which were performed by the sponsor. All authors had full access to these analyses and approved the final manuscript. The manuscript was drafted by employees of the sponsor in collaboration with academic authors. All authors vouch for the completeness and accuracy of the data presented.

VACCINE AND RANDOMIZATION

The quadrivalent HPV-6/11/16/18 L1 virus-like-particle vaccine with amorphous aluminum hydroxyphosphate sulfate (Gardasil, Merck) as an adjuvant and the aluminum-containing placebo were visually indistinguishable and have been described elsewhere.²³ A description of the randomization procedure used in the trial can be found in the Supplementary Appendix, available with the full text of this article at www.nejm.org. Vaccine or placebo was administered after a negative result on a pregnancy test of the urine or blood.

The women were observed for 30 minutes after vaccination. Each woman recorded oral temperatures on a vaccination report card 4 hours after receiving the injection and once daily for the next 4 days. Adverse events were recorded with the use of the vaccination report cards for 15 days after vaccination, as were all serious adverse events potentially related to the procedure or vaccine, deaths, and pregnancy outcomes throughout the trial.

FOLLOW-UP

At day 1 (the day of the first injection of vaccine or placebo), month 7 (1 month after administration of the third dose), and months 12, 24, 36, and 48, the women underwent a gynecologic examination. At day 1, month 3 (1 month after administration of the second dose), and months 7, 12, 18, 24, 30, 36, and 48, they underwent a comprehensive anogenital examination at which an endocervical and ectocervical swab specimen (considered to be one specimen), a combined labial-vulvar-perineal swab specimen, and a perianal swab specimen (pooled as one specimen) were collected. For a description of the anti-HPV testing and HPV DNA testing, see the Supplementary Appendix. At day 1 and months 7, 12, 18, 24, 30, 36, and 48, cervical samples for Papanicolaou cytologic testing (ThinPrep, Cytyc) were collected.

LESIONS

Each study site was provided with a detailed protocol describing the anogenital examination, which included visual inspection of the perianal, vulvar, and vaginal areas observed with the unaided eye, a magnifying glass, or a colposcope. Overt lesions were photographed. Biopsy specimens of lesions considered to be clinically associated with HPV or of unknown cause were obtained. Repeated biopsy of recurrent external anogenital or vaginal lesions was not performed. The treatment of lesions was based on local standards of care. Cervical cytologic specimens were classified according to the Bethesda system (2001) and read at a central laboratory (Diagnostic Cytology Laboratories).²⁴ For the criteria for referral for colposcopy, see the Supplementary Appendix. All biopsy specimens were processed independently to avoid contamination of HPV DNA and were read in a blinded fashion first for clinical management by pathologists at the central laboratory, then for end-point adjudication by a panel of four gynecologic pathologists, as described in the report by the FUTURE II study group elsewhere in this issue of the *Journal*.²⁵

CASE DEFINITION AND PRIMARY HYPOTHESES

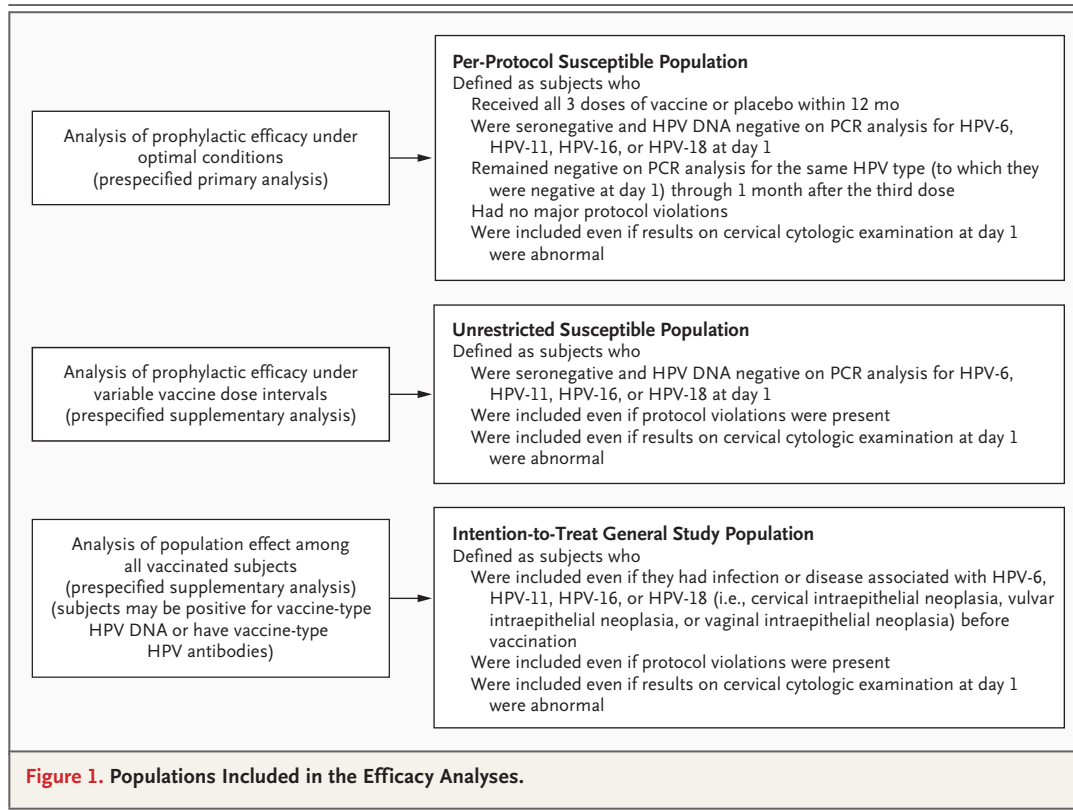
There were two efficacy hypotheses. The first stated that, as compared with placebo, the quadrivalent vaccine reduces the combined incidence of anogenital warts, vulvar or vaginal intraepithelial neoplasia grades 1 to 3, or cancer associated with vaccine-type HPV; the second stated that, as compared with placebo, the quadrivalent vaccine reduces the combined incidence of cervical intraepithelial neoplasia grades 1 to 3, adenocarcinoma in situ, or cancer associated with vaccine-type HPV. A case was defined as a consensus diagnosis by the pathology panel of one of these end-point events, with vaccine-type HPV DNA detected in an adjacent histologic section of the same biopsy specimen (Fig. 1 in the Supplementary Appendix). The subject and the investigator were informed of the need for further treatment if the panel rendered a more clinically significant diagnosis. Clinical impressions were recorded but were not used to determine an end point in the efficacy analysis.

STATISTICAL ANALYSIS

A fixed-event design was used for the statistical analysis. At least 38 cases of external anogenital or vaginal lesions associated with vaccine-type HPV

and at least 38 cases of cervical lesions associated with vaccine-type HPV were required for the study to have 91% power to declare the vaccine efficacious against at least one of the primary composite end points with a one-sided alpha level of significance of 0.0125 (incorporating multiplicity adjustment), assuming a true vaccine efficacy of at least 80%. To reach the requisite numbers of each of the end points by month 36 in the primary analysis population, and an assumed event rate of 1% per year for each of the coprimary end points, approximately 5400 participants were required. An analysis was conducted when 38 external anogenital and vaginal end-point events and 37 cervical end-point events had occurred (at approximately 1.5 years of follow-up after administration of the third dose, and including all data from visits occurring on or before July 15, 2005). This analysis was included in the application for vaccine licensure, which was approved by the Food and Drug Administration on June 8, 2006. The efficacy and safety analyses presented here include an additional year of follow-up from this ongoing study and data from visits that occurred on or before June 15, 2006.

For each of the primary composite end points, the primary efficacy analysis (Fig. 1) was conducted in the HPV-type-specific per-protocol susceptible populations, defined as subjects who were negative on polymerase-chain-reaction (PCR) analysis and serologic testing for the relevant vaccine-type HPV at enrollment, remained negative for the same vaccine-type HPV through 1 month after administration of the third dose of vaccine or placebo, received three doses of vaccine or placebo within 1 year, and did not have protocol violations. Follow-up for case ascertainment started 1 month after administration of the third dose. An exact conditional procedure was used to evaluate vaccine efficacy, assuming that the numbers of cases in the vaccine group and the placebo group were independent Poisson random variables.²⁶ A point estimate of vaccine efficacy and the 95% confidence interval (CI) were calculated on the basis of the observed split in cases between the vaccine and placebo recipients and the accrued person-time. For subjects who had more than one end-point event, only the first event in a category was counted as a case (defined as a consensus diagnosis), but a subject with more than one end-point event could be counted in more than one category of end-point events.



The analyses were performed with respect to the primary composite end points and were further characterized according to type of lesion and vaccine-type HPV. A woman who had a single lesion containing more than one vaccine-type HPV or multiple lesions of different histologic grades was counted once toward the composite end points and once toward the type-specific and lesion-specific end points. For example, for a woman found by consensus diagnosis to have a cervical intraepithelial neoplasia grade 2 lesion associated with HPV-16 at month 12, this end-point event would be counted as a case at month 12. Subsequently, the same subject may have been diagnosed with an HPV-16-associated cervical intraepithelial neoplasia grade 3 lesion and an HPV-18-associated cervical intraepithelial neoplasia grade 2 lesion at month 19. Overall, on the basis of these consensus diagnoses, this subject would be counted once toward the primary composite end point, once toward HPV-16-associated end points, once toward HPV-18-associated end points, once toward cervical intraepithelial neoplasia grade 2, and once toward cervical intraepithelial neoplasia grade 3.

A description of the two additional populations

that were included in the prespecified analyses supportive of the primary analysis is shown in Figure 1. Vaccine efficacy was estimated in an unrestricted susceptible population that included all women who were negative on PCR analysis and serologic testing for the relevant vaccine-type HPV at enrollment. We also estimated vaccine efficacy in an intention-to-treat population that included all subjects who had undergone randomization, regardless of their baseline HPV status or evidence of HPV-associated anogenital disease. Follow-up for end-point ascertainment in these two additional populations started after day 1. The analyses in the intention-to-treat population evaluated vaccine efficacy against diseases associated with vaccine-type HPV and the overall effect of vaccination on the number of cases of prevalent and incident disease (caused by vaccine-type HPV or other HPV types). For the intention-to-treat analysis, the cumulative incidence distribution²⁷ was computed for subjects in the vaccine and placebo groups for whom follow-up data were available and was presented graphically for the composite end points, with 95% CIs calculated at 6-month intervals.

Geometric mean antibody titers for vaccine-

type HPV and seroconversion rates were measured in subjects included in the type-specific, per-protocol immunogenicity analysis. These subjects were members of the per-protocol population from whom serum samples had been collected during predefined periods.

Adverse events were summarized as frequencies and percentages according to study group and the type of adverse event reported at all visits for the administration of a dose of vaccine or placebo. Risk differences and the associated 95% CIs were calculated by comparing the vaccine and placebo groups for all vaccination visits. A 95% CI (unadjusted for multiplicity testing) that does not include 0 indicates a nominally significant difference at an alpha level of 0.05 (two-sided).

RESULTS

From January 2002 through March 2003, a total of 6463 women between the ages of 16 and 24 years were screened for eligibility at 62 study sites in the Asia-Pacific region, Europe, and North, Central, and South America. Of these women, 5455 met the inclusion criteria, and 2723 women were randomly assigned to receive quadrivalent vaccine and 2732 were assigned to receive placebo. Only a small percentage (8 of 5388 subjects [0.15%]) had serologic evidence or HPV DNA evidence of infection with all the HPV types covered by the quadrivalent vaccine (Table 1). The two study groups were well balanced with regard to baseline characteristics and were also similar in the numbers of subjects excluded from the populations analyzed. Subjects in whom vaccine-type HPV was detected at baseline were excluded from the analyses for prophylactic efficacy (Table 2).

Subjects in this ongoing trial were followed for an average of 3 years after administration of the first dose of vaccine or placebo. At least 83% of those who underwent randomization were included in one or more of the type-specific, per-protocol susceptible populations for external anogenital or vaginal lesions (2261 subjects in the vaccine group and 2279 in the placebo group). The HPV vaccine was 100% effective (95% CI, 94 to 100; 0 cases in the vaccine group vs. 60 cases in the placebo group) in preventing vaginal, vulvar, perineal, and perianal intraepithelial lesions or warts in association with vaccine-type HPV. In the type-specific, per-protocol susceptible populations, in the analysis for cervical end points, among 2241

subjects in the vaccine group and 2258 in the placebo group, the vaccine was 100% effective (95% CI, 94 to 100; 0 vs. 65 cases, respectively) in preventing cervical intraepithelial neoplasia of grades 1 to 3 or adenocarcinoma in situ in association with vaccine-type HPV (Table 3). The estimates of vaccine efficacy made on the basis of the diagnoses at the central laboratory were similar to the estimates made by the pathology panel (data not shown).

More than 95% of the subjects who underwent randomization were included in one or more of the type-specific, unrestricted susceptible populations. The vaccine efficacy was 95% when all grades of external anogenital or vaginal lesions were combined (4 cases in the vaccine group vs. 81 cases in the placebo group), 98% when all grades of cervical lesions were combined (2 vs. 89 cases, respectively), with an efficacy of 91% for high-grade vulvar or vaginal lesions (1 vs. 11 cases, respectively), and 100% for adenocarcinoma in situ (0 vs. 6 cases, respectively) (Table 3). Overall, more than 95% of the subjects received the complete regimen of three doses of vaccine or placebo.

Because the public health benefit of a safe and effective HPV vaccine will be measured by its effect in all vaccinated women, we estimated vaccine efficacy in an intention-to-treat population, regardless of the baseline HPV status of the subjects included in the analysis (Table 3). The analysis included women with prevalent infections with vaccine-type HPV or diseases associated with these HPV types. The efficacy against vaccine-type HPV was 73% (95% CI, 58 to 83) when all grades of external anogenital or vaginal lesions were combined (28 cases in the vaccine group vs. 102 cases in the placebo group) and 55% (95% CI, 40 to 66) when all grades of cervical lesions were combined (71 vs. 155 cases, respectively) (Table 3). In the intention-to-treat population, in the placebo group, the incidence of external anogenital or cervical disease associated with vaccine-type HPV continued to increase over time, whereas in the vaccine group the incidence began to plateau (Fig. 2). There was no clear evidence that vaccination altered the course of disease or infection present before administration of the first dose (Table 2 in the Supplementary Appendix). No cancers associated with any vaccine-type HPV were identified.

A second intention-to-treat analysis in the

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Vaccine Group (N = 2723)	Placebo Group (N = 2732)
General		
Mean age — yr	20.2±1.8	20.3±1.8
Geographic region — no./total no. (%)		
Asia–Pacific	257/2723 (9.4)	264/2732 (9.7)
North America	796/2723 (29.2)	801/2732 (29.3)
Latin America	1107/2723 (40.7)	1108/2732 (40.6)
Europe	563/2723 (20.7)	559/2732 (20.5)
Current smoker — no. (%)	696/2723 (25.6)	716/2732 (26.2)
Sexual and gynecologic history		
Mean age at first sexual intercourse — yr	16.9±1.9	16.9±1.9
Median lifetime no. of sex partners†	2	2
Past pregnancy — no./total no. (%)	752/2723 (27.6)	753/2732 (27.6)
Type of contraceptive use — no./total no. (%)		
Barrier	872/2717 (32.1)	874/2725 (32.1)
Behavioral‡	487/2717 (17.9)	498/2725 (18.3)
Hormonal	1568/2717 (57.7)	1539/2725 (56.5)
Other	125/2717 (4.6)	138/2725 (5.1)
Prevalence of <i>Chlamydia trachomatis</i> — no./total no. (%)	118/2683 (4.4)	135/2680 (5.0)
Prevalence of <i>Neisseria gonorrhoeae</i> — no./total no. (%)	10/2679 (0.4)	9/2679 (0.3)
Baseline HPV-associated pathological finding — no./total no. (%)		
Abnormality on cervical cytologic examination	288/2648 (10.9)	316/2642 (12.0)
DNA positive for one or more types of vaccine-type HPV on PCR analysis	385/2693 (14.3)	358/2705 (13.2)
HPV-6	102/2687 (3.8)	94/2704 (3.5)
HPV-11	17/2688 (0.6)	16/2703 (0.6)
HPV-16	238/2684 (8.9)	227/2698 (8.4)
HPV-18	86/2686 (3.2)	83/2704 (3.1)
Positive for one or more types of vaccine-type HPV on serologic testing	545/2717 (20.1)	522/2724 (19.2)
HPV-6	207/2714 (7.6)	194/2722 (7.1)
HPV-11	60/2714 (2.2)	61/2722 (2.2)
HPV-16	312/2714 (11.5)	319/2722 (11.7)
HPV-18	93/2714 (3.4)	90/2722 (3.3)
Positive for one or more types of vaccine-type HPV on PCR analysis or serologic testing	731/2687 (27.2)	711/2701 (26.3)
Positive for all vaccine-type HPV on PCR analysis or serologic testing	1/2687 (<0.04)	7/2701 (<0.3)

* For each study group, percentages were calculated as the number of subjects with the characteristic divided by the number of subjects with a known response or satisfactory test result times 100. Plus–minus values are means ±SD.

† The median lifetime number of sex partners was calculated only for subjects who were nonvirgins.

‡ Behavioral methods of contraception include abstinence, rhythm, and withdrawal.

population of all women who underwent randomization was performed to evaluate the effectiveness of the vaccine against all anogenital disease (i.e., caused by either a vaccine-type HPV or one

not covered by the vaccine). For the primary composite disease end points, in the vaccine group there was a reduction of 34% (95% CI, 15 to 49; 104 cases in the vaccine group vs. 157 cases in

Table 2. Subjects Included in and Excluded from the Different Analyses.*		
Variable	Vaccine Group (N = 2723)	Placebo Group (N = 2732)
	<i>no. (%)</i>	
Per-protocol susceptible population†		
Analysis of external anogenital and vaginal lesions for vaccine-type HPV		
HPV-6 and HPV-11	1978 (72.6)	1991 (72.9)
HPV-16	1890 (69.4)	1855 (67.9)
HPV-18	2120 (77.9)	2136 (78.2)
Analysis of CIN for vaccine-type HPV		
HPV-6 and HPV-11	1961 (72.0)	1975 (72.3)
HPV-16	1888 (69.3)	1847 (67.6)
HPV-18	2102 (77.2)	2120 (77.6)
Unrestricted susceptible population‡		
Analysis of external anogenital and vaginal lesions for vaccine-type HPV		
HPV-6 and HPV-11	2373 (87.1)	2399 (87.8)
HPV-16	2248 (82.6)	2259 (82.7)
HPV-18	2523 (92.7)	2550 (93.3)
Analysis of CIN for vaccine-type HPV		
HPV-6 and HPV-11	2373 (87.1)	2399 (87.8)
HPV-16	2248 (82.6)	2259 (82.7)
HPV-18	2523 (92.7)	2550 (93.3)
Intention-to-treat general population§		
Analysis of external anogenital and vaginal lesions for vaccine-type HPV		
	2723 (100)	2732 (100)
Analysis of CIN for vaccine-type HPV		
	2723 (100)	2732 (100)
Reasons for exclusion in the per-protocol susceptible population and the unrestricted susceptible population¶		
Seropositive, positive on PCR, or both for HPV-6 or HPV-11 at day 1	315 (11.6)	302 (11.1)
Seropositive, positive on PCR, or both for HPV-16 at day 1	441 (16.2)	441 (16.1)
Seropositive, positive on PCR, or both for HPV-18 at day 1	163 (6.0)	151 (5.5)
Missing blood samples or results of serologic testing for day 1	0	1 (0.04)
Blood sample for day 1 out of acceptable range**	3 (0.1)	2 (<0.1)
Missing swab specimen or results for day 1	51 (1.9)	42 (1.5)
Swab specimen for day 1 out of acceptable range††	0	1 (0.04)

the placebo group) in the incidence of external anogenital or vaginal lesions and a reduction of 20% (95% CI, 8 to 31; 344 vs. 421 cases, respectively) in cervical lesions, regardless of the causal HPV type (Table 3 and Fig. 2).

For each HPV type covered by the quadrivalent vaccine, at least 99.5% of the subjects in the respective per-protocol immunogenicity cohort had seroconversion at 1 month after the third dose. (For details on the persistence of immune titers, see the Supplementary Appendix.) Five of six re-

cipients of the quadrivalent vaccine in the unrestricted susceptible population who had a genital lesion associated with vaccine-type HPV had antibody titers for an anti-HPV response that were similar to the corresponding anti-HPV antibody response in the per-protocol immunogenicity population. The sixth subject had incorrectly received three doses of placebo.

Vaccine recipients (87%) were more likely than placebo recipients (77%) to have adverse events at the injection site, the most common of these

Table 2. (Continued.)

Variable	Vaccine Group (N=2723)	Placebo Group (N=2732) <i>no. (%)</i>
Reasons for exclusion in the per-protocol susceptible population only¶		
General protocol violations‡‡	199 (7.3)	187 (6.8)
Missed second and third doses of vaccine or placebo	63 (2.3)	69 (2.5)
Missed third dose of vaccine or placebo	117 (4.3)	126 (4.6)
Missing swab specimens or results for month 3§§	148 (5.4)	170 (6.2)
Missing swab specimens or results for month 7¶¶	60 (2.2)	48 (1.8)
Seropositive, positive on PCR, or both for HPV-6 or HPV-11 at or before month 7 (inclusive)¶	363 (13.3)	374 (13.7)
Seropositive, positive on PCR, or both for HPV-16 at or before month 7 (inclusive)¶	476 (17.5)	539 (19.7)
Seropositive, positive on PCR, or both for HPV-18 at or before month 7 (inclusive)¶	195 (7.2)	204 (7.5)

* CIN denotes cervical intraepithelial neoplasia.
 † The per-protocol susceptible population was defined as subjects who were negative on PCR analysis and serologic testing for the relevant HPV type at enrollment, remained negative on PCR analysis for the same HPV type through 1 month after administration of the third dose of vaccine or placebo, received three doses of vaccine or placebo within 1 year, and did not have protocol violations.
 ‡ The unrestricted susceptible population was defined as subjects who did not test positive for the relevant HPV type at enrollment.
 § The intention-to-treat population was defined as subjects who underwent randomization, including those with prevalent anogenital disease or infections caused by any high- or low-risk HPV type before the administration of vaccine or placebo.
 ¶ Subjects may have been excluded for more than one reason.
 || This reason for exclusion applies only to the populations included in the analysis for the respective HPV type. For day 1, the analysis includes a positive result on either serologic testing or PCR. Through month 7, the analysis includes a positive result only on PCR.
 ** Blood samples obtained more than 14 days before administration of the first dose of vaccine or placebo were considered to be unacceptable.
 †† Swab specimens obtained more than 14 days before or 10 days after administration of the first dose of vaccine or placebo were considered to be unacceptable.
 ‡‡ The most common general protocol violations were collection of a specimen or sample at month 7 beyond the acceptable range (147 subjects) and receipt of nonstudy vaccine (72 subjects).
 §§ The month 3 visit was defined as the visit 1 month after administration of the second dose of vaccine or placebo.
 ¶¶ The month 7 visit was defined as the visit 1 month after administration of the third dose of vaccine or placebo.

being pain at the site (risk difference, 10 percentage points; 95% CI, 7.8 to 12.1). Erythema, pruritus, and swelling at the injection site were also more common among vaccine recipients than among placebo recipients (Table 4). With respect to systemic adverse events, a nominally higher proportion of vaccine recipients (13.3%), as compared with placebo recipients (10.3%), reported fever between 100°F (37.8°C) and 102°F (38.9°C) (risk difference, 3.0; 95% CI, 1.3 to 4.8) (Table 4). Similar proportions of vaccine and placebo recipients reported a serious adverse event. All systemic and serious adverse events, categorized according to organ system and treatment group, are shown in Tables 3 and 4 in the Supplementary Appendix.

Among the subjects who were seropositive for one or more of the four HPV types at day 1, the profile of adverse events was similar to that of the entire study cohort. For example, of 529 vaccine recipients, 452 (85%) reported one or more injection-site adverse events, as compared with 388 of 507 placebo recipients (77%), with injec-

tion-site pain reported as the most frequent adverse event in 84% of the vaccine recipients and 74% of the placebo recipients (risk difference, 10.1; 95% CI, 5.2 to 15.1) (Table 4). One subject in this subgroup had a serious vaccine-related adverse event (bronchospasm 1 day after receipt of the third dose). No multiplicity adjustments were made for these comparisons. For a summary of the pregnancy outcomes in the combined phase 3 quadrivalent vaccine studies, see the report by the FUTURE II study group (and Tables 2, 3, and 4 in that article's Supplementary Appendix).²⁵

DISCUSSION

These results of the FUTURE I study show that a prophylactic quadrivalent HPV vaccine is highly effective in preventing clinical disease, including anogenital warts and intraepithelial neoplasia of the cervix, vagina, and vulva, associated with HPV-6, HPV-11, HPV-16, and HPV-18. There appears to be no interference among the four HPV types

Table 3. Vaccine Efficacy against External Anogenital, Vaginal, and Cervical Lesions Associated with HPV-6, HPV-11, HPV-16, or HPV-18 or Regardless of HPV Type.*

End Point	Vaccine Group (N=2723)			Placebo Group (N=2732)			Efficacy % (95% CI)
	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	
Lesions associated with vaccine-type HPV							
Per-protocol susceptible population†							
External anogenital and vaginal lesions	2261	0	0	2279	60	1.1	100 (94–100)
According to type of lesion							
Condyloma	2261	0	0	2279	48	0.9	100 (92–100)
Vulvar condyloma	2261	0	0	2279	47	0.8	100 (92–100)
Vaginal condyloma	2261	0	0	2279	6	0.1	100 (14–100)
VIN grade 1 or VaIN grade 1	2261	0	0	2279	9	0.2	100 (49–100)
VIN grade 2 or 3 or VaIN grade 2 or 3	2261	0	0	2279	9	0.2	100 (49–100)
According to vaccine-type HPV							
HPV-6	1978	0	0	1991	41	0.8	100 (91–100)
HPV-11	1978	0	0	1991	12	0.2	100 (64–100)
HPV-16	1890	0	0	1855	12	0.3	100 (65–100)
HPV-18	2120	0	0	2136	3	0.1	100 (<0–100)
Cervical lesions	2241	0	0	2258	65‡	1.2	100 (94–100)
According to grade of lesion							
CIN grade 1	2241	0	0	2258	49	0.9	100 (92–100)
CIN grade 2	2241	0	0	2258	21	0.4	100 (81–100)
CIN grade 3	2241	0	0	2258	17	0.3	100 (76–100)
Adenocarcinoma in situ	2241	0	0	2258	6	0.1	100 (15–100)
According to vaccine-type HPV							
HPV-6	1961	0	0	1975	12	0.3	100 (64–100)
HPV-11	1961	0	0	1975	4	0.1	100 (<0–100)
HPV-16	1888	0	0	1847	39	0.9	100 (90–100)
HPV-18	2102	0	0	2120	16	0.3	100 (74–100)
Unrestricted susceptible population§							
External anogenital and vaginal lesions¶	2667	4	0.1	2684	81	1.1	95 (87–99)
According to type of lesion							
Condyloma	2667	3	<0.1	2684	67	0.9	96 (86–99)
Vulvar condyloma	2667	2	<0.1	2684	65	0.8	97 (88–100)
Vaginal condyloma	2667	1	<0.1	2684	8	0.1	87 (6–100)
VIN grade 1 or VaIN grade 1	2667	2	<0.1	2684	11	0.1	82 (16–98)
VIN grade 2 or 3 or VaIN grade 2 or 3	2667	1	<0.1	2684	11	0.1	91 (37–100)
According to vaccine-type HPV							
HPV-6	2373	2	<0.1	2399	53	0.8	96 (86–100)
HPV-11	2373	1	<0.1	2399	17	0.2	94 (62–100)
HPV-16	2248	1	<0.1	2259	17	0.3	94 (62–100)
HPV-18	2523	0	0	2550	8	0.1	100 (41–100)

Table 3. (Continued.)

End Point	Vaccine Group (N=2723)			Placebo Group (N=2732)			Efficacy % (95% CI)
	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	
Cervical lesions	2667	2**	<0.1	2684	89††	1.2	98 (92–100)
According to type of lesion							
CIN grade 1	2667	2	<0.1	2684	68	0.9	97 (89–100)
CIN grade 2	2667	0	0	2684	28	0.4	100 (86–100)
CIN grade 3	2667	0	0	2684	24	0.3	100 (83–100)
Adenocarcinoma in situ	2667	0	0	2684	6	0.1	100 (15–100)
According to vaccine-type HPV							
HPV-6	2373	1	<0.1	2399	17	0.3	94 (62–100)
HPV-11	2373	0	0	2399	7	0.1	100 (31–100)
HPV-16	2248	0	0	2259	53	0.8	100 (93–100)
HPV-18	2523	1	<0.1	2550	22	0.3	95 (72–100)
Intention-to-treat population							
External anogenital and vaginal lesions‡‡	2723	28	0.4	2732	102	1.3	73 (58–83)
According to type of lesion							
Condyloma	2723	21	0.3	2732	86	1.1	76 (61–86)
Vulvar condyloma	2723	18	0.2	2732	82	1.1	78 (63–88)
Vaginal condyloma	2723	3	<0.1	2732	10	0.1	70 (<0–95)
VIN grade 1 or VaIN grade 1	2723	6	0.1	2732	16	0.2	63 (<0–88)
VIN grade 2 or 3 or VaIN grade 2 or 3	2723	5	0.1	2732	13	0.2	62 (<0–89)
According to vaccine-type HPV							
HPV-6	2723	20	0.3	2732	70	0.9	72 (53–84)
HPV-11	2723	2	<0.1	2732	19	0.2	90 (57–99)
HPV-16	2723	6	0.1	2732	22	0.3	73 (31–91)
HPV-18	2723	1	<0.1	2732	9	0.1	89 (20–100)
Cervical lesions§§	2723	71¶¶	0.9	2732	155¶¶	2.1	55 (40–66)
According to grade of lesion							
CIN grade 1	2723	45	0.6	2732	118	1.6	62 (46–74)
CIN grade 2	2723	36	0.5	2732	51	0.7	30 (<0–56)
CIN grade 3	2723	39	0.5	2732	44	0.6	12 (<0–44)
Adenocarcinoma in situ	2723	1	<0.1	2732	6	0.1	83 (<0–100)
According to vaccine-type HPV							
HPV-6	2723	7	0.1	2732	26	0.3	73 (37–90)
HPV-11	2723	0	0	2732	11	0.1	100 (60–100)
HPV-16	2723	58	0.8	2732	106	1.4	46 (25–61)
HPV-18	2723	8	0.1	2732	33	0.4	76 (47–90)
Lesions associated with any HPV type							
All external anogenital and vaginal lesions‡‡	2723	104	1.3	2732	157	2.1	34 (15–49)
According to type of lesion							
Condyloma	2723	55	0.7	2732	111	1.4	51 (32–65)
Vulvar condyloma	2723	48	0.6	2732	100	1.3	52 (32–67)
Vaginal condyloma	2723	8	0.1	2732	17	0.2	53 (<0–82)

Table 3. (Continued.)

End Point	Vaccine Group (N=2723)			Placebo Group (N=2732)			Efficacy % (95% CI)
	No. of Subjects	No. of Cases	Rate per 100 Person- Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person- Years at Risk	
Lesions associated with any HPV type							
VIN grade 1 or VaIN grade 1	2723	45	0.6	2732	55	0.7	18 (<0–46)
VIN grade 2 or 3 or VaIN grade 2 or 3	2723	17	0.2	2732	23	0.3	26 (<0–63)
Vulvar cancer ^{¶¶}	2723	1	<0.1	2732	0	0	NA
All cervical lesions (any HPV type) ^{§§}	2723	344	4.7	2732	421	5.9	20 (8–31)
According to grade of lesion							
CIN grade 1	2723	277	3.8	2732	363	5.0	25 (12–36)
CIN grade 2	2723	102	1.3	2732	116	1.5	13 (<0–34)
CIN grade 3	2723	79	1.0	2732	72	1.0	–9 (<0–22)
Adenocarcinoma in situ	2723	1	<0.1	2732	6	0.1	83 (<0–100)

- * In each category, a subject is counted only once, but some subjects are counted in more than one category. VIN denotes vulvar intraepithelial neoplasia, VaIN vaginal intraepithelial neoplasia, CIN cervical intraepithelial neoplasia, and NA not applicable.
- † The per-protocol susceptible population was defined as subjects who were negative on PCR analysis and serologic testing for the relevant HPV type at enrollment, remained negative on PCR analysis for the same HPV type through 1 month after administration of the third dose of vaccine or placebo, received three doses of vaccine or placebo within 1 year, and did not have protocol violations.
- ‡ Among the 65 subjects in the placebo group with end-point events (cases, defined by consensus diagnosis) of cervical lesions associated with vaccine-type HPV presented according to the severity of the histologic findings, 33 subjects with CIN had grade 1 lesions, 13 had grade 2 lesions, 13 had grade 3 lesions, and 6 subjects had adenocarcinoma in situ.
- § The unrestricted susceptible population included subjects who did not test positive for the relevant HPV type at enrollment.
- ¶ Of subjects in the unrestricted susceptible population who received at least one dose of vaccine or placebo and had at least one follow-up visit after administration of the first dose, 2621 in the vaccine group and 2629 in the placebo group were included in the analysis for end points associated with vaccine-type HPV: 2335 and 2353, respectively, were included in the analysis for end points associated with HPV-6 and HPV-11; 2216 and 2216, respectively, in the analysis for end points associated with HPV-16; and 2481 and 2503, respectively, in the analysis for end points associated with HPV-18.
- ¶¶ Of subjects in the unrestricted susceptible population who received at least one dose of vaccine or placebo and had at least one follow-up visit after administration of the first dose, 2559 in the vaccine group and 2576 in the placebo group were included in the analysis for end points associated with vaccine-type HPV: 2282 and 2307, respectively, in the analysis for end points associated with HPV-6 and HPV-11; 2159 and 2173, respectively, in the analysis for end points associated with HPV-16; and 2425 and 2452, respectively, in the analysis for end points associated with HPV-18.
- ** One subject in the vaccine group received three doses of placebo in error.
- †† Among the 89 subjects in the placebo group with end-point events (cases, defined as consensus diagnosis) of cervical lesions associated with vaccine-type HPV presented according to the severity of the histologic findings, 46 subjects with CIN had grade 1 lesions, 17 had grade 2 lesions, 20 had grade 3 lesions, and 6 subjects had adenocarcinoma in situ.
- ‡‡ Of the randomized subjects, 2672 in the vaccine group and 2669 in the placebo group received at least one dose of the assigned treatment and had at least one follow-up visit for the end-point analysis for external anogenital lesions.
- §§ Of the randomized subjects, 2609 in the vaccine group and 2615 in the placebo group received at least one dose of the assigned treatment and had at least one follow-up visit for end-point analysis for cervical lesions.
- ¶¶¶ Among the 226 subjects in the two groups with end-point events (cases, as defined by consensus diagnosis) of cervical lesions associated with vaccine-type HPV presented according to the severity of the histologic findings, in the vaccine group, 19 subjects had grade 1 lesions, 13 had grade 2 lesions, 38 had grade 3 lesions, and 1 subject had adenocarcinoma in situ, and in the placebo group, 75 subjects with CIN had grade 1 lesions, 34 had grade 2 lesions, 40 had grade 3 lesions, and 6 subjects had adenocarcinoma in situ.
- ¶¶¶¶ Perineal cancer developed in one subject who received three doses of the quadrivalent vaccine. At day 1, she was negative on PCR analysis and serologic testing for all vaccine-type HPV, negative on PCR analysis for seven other oncogenic HPV types, and negative on Papanicolaou testing. At the scheduled month 24 visit, she was noted to have a perineal lesion. On biopsy 1 month later, the lesion was found to be a well-differentiated squamous-cell carcinoma; PCR analysis of paraffin-embedded specimens was negative for vaccine-type HPV and for 10 other oncogenic HPV types. She was negative on Papanicolaou testing at all scheduled visits (months 7, 12, 18, 24, 30, and 36). Cervicovaginal swabs collected during these visits were negative for HPV, except at month 24, when an external genital swab sample (of the labial–vulvar–perineal and perianal regions) was positive for HPV-16 and HPV-59. Although the external genital swab sample collected at month 24 was positive for HPV-16 and HPV-59, PCR analysis of paraffin-embedded specimens was negative for all HPV types tested (vaccine-type HPV and other types). For further discussion of the clinical findings in this case, see the Supplementary Appendix.

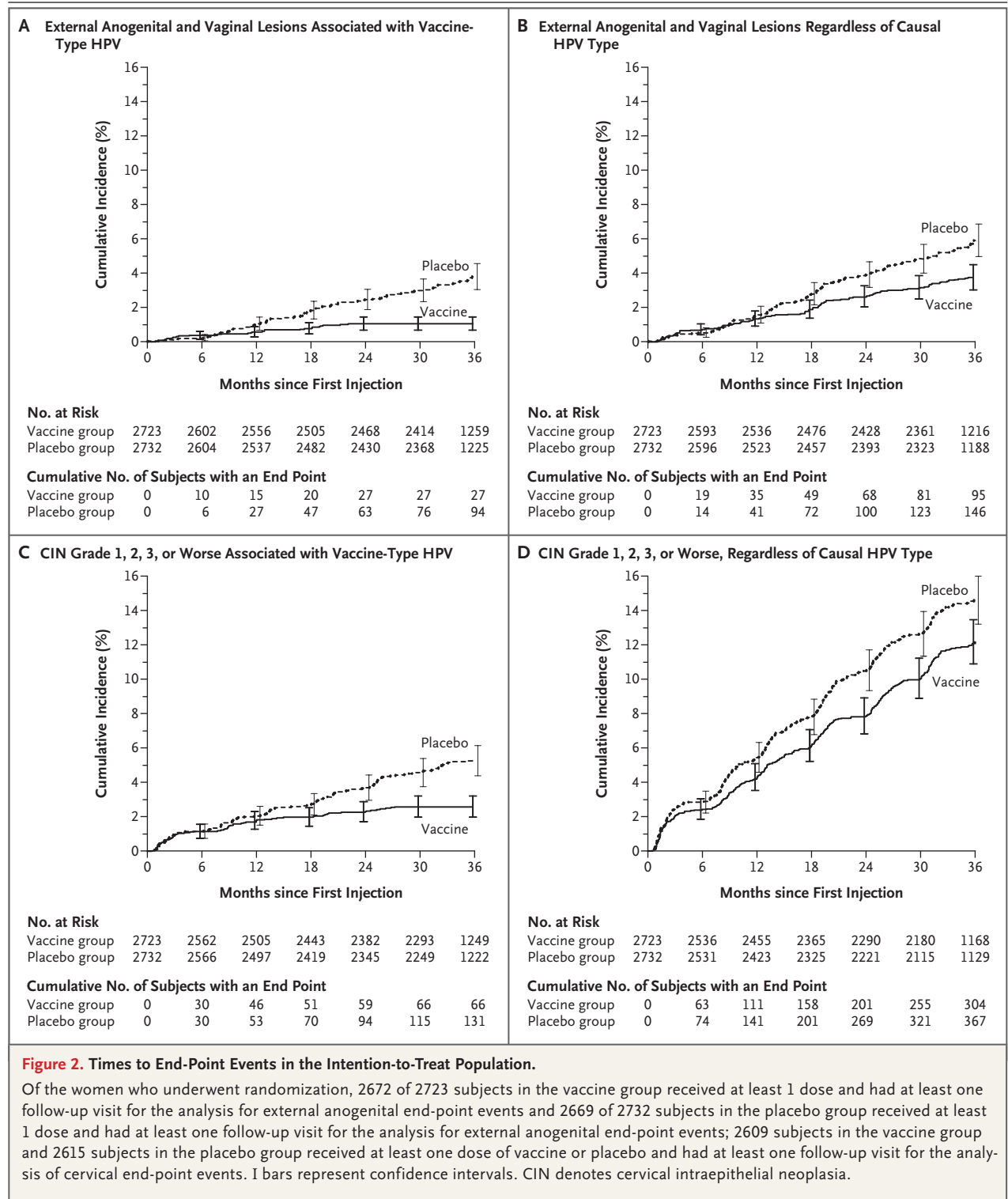


Table 4. Adverse Events.*

Event	Vaccine Group	Placebo Group	Difference in Risk (95% CI) [†]
Subjects with follow-up — no.	2673	2672	
Subjects with one or more events — no./total no. (%)			
Injection-site event	2320/2673 (86.8)	2068/2672 (77.4)	9.4 (7.3 to 11.5)
Erythema	659/2673 (24.7)	450/2672 (16.8)	7.9 (5.6 to 10.0)
Pain	2281/2673 (85.3)	2014/2672 (75.4)	10.0 (7.8 to 12.1)
Pruritus	109/2673 (4.1)	80/2672 (3.0)	1.1 (0.1 to 2.1)
Swelling	694/2673 (26.0)	413/2672 (15.5)	10.5 (8.3 to 12.7)
Systemic event	1745/2673 (65.3)	1701/2672 (63.7)	1.6 (−1.0 to 4.2)
Injection-related systemic event [‡]	1161/2673 (43.4)	1085/2672 (40.6)	2.8 (0.2 to 5.5)
Pyrexia	361/2673 (13.5)	272/2672 (10.2)	3.3 (1.6 to 5.1)
Fever during the first 5 days reported on vaccination report card			
<37.8°C	2268/2662 (85.2)	2359/2666 (88.5)	−3.3 (−5.1 to −1.5)
37.8 to <38.9°C	354/2662 (13.3)	274/2666 (10.3)	3.0 (1.3 to 4.8)
38.9 to <39.9°C	35/2662 (1.3)	26/2666 (1.0)	0.3 (−0.2 to 0.9)
39.9 to <40.9°C	5/2662 (0.2)	4/2666 (0.2)	0 (−0.2 to 0.3)
≥40.9°C	0/2662 (0)	3/2666 (0.1)	−0.1 (−0.3 to 0.0)
Serious event	48/2673 (1.8)	45/2672 (1.7)	0.1 (−0.6 to 0.8)
Vaccine-related event	1/2673 (<0.1)	0/2672 (0)	0 (−0.1 to 0.2)
Discontinuation because of event	2/2673 (0.1)	3/2672 (0.1)	0 (−0.3 to 0.2)
Discontinuation because of vaccine-related event	0/2673 (0)	0/2672 (0)	0 (−0.2 to 0.2)
Death [§]	2/2673 (0.1)	2/2672 (0.1)	0 (−0.2 to 0.2)

covered by the vaccine, since 100% HPV-type-specific efficacy was observed in the per-protocol analysis. There were relatively few adverse events among the vaccine recipients.

Several steps were taken to ensure that this study would provide a high level of confidence in the safety and efficacy of the quadrivalent vaccine. A diverse population of young women participating in developed and developing countries were enrolled. Data on serious vaccine-related or procedure-related adverse events and pregnancy outcomes were collected for the entire follow-up period. Since HPV-associated vaginal and vulvar lesions may have an ambiguous clinical presentation, an intensive visit schedule with aggressive regimens for genital inspection, biopsy of suspect lesions and cytologic screening, and colposcopy with biopsy were used to ensure a high sensitivity for HPV-associated lesions. High diagnostic accuracy for end-point determinations was provided by a panel of expert pathologists who were unaware

of the treatment assignments. Estimates of vaccine efficacy were high whether the diagnoses were made by the pathology panel or by the central laboratory, indicating robust efficacy measurements.

When we evaluated the quadrivalent vaccine's effectiveness against disease associated with the HPV types covered by the vaccine in the intention-to-treat population (as compared with the unrestricted susceptible population), all additional cases detected in the vaccine group occurred in subjects who were infected with vaccine-type HPV before vaccination. Among all randomized subjects with an end-point event within the first year of follow-up, both the vaccine group (57 [97%] cases of disease in 59 subjects) and the placebo group (59 [81%] cases of disease in 73 subjects) had evidence of infection or disease that was prevalent at enrollment. During the second year of follow-up, the incidence of disease associated with vaccine-type HPV in the placebo group

Table 4. (Continued.)

Event	Vaccine Group	Placebo Group	Difference in Risk (95% CI) [†]
Subjects seropositive for one or more of vaccine HPV types at day 1			
Subjects with follow-up — no.	529	507	
Injection-site event — no./total no. (%)	452/529 (85.4)	388/507 (76.5)	8.9 (4.2 to 13.7)
Pain	445/529 (84.1)	375/507 (74.0)	10.1 (5.2 to 15.1)
Erythema	142/529 (26.8)	72/507 (14.2)	12.6 (7.8 to 17.5)
Hypersensitivity	9/529 (1.7)	2/507 (0.4)	1.3 (0.1 to 2.9)
Swelling	154/529 (29.1)	79/507 (15.6)	13.5 (8.5 to 18.5)
Systemic event — no./total no. (%)	334/529 (63.1)	292/507 (57.6)	5.5 (−0.4 to 11.5)
Injection-related systemic event [‡]	248/529 (46.9)	194/507 (38.3)	8.6 (2.6 to 14.6)
Pyrexia	92/529 (17.4)	52/507 (10.3)	7.1 (2.9 to 11.4)
Fever during the first 5 days reported on vaccination report card			
<37.8°C	381/481 (79.2)	375/428 (87.6)	−8.4 (−13.2 to −3.6)
37.8 to <38.9°C	86/481 (17.9)	45/428 (10.5)	7.4 (2.8 to 11.9)
38.9 to <39.9°C	14/481 (2.9)	6/428 (1.4)	1.5 (−0.5 to 3.6)
39.9 to <40.9°C	0/481 (0)	2/428 (0.5)	−0.5 (−1.7 to 0.3)
≥40.9°C	0/481 (0)	0/428 (0)	0 (−0.9 to 0.8)

* Of the subjects included in the analysis, 466 in the vaccine group received hepatitis B vaccine and quadrivalent HPV vaccine concurrently and 467 in the placebo group received hepatitis B vaccine and placebo concurrently. Data for these subjects are included in the safety analyses. Injection-site adverse events that were considered to be related to hepatitis B vaccine are not included in the category of injection-site adverse events. Injection-site adverse events included were reported during the first 5 days after vaccination. Systemic adverse events included were reported during the first 15 days after vaccination. All other adverse events reflect the entire follow-up period as of June 15, 2006.

[†] The risk difference is the value for the HPV vaccine minus the value for placebo. The 95% CIs that do not include 0 indicate a statistically significant difference at an alpha level of 0.05 (two-sided). No multiplicity adjustments were made for these comparisons.

[‡] This event was considered to be possibly, probably, or definitely injection-related.

[§] There were two deaths in the vaccine group, one as a result of a car accident 342 days after administration of the third dose, and one by suicide 1373 days after enrollment. There were two deaths in the placebo group, one from deep-vein thrombosis, renal insufficiency, and shock to the lung 204 days after administration of the third dose, and one as a result of a traffic accident 1 day after administration of the second dose. None of these deaths were considered by the investigator to be related to the vaccine or placebo.

continued to increase, whereas in the vaccine group the incidence appeared to reach a plateau, as cases of disease due to prevalent infection were no longer detected and vaccine appeared to reduce the incidence of new infections and associated disease.

A decrease (unadjusted for multiplicity) in overall rates of anogenital disease, regardless of causal HPV type, was also observed. The development of vulvar cancer, though rare, in one subject in the vaccine group highlights the importance of continued screening. Since vaccinated women remain at risk for cervical and genital disease resulting from infections with vaccine-type HPV that might be present at the time of vaccination and from newly acquired infections with HPV types that are not targeted by the quadrivalent HPV vac-

cine, such women should continue to undergo regular cervical screening for cancer and genital examination, as clinically indicated.

A limitation of our study is the lack of long-term follow-up. The duration of the efficacy of the quadrivalent HPV vaccine and whether boosters are needed are not known. Similarly, to date, no minimum protective anti-HPV antibody titers have been identified. A phase 2 trial of the quadrivalent vaccine showed that at 5 years the vaccine is highly efficacious against infection and disease associated with vaccine-type HPV and that vaccine-induced anti-HPV antibody levels are maintained at or above the levels observed in natural infection.^{28,29} At 5 years in this phase 2 study, an antigen challenge resulted in strong anamnestic responses, with sharp rises in antibody titer, in-

dicating the presence of strong, long-lived immune memory.²⁹ The FUTURE I study had limited power to definitively address individual components of the composite study end points; however, the consistency of the results for all components and the results of the FUTURE II study²⁵ are encouraging.

As in other trials of prophylactic vaccines,³⁰ our primary analysis focused on women who at baseline were not infected with vaccine-type HPV. Under conditions that may reflect deviations in vaccine dosing intervals, such as in the unrestricted susceptible population, the efficacy against these HPV types remained high — 95% for external anogenital or vaginal lesions and 98% for cervical lesions. These data also suggest that there is some flexibility in the timing of the vaccination regimen. Adolescent men and women mount higher antibody responses to the quadrivalent vaccine³¹ than do young adult women, but whether the quadrivalent HPV vaccine will prevent genital infection and lesions in men is unknown.

Our data demonstrate the efficacy of a prophylactic quadrivalent HPV vaccine against lesions caused by all the targeted types of HPV. There was

also a reduction in the overall incidence of anogenital lesions in the vaccine group. Widespread vaccination of young women and adolescent girls should reduce the incidence of cervical and external anogenital disease associated with HPV-6, HPV-11, HPV-16, and HPV-18. Further research is needed to evaluate the effect of large-scale vaccination programs on the overall burden of HPV disease.

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APPENDIX

The following investigators participated in the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I study (listed in alphabetical order): **Data and Safety Monitoring Board:** M. Boulos, J.T. Cox, F. Langmark, J. Modlin (chair), A. Muñoz, V. Odlind, E. Wilkinson; **Pathology Panel:** A. Ferenczy, R. Kurman, B. Ronnett, M. Stoler; **Principal Investigators** (with asterisks indicating coauthors): *Australia* — S.M. Garland*; *Austria* — S. Leodolter*; *Brazil* — G.I. Andreoni, R.L. Costa, R.P. De Andrade, R. Ferriani, D. Lewi, C. Petta; *Canada* — N. Aytte, C. Bouchard, M. Boucher, L. Gilbert, M. Steben,* M. Tolszczuk; *Colombia* — J. Luna, G. Perez*; *Czech Republic* — V. Dvorak, B. Micanik, J. Stepan; *Germany* — E. Barthell, Y. Garnier, T. Grubert, F. Jaenicke, W. Lichtenegger; *Hong Kong* — G.W.K. Tang*; *Italy* — G. Carosi, S. Greggi, L. Mariani, M. Moscarini, A. Perino; *Mexico* — M. Hernandez-Avila,* E. Lazcano; *New Zealand* — S. Bagshaw, H. Roberts; *Peru* — L. Jefferson; *Puerto Rico* — R. Barnes, J. Romaguera; *Russia* — I. Manukhin, N. Mikhailova, N. Tsvetkova; *Thailand* — P. Pitisuttithum; *United Kingdom* — K. Neal, C. Lacey, A. Wade; *United States* — M. Akin, K. Beutner, D.G. Ferris,* S. Gall, M. Gold, D.M. Harper,* W. Koltun, L.A. Koutsky,* K. Kreutner, W. Ledger, C. Livengood III, S.G. McNeely, Jr., W. Nebel, P. Rogge, S. Sharma, S. Trupin, Y. Wade, E. Wegner, C.M. Wheeler,* D.M. Whitaker, and M. Yardley; **Statistical and Programming Support:** K. McCarroll, L. Zhang, H. Zhou.

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