

Prophylactic Efficacy of a Quadrivalent Human Papillomavirus (HPV) Vaccine in Women with Virological Evidence of HPV Infection

The FUTURE II Study Group^a

(See the article by Kjær et al., on pages 1447–54, and the editorial commentary by Hildesheim and Herrero, on pages 1431–2.)

Background. A quadrivalent (types 6, 11, 16, and 18) human papillomavirus (HPV) L1 virus-like-particle (VLP) vaccine has been shown to be 95%–100% effective in preventing cervical and genital disease related to HPV-6, -11, -16, and -18 in 16–26-year-old women naive for HPV vaccine types. Because most women in the general population are sexually active, some will have already been infected with ≥ 1 HPV vaccine types at the time vaccination is offered. Here, we assessed whether such infected women are protected against disease caused by the remaining HPV vaccine types.

Methods. Two randomized, placebo-controlled trials of the quadrivalent (types 6, 11, 16, and 18) HPV vaccine enrolled 17,622 women without consideration of baseline HPV status. Among women infected with 1–3 HPV vaccine types at enrollment, efficacy against genital disease related to the HPV vaccine type or types for which subjects were naive was assessed.

Results. Vaccination was 100% effective (95% confidence interval [CI], 79%–100%) in preventing incident cervical intraepithelial neoplasia 2 or 3 or cervical adenocarcinoma in situ caused by the HPV type or types for which the women were negative at enrollment. Efficacy for preventing vulvar or vaginal HPV-related lesions was 94% (95% CI, 81%–99%).

Conclusions. Among women positive for 1–3 HPV vaccine types before vaccination, the quadrivalent HPV vaccine protected against neoplasia caused by the remaining types. These results support vaccination of the general population without prescreening.

Anogenital human papillomavirus (HPV) infection can cause invasive cervical, vaginal, and vulvar cancer; cer-

vical, vulvar, and vaginal intraepithelial neoplasia (CIN, VIN, and VaIN, respectively); and anogenital warts [1–4]. HPV-16 and -18 cause 70% of cervical and HPV-related vulvar and vaginal cancers; >70% of cervical adenocarcinomas in situ (AIS); 50 to 60% of high-grade CIN, VIN, and VaIN (CIN2/3, VIN2/3, and VaIN2/3, respectively) cases; and 25% of low-grade CIN (CIN1) cases. HPV-6 and -11 are responsible for 90% of genital wart cases and 10% of CIN1 cases.

Prevention of persistent cervical HPV-16 and -18 infections and related CIN has been shown with monovalent or bivalent HPV virus-like-particle (VLP) vaccines [5–7]. An effective quadrivalent HPV (types 6, 11, 16,

Received 19 December 2006; accepted 17 April 2007; electronically published 31 October 2007.

Potential conflicts of interest: L.L.V., G.P., S.K.K., J.P., N.M., K.S., M.H.-A., O.E.I., S.T., P.J.G., S.M., J.D., S.-E.O., E.H.T., F.X.B., K.A.A., D.R.B., D.G.F., L.A.K., R.J.K., and E.R.M. have received honoraria from Merck Research Laboratories. These honoraria were given for consultation work and membership in the Phase III HPV Vaccine Steering and/or Registries Oversight Committees. R.J.K. is a member of the HPV Vaccine Program Pathology Panel; as such, he has been paid for his efforts in developing the Pathology Panel's standard operating procedures and for its histopathological readings of biopsy slides. G.P., S.K.K., J.P., K.S., M.H.-A., O.E.I., S.T., P.J.G., S.E.O., E.H.T., K.A.A., D.R.B., D.G.F., and L.A.K. led clinical sites that participated in the study. These investigators were compensated for all activities related to execution of the study. J.D., S.M., D.G.F., and N.M. have been given honoraria for lectureships on behalf of Merck's HPV vaccine program. D.R.B. has been paid for consultations regarding the HPV vaccine program in men. D.G.F. has been paid for consultation regarding colposcopy quality control. K.A.A. is a member of Merck's HPV Vaccine Obstetrics and Gynecology Advisory Board and, as such, receives honoraria for his consultative work.

The Journal of Infectious Diseases 2007; 196:1438–46

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0022-1899/2007/19610-0004\$15.00

DOI: 10.1086/522864

Presented in part: European Research Organization on Genital Infection and Neoplasia Meeting, Paris, 23–26 April 2006 (abstract S11-2).

Financial support: Merck Research Laboratories (a division of Merck & Co., Inc.).

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and 18) L1 VLP vaccine improves on these vaccines by increasing their public health impact. In trials conducted in >17,500 young adult women, such a vaccine was 95%–100% effective in preventing cervical, vaginal, and vulvar neoplasias and anogenital condylomata related to HPV-6, -11, -16, and -18 in women naive for the respective HPV vaccine types at enrollment [8–10].

Efficacy trials for this quadrivalent HPV vaccine did not include an HPV screening phase. More than 25% of the 16–26-year-old women enrolled in these trials had serological or polymerase chain reaction (PCR) evidence of previous or current infection with HPV-6, -11, -16, or -18. The design of the quadrivalent HPV vaccine studies stand in contrast with a recent trial of a bivalent HPV vaccine, in which HPV infection was a contraindication to enrollment [5]. Although a vaccination strategy targeting non–sexually active (HPV-naive) adolescents is intuitively advantageous, many women who are beyond sexual debut, some of whom may have already been exposed to HPV, are likely to benefit from vaccination.

Because vaccination programs are likely to target the general population of adolescent and young adult women, some women will have been previously exposed to HPV at the time of vaccination [11]. It has been unknown, however, whether women already exposed to 1 or more HPV types included in the quadrivalent HPV vaccine would still benefit from protection against disease caused by the other HPV types in the vaccine. Furthermore, the potential for vaccine-related adverse experiences in women who had already mounted anti-HPV responses to natural infection has not yet been ruled out [12, 13].

The purpose of the present report is to address these questions by assessing the prophylactic efficacy of the quadrivalent HPV vaccine in preventing CIN, VIN, VaIN, and anogenital condylomata related to HPV-6, -11, -16, and -18 in women who were either seropositive or PCR positive for at least 1 of the HPV vaccine types at enrollment.

SUBJECTS, MATERIALS, AND METHODS

Data sources and objective. The combined database of 2 phase 3 efficacy trials of the quadrivalent HPV vaccine was used for the present analyses. Protocols 013 (NCT00092521) and 015 (NCT00092534) (termed FUTURE I and FUTURE II, respectively) were randomized, double-blind, placebo-controlled phase 3 clinical trials designed to investigate the prophylactic efficacy of the quadrivalent (types 6, 11, 16, and 18) HPV L1 VLP vaccine (Gardasil; Merck) on HPV-6/11/16/18–related CIN, AIS, or cervical cancer (protocol 013 coprimary end point); HPV-6/11/16/18–related condyloma acuminata, VIN, VaIN, vulvar cancer, or vaginal cancer (protocol 013 coprimary end point); and HPV-16/18–related CIN2/3, AIS, or cervical cancer (protocol 015 primary end point) [8–10].

Population and study design. Between December 2001 and May 2003, 17,622 women 15–26 years old were enrolled in the 2

trials. The trials enrolled women who at day 1 reported 0–4 lifetime sex partners. Enrolled subjects with clinical evidence of genital HPV disease at day 1 were discontinued from the study before randomization. Subjects received intramuscular injections of the quadrivalent HPV vaccine or visually indistinguishable placebo at enrollment (day 1), month 2, and month 6. Each protocol was approved by the institutional review boards (ethical review committees) at participating centers, and informed consent was received from all subjects enrolled. The designs of protocols 013 and 015 and the composition of the quadrivalent HPV vaccine have been described elsewhere [9, 10].

All subjects enrolled in the study were included within the overall safety population. This population underwent full evaluation of serious adverse experiences (i.e., events that in the opinion of the investigator substantially impacted the health of the subject or that led to hospitalization). A subset of the overall safety population, termed the detailed safety population, was also asked to fill out vaccination diary cards designed to capture all generally nonserious injection-site and systemic adverse experiences, including fevers, occurring in the days after vaccination.

Clinical follow-up and laboratory testing. Examination for the presence of genital warts and vulvar and vaginal lesions was performed at enrollment (day 1), month 3 (protocol 013 only), and months 7, 12, 24, 36, and 48 (also at months 18 and 30 for protocol 013). ThinPrep (Cytyc) cytology specimens for Pap testing were collected at enrollment (day 1), month 7, and 6–12-month intervals thereafter. Cytology specimens were classified using the 2001 Bethesda System [14]. Procedures for algorithm-based cytology, colposcopy, and biopsy referral have been described elsewhere [9, 10]. Biopsy material was first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories) and then read for end-point determination by a blinded panel of 4 pathologists, as described elsewhere [7–10].

Blood samples were obtained at enrollment (day 1) for anti-HPV serological testing for HPV-6, -11, -16, and -18 by competitive immunoassays (developed by Merck Research Laboratories, using technology from Luminex) [15]. Ascertainment of HPV infection involved HPV PCR analysis performed on genital swabs obtained at enrollment (day 1), month 3 (protocol 013 only), and month 7. For each subject, genital swabs were tested for the presence of HPV-6, -11, -16, and -18 DNA. For PCR analysis, swabs, biopsy samples, and thin tissue sections cut adjacent to sections used for histopathological analysis were used to detect HPV DNA with primers specific for HPV-6, -11, -16, or -18.

Case definition. End points for the present analyses consisted of a pathology-panel diagnosis of CIN, AIS, condyloma acuminata, VIN, or VaIN, with HPV vaccine type DNA detected in a tissue section adjacent to the section used for histological diagnosis. The method for case counting in the analysis of prophylactic efficacy among women with evidence of prior expo-

Table 1. Study design and comparison of protocols 013 and 015.

Design feature	Protocol 013			Protocol 015		
General						
Sample size	5455			12,167		
Study dates	2001–2007			2002–2007		
Study design	International, multicenter, double-blind, prospective parallel trial			International, multicenter, double-blind, prospective parallel trial		
Study vaccine and regimen	Quadrivalent vaccine or placebo; 0, 2, 6 months			Quadrivalent vaccine or placebo; 0, 2, 6 months		
Visit schedule	Months	0,	3, 7, 12, 18, 24, 30, 36 months	Months	0,	7, 12, 24, 36 months
Inclusion/exclusion criteria						
Age, years	16–23			15–26		
Lifetime no. of male sex partners	0–4			0–4		
Previous abnormal Pap test result or HPV disease	Not allowed ^a			Not allowed ^a		
Cervical cancer screening						
Pap test screening interval	Approximately every	6 months		Approximately every	12 months	
Screening triage strategy	Mandatory			Mandatory		
Pap test referral threshold	ASCUS	or	HPV positive on HC-II	ASCUS	or	HPV positive on HC-II
Colposcopy, biopsy, and LEEP						
Requirement for biopsy	All abnormal areas			All abnormal areas		
Pathology interpretation (end points)	Blinded pathology panel			Blinded pathology panel		
HPV causality assessment	PCR assay on paraffin-embedded specimens			PCR assay on paraffin-embedded specimens		
LEEP tissue analyzed	Entire	LEEP specimen		Entire	LEEP specimen	

NOTE. ASCUS, atypical squamous cells of undetermined significance; HC-II, hybrid capture II; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; PCR, polymerase chain reaction.

^a However, there was no exclusion on the basis of current/ongoing infection or disease (i.e., subjects who had an abnormal Pap test result at day 1 were enrolled); subjects with visible genital warts were not enrolled.

sure or with current infection excluded cases related to the HPV type with which the woman was infected at baseline.

Statistical methods. This post hoc analyses was restricted to the subset of subjects who received at least 1 vaccination and at enrollment had evidence of current or previous infection with 1–3 of the 4 HPV vaccine types (6, 11, 16, and 18). Each woman was evaluated for subsequent development of disease due to the HPV type or types for which she was seronegative and PCR negative at enrollment. Protocol violators were included. Case counting began 30 days after the first vaccination.

A point estimate of vaccine efficacy and the 95% confidence interval (CI) were calculated on the basis of the observed split between vaccine and placebo recipients and the accrued person-time. The statistical criterion for success ($P < .05$) was equivalent to requiring that the lower bound of the 95% CI for vaccine efficacy exclude 0%. An exact conditional procedure was used to evaluate vaccine efficacy under the assumption that the numbers of cases in the vaccine and placebo groups were independent Poisson random variables. If a subject developed >1 end point, she was counted as a case at the date of the first end point.

RESULTS

The study designs of protocols 013 and 015 are compared in table 1. The protocols were similar with respect to general de-

sign, inclusion and exclusion criteria, cervical cancer screening, and diagnostic and therapeutic intervention. However, the trials differed by subject visit schedule, age range, and Pap test interval.

Subject demographics of women who were PCR positive and/or seropositive for at least 1 HPV vaccine type at enrollment as well as of the overall population are listed in table 2. Subjects with evidence of prior or ongoing infection with 1 or more HPV vaccine types at day 1 were more likely to have been pregnant, more likely to be infected with *Chlamydia trachomatis*, and more likely to have an abnormal Pap test result at day 1 than were the general study population. Among subjects who were positive for at least 1 HPV vaccine type at day 1, there were more subjects with a diagnosis of high- or low-grade squamous intraepithelial lesions in the quadrivalent HPV vaccine group than in the placebo group.

In the combined protocol 013 and 015 study populations, 19.8% were seropositive for HPV-6, -11, -16, and/or -18; 14.9% were PCR positive; and 26.8% were positive by either PCR or serological analysis (2368 vaccine recipients [26.9%] and 2354 placebo recipients [26.7%]). The baseline prevalence of positivity for ≥ 1 HPV vaccine type was comparable between the 2 vaccination groups. Most subjects who were positive for ≥ 1 HPV vaccine type were positive for exactly 1 vaccine HPV type. Among the 4 HPV vaccine types, HPV-16 positivity at day 1 was

Table 2. Baseline demographics.

Characteristic	PCR positive and/or seropositive at enrollment				Overall population			
	Vaccine		Placebo		Vaccine	Placebo		
Age, mean, years	20.4	(n=2368)	20.3	(n=2354)	20.0	(n=8810)	20.0	(n=8812)
Among nonvirgins								
Age at sexual debut, mean, years	16.5	(n=2350)	16.5	(n=2342)	16.7	(n=8306)	16.7	(n=8260)
Lifetime no. of sex partners, mean	2.6		2.5		2.1		2.1	
Past pregnancy	719/2368	(30.4)	718/2354	(30.5)	1994/8806	(22.6)	1971/8810	(22.4)
<i>Chlamydia trachomatis</i> at day 1	172/2340	(7.4)	185/2321	(8.0)	376/8664	(4.3)	360/8641	(4.2)
Cytological abnormality at day 1	537/2348	(22.9)	518/2324	(22.3)	985/8726	(11.3)	970/8707	(11.1)
ASC-US	162/2348	(6.9)	178/2324	(7.7)	382/8726	(4.4)	404/8707	(4.6)
ASC-H	16/2348	(0.7)	19/2324	(0.8)	28/8726	(0.3)	25/8707	(0.3)
LSIL	310/2348	(13.2)	283/2324	(12.2)	509/8726	(5.8)	493/8707	(5.7)
HSIL	49/2348	(2.1)	35/2324	(1.5)	61/8726	(0.7)	45/8707	(0.5)
Atypical glandular cells	0/2348	(0.0)	3/2324	(0.1)	5/8726	(0.1)	3/8707	(0.0)

NOTE. Data are no. of subjects in respective category/no. of subjects with nonmissing data (%), unless otherwise indicated. ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, favor HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; PCR, polymerase chain reaction.

most common (HPV-16 seropositivity, 11%; HPV-16 PCR positivity, 9%; HPV-16 seropositivity and/or PCR positivity, 20%), and HPV-11 positivity was the least prevalent (HPV-11 seropositivity, 2%; HPV-11 PCR positivity, 0.7%; HPV-11 seropositivity and/or PCR positivity, 3%). Only 0.1% of the population was positive for all 4 HPV vaccine types by serological analysis and/or PCR.

Table 3 presents the sizes of the subject populations that were eligible for analyses of each end point in the prophylactic efficacy analyses on the basis of HPV positivity at enrollment. For example, 1722 subjects who were positive for HPV-6, -11, and/or -16

were eligible for evaluation of HPV-18–related end points. Of these subjects, 863 were positive for HPV-6 or -11, and 1133 were positive for HPV-16 (note that some of the subjects who were positive for HPV-6 or -11 were also positive for HPV-16). The population sizes for the other HPV types are derived in a similar manner.

Given that subjects who were positive for at least 1 HPV vaccine type (but <4 types) at day 1 had evidence of more frequent and more risky sexual behavior than did the general study population, it was of interest to determine whether these subjects were at higher risk for acquisition of a new infection with an

Table 3. Baseline human papillomavirus (HPV) positivity (by polymerase chain reaction [PCR] or serological analysis) of efficacy population, by HPV-related end point.

Population, HPV type	Vaccine			Placebo				
	Eligible population, no. ^a	HPV positivity at day 1, no. ^b			Eligible population, no. ^a	HPV positivity at day 1, no. ^b		
		6/11	16	18		6/11	16	18
CIN end-point populations								
HPV-6/11 related	1245	...	973	386	1230	...	973	370
HPV-16 related	941	669	...	352	905	648	...	341
HPV-18 related	1722	863	1133	...	1728	868	1164	...
External anogenital and vaginal lesion end-point populations								
HPV-6/11 related	1262	...	986	391	1248	...	990	374
HPV-16 related	954	678	...	358	918	660	...	344
HPV-18 related	1744	873	1148	...	1756	882	1182	...

NOTE. Subjects who are positive for 1 HPV type may also be positive for other HPV types. CIN, cervical intraepithelial neoplasia.

^a No. of subjects eligible for evaluation for the given end point.

^b No. of subjects in the given population who were negative for the indicated HPV type at day 1 but were positive for another HPV vaccine type or types.

Table 4. Incidence of human papillomavirus (HPV)-related cervical, vulvar, or vaginal disease caused by new infections with HPV vaccine types among placebo recipients who were positive for at least 1 HPV vaccine type at day 1 and placebo recipients who were naive for all 4 HPV vaccine types at day 1.

End point (HPV type for which the relevant population is naive)	Subjects positive ^b for 1–3 HPV vaccine types at day 1			Subjects naive ^d for all HPV vaccine types at day 1		
	No. ^a	Cases	Rate ^c (95% CI)	No. ^a	Cases	Rate ^c (95% CI)
HPV-6/11-related CIN or EGL	1249	52	1.5(1.1–1.9)	6290	201	1.1(1.0–1.3)
HPV-6/11-related CIN	1230	12	0.4(0.2–0.6)	6210	38	0.2(0.1–0.3)
HPV-6/11-related EGL	1248	44	1.2(0.9–1.7)	6285	179	1.0(0.9–1.2)
HPV-16-related CIN or EGL	918	21	0.8(0.5–1.2)	6290	156	0.9(0.7–1.0)
HPV-16-related CIN	905	17	0.7(0.4–1.1)	6210	120	0.7(0.6–0.8)
HPV-16-related EGL	918	5	0.2(0.1–0.4)	6285	47	0.3(0.2–0.3)
HPV-18-related CIN or EGL	1757	25	0.5(0.3–0.7)	6290	48	0.3(0.2–0.3)
HPV-18-related CIN	1728	22	0.5(0.3–0.7)	6285	20	0.1(0.1–0.2)
HPV-18-related EGL	1756	3	0.1(0.0–0.2)	6210	31	0.2(0.1–0.2)

NOTE. CI, confidence interval; CIN, cervical intraepithelial neoplasia; EGL, external genital lesion (vaginal intraepithelial neoplasia, vulvar intraepithelial neoplasia, and/or condylomata); PCR, polymerase chain reaction.

^a No. of evaluable subjects randomized to the placebo group who received at least 1 injection.

^b By either PCR or serological analysis (or both).

^c Incidence rate per 100 person-years at risk.

^d By both PCR and serological analysis.

HPV vaccine type than were subjects who were naive for all 4 HPV vaccine types at day 1. Table 4 displays a comparison of event rates between the placebo arms of the 2 populations. As expected, subjects who were positive for at least 1 HPV vaccine type at baseline had slightly higher rates of acquisition of new HPV-related cervical, vulvar, and vaginal diseases.

Among women positive for HPV-6, -11, -16, or -18 at enrollment, vaccine efficacy was 100% (95% CI, 79%–100%) for the prevention of CIN2, CIN3, and AIS—lesions that represent true

precursors of squamous cell and adenocarcinoma of the cervix. The observed quadrivalent vaccine efficacy for the prevention of all CIN due to the remaining HPV types in this population was 91% (95% CI, 76%–98%) (table 5) after an average of 3 years of follow-up. All 4 cases of CIN in the vaccine group were CIN1 lesions (1 lesion related to each HPV vaccine type; all 4 subjects received all 3 doses of vaccine). One subject who was PCR positive for HPV-18 at day 1 was given a diagnosis of HPV-6-related CIN1 at month 3. Another subject who was PCR positive

Table 5. Analysis of prophylactic efficacy against cervical intraepithelial neoplasia (CIN) related to human papillomavirus (HPV)-6, -11, -16, or -18 in a subset of subjects who were polymerase chain reaction (PCR) positive or seropositive for at least 1 HPV vaccine type at day 1.

End point	Vaccine recipients			Placebo recipients			Observed efficacy (95% CI), %
	No. ^a	Cases	Rate ^b	No. ^a	Cases	Rate ^b	
HPV-6/11/16/18-related CIN	2188	4	0.1	2182	45	0.8	91.1 (75.7–97.7)
HPV type							
HPV-6-related CIN	1245	1	0.0	1230	10	0.3	90.2 (31.3–99.8)
HPV-11-related CIN	1245	1	0.0	1230	2	0.1	51.0 (<0.0–99.2)
HPV-16-related CIN	941	1	0.0	905	17	0.7	94.3 (63.7–99.9)
HPV-18-related CIN	1722	1	0.0	1728	22	0.5	95.4 (71.8–99.9)
Lesion type							
CIN1	2188	4	0.1	2182	34	0.6	88.3 (67.1–97.0)
CIN2 or worse	2188	0	0.0	2182	19	0.3	100.0 (78.6–100.0)
CIN2	2188	0	0.0	2182	12	0.2	100.0 (64.0–100.0)
CIN3/AIS	2188	0	0.0	2182	10	0.2	100.0 (55.3–100.0)

NOTE. A subject is counted only once within each applicable row. Some subjects are counted in >1 row. AIS, adenocarcinoma in situ; CI, confidence interval.

^a No. of subjects in the given population with at least 1 follow-up visit 30 days after day 1 who received at least 1 injection.

^b Per 100 person-years at risk.

Table 6. Analysis of prophylactic efficacy against external anogenital and vaginal lesions related to human papillomavirus (HPV)–6, -11, -16, or -18 in a subset of subjects who were polymerase chain reaction (PCR) positive or seropositive for at least 1 HPV vaccine type at day 1.

End point	Vaccine recipients			Placebo recipients			Observed efficacy (95% CI), %
	No. ^a	Cases	Rate ^b	No. ^a	Cases	Rate ^b	
HPV-6/11/16/18–related external anogenital and vaginal lesions	2217	3	0.0	2216	48	0.8	93.8 (80.7–98.8)
HPV type							
HPV-6 related	1262	3	0.1	1248	35	1.0	91.6 (73.4–98.3)
HPV-11 related	1262	0	0.0	1248	10	0.3	100.0 (56.0–100.0)
HPV-16 related	954	0	0.0	918	5	0.2	100.0 (<0.0–100.0)
HPV-18 related	1744	0	0.0	1756	3	0.1	100.0 (<0.0–100.0)
Lesion type							
Condyloma	2217	3	0.0	2216	45	0.7	93.4 (79.3–98.7)
VIN1 or VaIN1	2217	1	0.0	2216	5	0.1	80.0 (<0.0–99.6)
VIN2/3 or VaIN2/3	2217	0	0.0	2216	2	0.0	100.0 (<0.0–100.0)

NOTE. A subject is counted only once within each applicable row. Some subjects are counted in >1 row. CI, confidence interval; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

^a No. of subjects in the given population with at least 1 follow-up visit 30 days after day 1 who received at least 1 injection.

^b Per 100 person-years at risk.

for HPV-18 at day 1 was given a diagnosis of HPV-16–related CIN1 at month 7. For these 2 subjects, the index infection occurred before completion of the 3-dose vaccination regimen. The remaining 2 subjects received diagnoses of CIN1 lesions at month 12. One subject was seropositive for HPV-6 at baseline and was given a diagnosis of a CIN1 lesion related to HPV-18, and the other subject was PCR positive for HPV-16 at baseline and was given a diagnosis of a CIN1 lesion related to HPV-11.

In this same population, the efficacy of the quadrivalent vaccine in preventing external anogenital and vaginal lesions was 94% (95% CI, 81%–99%) (table 6). All 3 cases of external anogenital or vaginal lesions in quadrivalent HPV vaccine recipients were HPV-6 related, and none of these lesions were diagnosed as potential precursors of lower genital tract cancer (VIN2/3 or VaIN2/3). One subject was seropositive for HPV-18 at baseline and was diagnosed with VIN1 and condyloma at month 7. The other 2 subjects who developed cases of external genital lesions were PCR positive for HPV-16 at baseline and received a diagnosis of condyloma—1 subject at month 7 and the other at month 24. Thus, in 2 of 3 cases, the infections that resulted in the index events are likely to have occurred before the completion of the 3-dose vaccination regimen.

Adverse experiences were compared between the quadrivalent HPV vaccine and placebo groups stratified into 3 cohorts: seropositive and/or PCR positive for ≥ 1 HPV type, seropositive regardless of PCR status, and the overall population regardless of serostatus and PCR status (table 7). For each cohort, a higher proportion of subjects given quadrivalent HPV vaccine experienced 1 or more adverse experiences than did those women given placebo, a finding predominantly attributable to injection-site reactions. Systemic adverse experiences, serious adverse ex-

periences, and discontinuation due to adverse experiences were similar between vaccine and placebo recipients within each cohort. Systemic adverse experiences occurring in >2% (days 1–15 after vaccination) of subjects and more frequently in the vaccine group included headache (11.1% vs. 10.7%), pyrexia (5.5% vs. 4.6%), nasopharyngitis (2.6% vs. 2.3%), and nausea (2.9% vs. 2.5%). In the overall population, 4 subjects given quadrivalent vaccine and 2 subjects given placebo had 6 and 4 serious vaccine-related adverse experiences, respectively. Serious vaccine-related adverse experiences in subjects given the quadrivalent HPV vaccine included bronchospasm, gastroenteritis, injection-site movement impairment, injection-site pain, headache, and hypertension. Serious vaccine-related adverse experiences in subjects given placebo include hypersensitivity, chills, headache, and pyrexia.

DISCUSSION

The analyses provided here demonstrate that women who are infected with HPV-6, -11, -16, or -18 benefit from administration of the quadrivalent HPV (types 6, 11, 16, and 18) L1 VLP vaccine because they are protected from infections and disease caused by HPV types for which they are naive at the start of vaccination. This benefit is important because the incidence of new HPV infections among such subjects is higher than that among women who are naive for all 4 HPV vaccine types. Administration of the quadrivalent HPV vaccine to these previously exposed individuals was generally well tolerated.

The rates of infection with HPV-6, -11, -16, or -18 shortly after sexual debut are well defined. The phase 3 clinical efficacy studies for the quadrivalent HPV vaccine enrolled an ethnically

Table 7. Adverse experience (AE) summary (protocols 013 and 015).

Category, parameter	PCR positive or seropositive at enrollment		Seropositive at enrollment		Overall population	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Overall safety population						
Subjects in analysis population	2255	2250	1732	1736	8788	8800
Subjects with follow-up	2220	2217	1701	1714	8692	8703
Subjects						
With 1 or more AEs	824/2220 (37.1)	729/2217 (32.9)	645/1701 (37.9)	564/1714 (32.9)	3155/8692 (36.3)	3007/8703 (34.6)
With injection-site AEs	734/2220 (33.1)	613/2217 (27.6)	571/1701 (33.6)	473/1714 (27.6)	2854/8692 (32.8)	2526/8703 (29.0)
With systemic AEs	533/2220 (24.0)	501/2217 (22.6)	416/1701 (24.5)	383/1714 (22.3)	2151/8692 (24.7)	2103/8703 (24.2)
With serious AEs	16/2220 (0.7)	12/2217 (0.5)	14/1701 (0.8)	10/1714 (0.6)	44/8692 (0.5)	40/8703 (0.5)
With vaccine-related serious AEs	4/2220 (0.2)	0/2217 (0.0)	3/1701 (0.2)	0/1714 (0.0)	4/8692 (0.0)	2/8703 (0.0)
Who died	1/2220 (0.0)	0/2217 (0.0)	2/1701 (0.2)	0/1714 (0.0)	2/8692 (0.0)	1/8703 (0.0)
Discontinued therapy due to an AE	4/2220 (0.2)	1/2217 (0.0)	5/1701 (0.3)	0/1714 (0.0)	8/8692 (0.1)	9/8703 (0.1)
Discontinued therapy due to a serious AE	1/2220 (0.0)	1/2217 (0.0)	2/1701 (0.1)	0/1714 (0.0)	2/8692 (0.0)	3/8703 (0.0)
Detailed safety population^a						
Subjects in analysis population	828	795	643	607	3170	3178
Subjects with follow-up	808	772	627	592	3121	3119
Subjects						
With 1 or more AEs	747/808 (92.5)	668/772 (86.5)	578/627 (92.2)	508/592 (85.8)	2888/3121 (92.5)	2770/3119 (88.8)
With injection-site AEs	689/808 (85.3)	588/772 (76.2)	533/627 (85.0)	451/592 (76.2)	2701/3121 (86.5)	2418/3119 (77.5)
With systemic AEs	495/808 (61.3)	456/772 (59.1)	383/627 (61.1)	341/592 (57.6)	2004/3121 (64.2)	1952/3119 (62.6)
With serious AEs	10/808 (1.2)	8/772 (1.0)	8/627 (1.3)	5/592 (0.8)	28/3121 (0.9)	24/3119 (0.8)
With vaccine-related serious AEs	1/808 (0.1)	0/772 (0.0)	1/627 (0.2)	0/592 (0.0)	1/3121 (0.0)	0/3119 (0.0)
Who died	0/808 (0.0)	0/772 (0.0)	1/627 (0.2)	0/592 (0.0)	1/3121 (0.0)	1/3119 (0.0)
Discontinued therapy due to an AE	2/808 (0.2)	1/772 (0.1)	3/627 (0.5)	0/592 (0.0)	5/3121 (0.2)	5/3119 (0.2)
Discontinued therapy due to a serious AE	0/808 (0.0)	1/772 (0.1)	1/627 (0.2)	0/592 (0.0)	1/3121 (0.0)	2/3119 (0.1)

NOTE. Data are no. of subjects in the given population with at least 1 follow-up visit 30 days after day 1/no. of subjects with follow-up data (%), unless otherwise indicated. Subjects are counted once in each applicable end-point category. A subject may appear in >1 category. AEs listed are from days 1–15 after receipt of a dose. PCR, polymerase chain reaction.

^a Detailed safety cohort only; filled out AE diary cards.

and geographically diverse population of 16–26-year-old women (mean age, 20.0 years). The mean age of sexual debut was 16.7 years. This means that, on average, 27% of subjects enrolled in protocols 013 and 015 were infected with at least 1 vaccine-related HPV type within 3.3 years after sexual debut. These findings are consistent with those of recent studies that have measured the incidence of new HPV-6, -11, -16, or -18 infection in young women [16–18]. Thus, a proportion of women who have recently experienced sexual debut will continue to be naive for all 4 HPV vaccine types and will likely benefit from the quadrivalent HPV vaccine.

Although a large proportion of 13–26-year-olds will be naive for all 4 HPV types included in the quadrivalent HPV vaccine, a proportion of subjects, increasing with age, will have been in-

fectured with at least 1 HPV vaccine type. Administration of the quadrivalent HPV vaccine has not been shown to impact the course of active infections present at the initiation of vaccination. Therefore, before implementation of a catch-up vaccination program in this age range, it is important to consider whether prescreening for the presence of HPV infection is needed. The analyses presented here strongly suggest that prescreening before vaccination of sexually experienced catch-up cohorts of young women is not advisable, because (1) infection with all 4 HPV vaccine types is very rare; (2) women who are infected with 1–3 of the 4 HPV types targeted by the quadrivalent HPV vaccine may be at high risk for acquisition of infection with the remaining HPV type(s); and (3) vaccination is highly effective in protecting these women against such incident infections.

The final consideration in institution of catch-up vaccination programs involves the cost-effectiveness of such catch-up programs relative to the routine vaccination program as well as other public health interventions. With respect to the quadrivalent HPV vaccine, a recent study using a validated population-dynamics model of HPV infection, disease, and health care costs has demonstrated that, in countries with existing cervical cancer screening programs, addition of a program of universal vaccination of 11–12-year-old girls along with catch-up vaccination in 13–24-year-old girls and women resulted in lower rates of cervical HPV disease and lower global costs compared with the addition of a program consisting solely of universal vaccination of 11–12-year-olds [19]. Similar results were seen in a recent report of the projected clinical benefits and cost-effectiveness of a bivalent (HPV-16 and -18) vaccine [20].

On the basis of the prophylactic efficacy of the quadrivalent HPV vaccine, the data presented here, and pharmacoeconomic considerations, the Advisory Committee for Immunization Practices of the Centers for Disease Control and Prevention, the group that sets vaccination policy in the United States, has stated that quadrivalent HPV vaccine programs in the United States should be implemented using a routine universal vaccination strategy in 11–12-year-old girls, supplemented by a universal catch-up vaccination strategy in 13–26-year-old girls and women. Similar recommendations have been made in other countries.

Severe Arthus-type reactions on reexposure to a given antigen have been noted with vaccines against such conditions as tetanus and hepatitis B [12, 13]. Concern of an Arthus-type adverse injection-site reaction against the quadrivalent HPV vaccine is mitigated by findings from this analysis. Statistical analysis of non-mutually exclusive populations such as those presented in this report (PCR positive and/or seropositive subjects are included in the overall population) is not ideal and, thus, is not presented. However, there was no appreciable increase in the frequency of local injection-site reactions in women who received quadrivalent HPV vaccine and had serological evidence of antibodies to an HPV vaccine type at enrollment, compared with that in the overall population.

In conclusion, women who received quadrivalent HPV vaccine were afforded high-level protection against precancerous cervical, vulvar, and vaginal lesions and genital warts related to the vaccine type or types to which they had not been previously exposed. These data provide support to the recommendation of universal catch-up immunization with the prophylactic quadrivalent HPV vaccine to prevent cervical and lower genital tract neoplasia.

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Acknowledgments

We thank the Data and Safety Monitoring Board (M. Boulos, J. T. Cox, F. Langmark, J. Modlin [Chair], A. Muñoz, V. Odland, and E. Wilkinson) and the Pathology Panel (A. Ferenczy, R. Kurman, B. Ronett, and M. Stoler). We also thank all of the study participants and investigators. Finally, we thank Liwen Xi, Margaret James, Carolyn Maas, and Haiping Zhou for assistance in preparation of the manuscript.

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