ORIGINAL ARTICLE

HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia

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ABSTRACT

BACKGROUND

The rate of anal cancer is increasing among both women and men, particularly men who have sex with men. Caused by infection with human papillomavirus (HPV), primarily HPV type 16 or 18, anal cancer is preceded by high-grade anal intraepithelial neoplasia (grade 2 or 3). We studied the safety and efficacy of quadrivalent HPV vaccine (qHPV) against anal intraepithelial neoplasia associated with HPV-6, 11, 16, or 18 infection in men who have sex with men.

METHODS

In a substudy of a larger double-blind study, we randomly assigned 602 healthy men who have sex with men, 16 to 26 years of age, to receive either qHPV or placebo. The primary efficacy objective was prevention of anal intraepithelial neoplasia or anal cancer related to infection with HPV-6, 11, 16, or 18. Efficacy analyses were performed in intention-to-treat and per-protocol efficacy populations. The rates of adverse events were documented.

RESULTS

Efficacy of the qHPV vaccine against anal intraepithelial neoplasia associated with HPV-6, 11, 16, or 18 was 50.3% (95% confidence interval [CI], 25.7 to 67.2) in the intention-to-treat population and 77.5% (95% CI, 39.6 to 93.3) in the per-protocol efficacy population; the corresponding efficacies against anal intraepithelial neoplasia associated with HPV of any type were 25.7% (95% CI, –1.1 to 45.6) and 54.9% (95% CI, 8.4 to 79.1), respectively. Rates of anal intraepithelial neoplasia per 100 person-years were 17.5 in the placebo group and 13.0 in the vaccine group in the intention-to-treat population and 8.9 in the placebo group and 4.0 in the vaccine group in the per-protocol efficacy population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI, 18.0 to 75.3) in the intention-to-treat population and by 74.9% (95% CI, 8.8 to 95.4) in the per-protocol efficacy population. The corresponding risks of persistent anal infection with HPV-6, 11, 16, or 18 were reduced by 59.4% (95% CI, 43.0 to 71.4) and 94.9% (95% CI, 80.4 to 99.4), respectively. No vaccine-related serious adverse events were reported.

CONCLUSIONS

Use of the qHPV vaccine reduced the rates of anal intraepithelial neoplasia, including of grade 2 or 3, among men who have sex with men. The vaccine had a favorable safety profile and may help to reduce the risk of anal cancer. (Funded by Merck and the National Institutes of Health; ClinicalTrials.gov number, NCT00090285.)

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Anal cancer is biologically similar to cervical cancer, including having a causal relationship with human papillomavirus (HPV) infection.[1] Although HPV type 6 (HPV-6) or HPV type 11 (HPV-11) alone is rarely causal, the proportion of anal cancers associated with infection with HPV type 16 (HPV-16) or HPV type 18 (HPV-18) is as high as or higher than the proportion of cervical cancers.[1] Just as cervical cancer is preceded by high-grade cervical intraepithelial neoplasia (grade ≥2), anal cancer is preceded by high-grade anal intraepithelial neoplasia (grade 2 or 3).[2-4] Although not yet formally demonstrated, prevention or treatment of high-grade anal intraepithelial neoplasia most likely reduces the incidence of anal cancer. Although anal cancer is rare, the incidence is increasing by approximately 2% per year among both men and women in the general population.[5] Anal cancer is particularly common among certain high-risk groups, including men who have sex with men and men and women infected with the human immunodeficiency virus (HIV). Women with cervical or vulvar cancer[6,7] and persons receiving immunosuppressive treatment to prevent solid-organ graft rejection[8] are also at increased risk as compared with the general population.

Other HPV-associated anal lesions are also clinically important. Anal condyloma, a variant of grade 1 anal intraepithelial neoplasia, is associated with infection with HPV-6 or 11 and is one of the most common sexually transmitted diseases among men who have sex with men. Women are also at risk for anal condyloma. Condyloma may cause substantial psychological distress, and treatment may be painful and expensive.[9]

The quadrivalent HPV vaccine (qHPV) is efficacious in preventing persistent cervical infection with HPV-6, 11, 16, or 18 and high-grade cervical intraepithelial neoplasia associated with these infections.[10,11] It is also efficacious in men against persistent external genital infection with HPV-6, 11, 16, or 18 and related external genital lesions.[12] A vaccine that can prevent anal HPV infection and anal intraepithelial neoplasia associated with the HPV types targeted by the vaccine could be an important tool to prevent anal cancer, particularly in the absence of a routine preventive screening and treatment program. We therefore evaluated the efficacy of qHPV vaccine in preventing anal intraepithelial neoplasia (including condyloma) and anal cancer related to HPV-6, 11, 16, or 18 infection in men who have sex with men who were negative for HIV infection at enrollment.

METHODS

STUDY CONDUCT

The trial was designed by the sponsor (Merck) in collaboration with three academic authors and an external data and safety monitoring board. The sponsor collated the data, monitored the conduct of the trial, performed statistical analyses, and coordinated the writing and revision of the manuscript among all the authors. All the authors were actively involved in the collection, analysis, and interpretation of the data; the decision to submit the manuscript for publication; and approval of the final version. The first draft was written by an academic author with contributions from another academic author and two industry authors. All the authors vouch for the completeness and accuracy of the analyses presented. The study was conducted in accordance with the protocol (Merck protocol 020), available with the full text of this article at NEJM.org.

The institutional review board at each participating center approved the protocol. All study participants gave written informed consent. Studies were conducted in conformity with applicable country or local requirements and informed-consent and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

STUDY POPULATION

Between September 3, 2004, and August 29, 2008, we enrolled 3463 heterosexual men and 602 men who have sex with men in a randomized, placebo-controlled, double-blind study of the qHPV vaccine to prevent external genital lesions.[12] Here, we describe a substudy of anal HPV infection and anal intraepithelial neoplasia in the men who have sex with men. We selected men who have sex with men for this substudy because the high incidence of anal infection and disease in this group was anticipated to allow for study completion within acceptable timelines.

The 602 men who have sex with men were enrolled in seven countries (Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States), but the study was not powered to detect significant differences in vaccine efficacy or safety among countries. Inclusion criteria included an age of 16 to 26 years, five or fewer lifetime sexual partners, and engagement in insertive or receptive anal intercourse or oral sex with another boy or man within the past year. Exclusion criteria in-

cluded a history or presence of clinically detectable anogenital warts or genital lesions suggesting other sexually transmitted diseases or an intra-anal lesion on anoscopy consistent with anal intraepithelial neoplasia or condyloma. Participants found to be HIV-positive before the first day of the study were excluded from the trial. Thirty-three participants diagnosed with HIV during the study were not withdrawn from the trial; they were referred for appropriate counseling and treatment and participated in all study procedures. Table S1 in the Supplementary Appendix (available at NEJM.org) provides further eligibility information.

VACCINE AND RANDOMIZATION

The qHPV L1 viruslike particle vaccine (Gardasil or Silgard, Merck) has been described previously.[13] Men who have sex with men were randomly assigned, in a 1:1 ratio and according to a computer-generated schedule produced by the sponsor, to receive qHPV vaccine or placebo at day 1, month 2 (±3 weeks), and month 6 (±4 weeks). Vaccine or placebo was administered as a 0.5-ml injection in the deltoid muscle, generally on the same side of the body throughout the study. All investigators and site personnel, participants, monitors, and laboratory personnel remained unaware of the treatment assignments throughout the study, as did the sponsor's staff from the time of study onset through the time of the database lock for analysis.

OBJECTIVES AND STUDY MEASUREMENTS

Serum specimens for HPV serologic testing were obtained on study day 1 and month 7. Detailed anal examinations were scheduled for day 1 and months 7, 12, 18, 24, 30, and 36. At each visit, consecutive Dacron swabs were inserted into the anal canal to collect cells for anal cytologic analysis and HPV DNA,[14] followed by a digital rectal examination and standard anoscopy. Participants underwent high-resolution anoscopy with biopsy of visible lesions if an abnormality was felt on digital rectal examination or seen on standard anoscopy, if anal cytologic testing showed atypical squamous cells of undetermined significance or more serious signs, or if HPV-related perianal lesions were histologically confirmed. All participants underwent high-resolution anoscopy and biopsy of any visible lesions at the exit visit.

Intra-anal samples were tested for HPV DNA with the use of multiplex polymerase-chain-reaction (PCR) assays, as described previously, to identify participants who were infected before enrollment or in whom new HPV infections developed during the study.[10,11] Each biopsy-obtained thin section and each swab specimen was evaluated with the use of three primer-pair sets per HPV type, which amplified a portion of three separate open reading frames. Thin sections for which a specific HPV type was amplified in two or more PCR assays for the same HPV type were classified as HPV-positive for that type. All biopsy specimens were processed independently to prevent contamination of HPV DNA and were read in a blinded fashion, first by pathologists at the central laboratory for purposes of clinical management and then by a panel of pathologists for end-point adjudication. HPV testing of thin-section specimens was performed at the central laboratory.

To assess vaccine safety, participants used vaccination report cards to record oral temperature and adverse events occurring at the injection site 1 to 5 days after each vaccination and systemic and serious adverse events occurring 1 to 15 days after each vaccination. In addition, all serious adverse events, including those considered related to the vaccine or a study procedure by the investigators, were recorded, as were all deaths.

STUDY END POINTS

Efficacy was measured in the per-protocol efficacy population: participants who were seronegative and had HPV DNA–negative swab and biopsy specimens at day 1 for relevant vaccine types, were negative for vaccine-type DNA through month 7, and did not violate the protocol. Case counting in this population commenced at month 7.

The intention-to-treat population consisted of participants who were or were not seropositive or DNA-positive for the vaccine HPV types at enrollment, received at least one dose of vaccine or placebo, and returned for follow-up. Case counting commenced after day 1.

The prespecified primary efficacy end point was HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia or anal cancer. End points were determined to have occurred in a biopsy specimen if the following were true: a consensus diagnosis by the pathology panel of anal intraepithelial neoplasia grade 1 (including condyloma), grade 2, or grade 3 or anal cancer; and detection of HPV-6, 11, 16, or 18 DNA by means of PCR assay in a section adjacent to the section used for histologic diagnosis. Some participants may have contributed more than one lesion to the analysis.

Table 1. Vaccine Efficacy against Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in the Intention-to-Treat Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
AIN due to any HPV type	275	74	569.0	13.0	276	103	588.4	17.5	25.7 (–1.1 to 45.6)
HPV-6, 11, 16, or 18	275	38	607.1	6.3	276	77	611.9	12.6	50.3 (25.7 to 67.2)
HPV-16 or 18	275	12	662.7	1.8	276	27	668.3	4.0	55.2 (8.5 to 79.3)
AIN due to a specific HPV type									
HPV-6	275	18	644.8	2.8	276	47	645.3	7.3	61.7 (32.8 to 79.1)
HPV-11	275	13	651.2	2.0	276	25	660.5	3.8	47.3 (–7.1 to 75.2)
HPV-16	275	8	668.7	1.2	276	18	678.6	2.7	54.9 (–9.0 to 83.0)
HPV-18	275	5	671.9	0.7	276	11	684.5	1.6	53.7 (–44.6 to 87.4)
By lesion type									
AIN grade 1	275	31	619.3	5.0	276	62	624.1	9.9	49.6 (21.2 to 68.4)
Condyloma acuminatum	275	13	651.3	2.0	276	31	664.2	4.7	57.2 (15.9 to 79.5)
Flat lesion	275	27	636.0	4.2	276	48	641.3	7.5	43.3 (7.3 to 66.0)
AIN grade 2 or 3	275	18	660.1	2.7	276	39	655.2	6.0	54.2 (18.0 to 75.3)
Grade 2	275	11	668.0	1.6	276	29	671.5	4.3	61.9 (21.4 to 82.8)
Grade 3	275	10	665.9	1.5	276	19	672.8	2.8	46.8 (–20.2 to 77.9)
Anal cancer	275	0	678.4	0.0	276	0	694.8	0.0	NA

* The intention-to-treat population consisted of study participants who received at least one dose of the study drug. A participant may have been counted more than once if multiple lesions in different categories developed. NA denotes not applicable.

The prespecified secondary efficacy end point of persistent HPV infection was defined as detection of the same HPV type (HPV-6, 11, 16, or 18) in an anal swab or biopsy specimen collected during two or more consecutive visits 6 months or more (±1 month) apart. Participants for whom HPV-6, 11, 16, or 18 DNA was detected in any swab or biopsy specimen during at least one visit were included in the end point of DNA detection at any time during the study.

STATISTICAL ANALYSIS

The primary efficacy end point was the incidence of HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia or anal cancer. Assuming a true vaccine efficacy for this end point of 85%, a lower bound for the confidence interval for vaccine efficacy greater than 0%, a one-sided α value of 0.025, and equal duration of follow-up in the vaccine and placebo groups, we calculated that 17 cases of the primary efficacy end point among men who have sex with men would be required in the per-protocol efficacy population for at least 90% power to declare the vaccine efficacious. For the purpose of calculating the necessary sample size, we conservatively assumed that the study would continue until the 17 cases had been observed in the placebo group (i.e., vaccine efficacy is 100%).

Multiple HPV types were sometimes detected in biopsy specimens of lesions. A post hoc case-assignment analysis was performed in the per-protocol efficacy population to identify the HPV type most likely to have caused a given lesion. The methods used to assign a specific HPV type to a lesion is described in the Supplementary Appendix.

RESULTS

STUDY PARTICIPANTS

A total of 602 men who have sex with men were enrolled (Table S1 in the Supplementary Appendix). Of these, 299 were vaccinated with qHPV

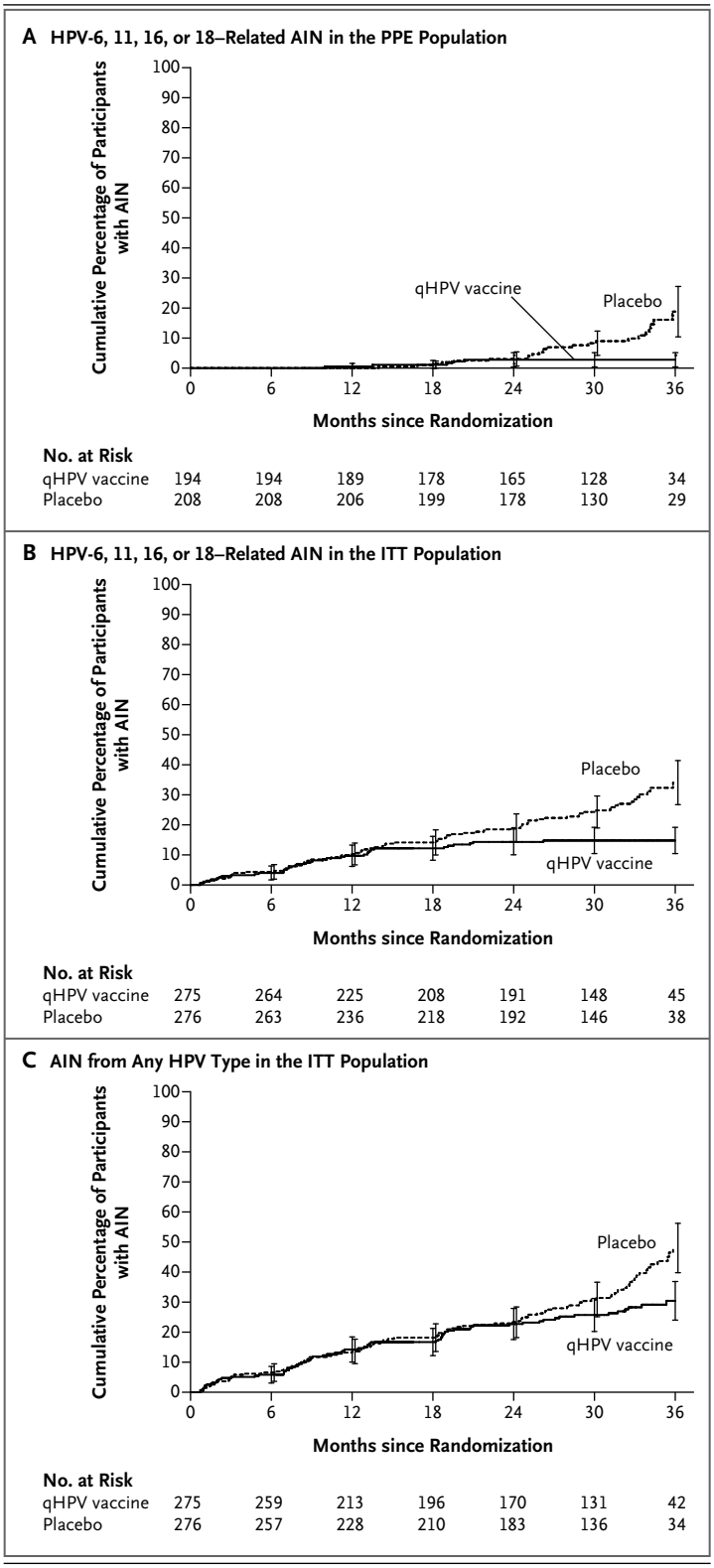

Figure 1. Cumulative Percentages of Participants with Human Papillomavirus (HPV)–Related Anal Intraepithelial Neoplasia.

Data are shown for HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia (AIN) in the per-protocol efficacy (PPE) population (Panel A) and the intention-to-treat (ITT) population (Panel B) and for AIN from infection by any HPV type in the ITT population (Panel C). The quadrivalent HPV (qHPV) vaccine is a recombinant vaccine against infection with HPV types 6, 11, 16, and 18. I bars indicate 95% confidence intervals.

vaccine and 299 with placebo. In all, 432 men who have sex with men (71.8%) had completed the 36-month follow-up period by the time the study was terminated. Roughly two thirds of participants were included in the per-protocol efficacy population, which was followed for a mean of 2.2 years after month 7.

The study groups were balanced with respect to age, race and ethnic group, region, smoking status, circumcision status, and sexual history (Table S2 in the Supplementary Appendix) as well as reason for discontinuation (data not shown). At baseline, 165 (27.4%) men were seropositive or HPV DNA–positive for HPV-6 or 11, 99 (16.4%) for HPV-16, and 68 (11.3%) for HPV-18. Among the 598 participants who received at least one dose of vaccine or placebo, 194 qHPV-vaccine recipients and 208 placebo recipients were eligible for the per-protocol efficacy analysis of HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia end points (Fig. S1 in the Supplementary Appendix).

EFFICACY IN PREVENTING ANAL INTRAEPITHELIAL NEOPLASIA IN INTENTION-TO-TREAT POPULATION

In the intention-to-treat population, vaccine efficacy against anal intraepithelial neoplasia due to any HPV type was 25.7% (95% confidence interval [CI], –1.1 to 45.6) (Table 1). Efficacy against HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia was 50.3% (95% CI, 25.7 to 67.2). Significant reductions in both anal intraepithelial neoplasia of grade 1 (49.6%; 95% CI, 21.2 to 68.4) and anal intraepithelial neoplasia of grade 2 or 3 (54.2%; 95% CI, 18.0 to 75.3) were seen in the intention-to-treat population. Efficacy ranged from 47.3 to 61.7% for anal intraepithelial neoplasia analyzed according to HPV type but was statistically significant only for HPV-6. Figure 1 shows the time to detection of HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia in the per-protocol efficacy population and intention-to-treat population, as well as the time to detection of anal intraepithelial neoplasia related to any HPV type in the intention-to-treat population.

Table 2. Vaccine Efficacy against HPV-6, 11, 16, or 18–Related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in the Per-Protocol Efficacy Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)†
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
AIN due to any HPV type‡	129	12	299.4	4.0	126	28	315.2	8.9	54.9 (8.4 to 79.1)
HPV-6, 11, 16, or 18	194	5	381.1	1.3	208	24	411.6	5.8	77.5 (39.6 to 93.3)
HPV-16 or 18	192	2	382.2	0.5	205	10	408.8	2.4	78.6 (–0.4 to 97.7)
AIN due to a specific HPV type									
HPV-6	141	3	275.2	1.1	144	10	298.5	3.4	67.5 (–26.4 to 94.2)
HPV-11	141	0	279.2	0.0	144	6	298.2	2.0	100 (9.3 to 100)
HPV-16	167	2	330.6	0.6	170	6	341.9	1.8	65.5 (–92.8 to 96.6)
HPV-18	173	0	345.3	0.0	193	4	387.4	1.0	100 (–70.0 to 100)
By lesion type									
AIN grade 1	194	4	383.1	1.0	208	16	413.8	3.9	73.0 (16.3 to 93.4)
Condyloma acuminatum	194	0	386.8	0.0	208	6	418.2	1.4	100 (8.2 to 100)
Flat lesion	194	4	383.1	1.0	208	11	416.7	2.6	60.4 (–33.5 to 90.8)
AIN grade 2 or 3	194	3	383.9	0.8	208	13	417.2	3.1	74.9 (8.8 to 95.4)
Grade 2	194	2	384.5	0.5	208	9	418.6	2.2	75.8 (–16.9 to 97.5)
Grade 3	194	2	385.4	0.5	208	6	419.7	1.4	63.7 (–103.0 to 96.4)
Anal cancer	194	0	386.8	0.0	208	0	421.1	0.0	NA

* The per-protocol efficacy population consisted of participants who were seronegative and had HPV DNA–negative swab and biopsy specimens on day 1 for relevant vaccine types, were negative for vaccine-type DNA through month 7, and did not have any protocol violations. To eliminate potential ascertainment bias, analyses in the per-protocol efficacy population excluded AIN diagnosed by the presence of perianal external lesions on high-resolution anoscopy. A participant may have been counted more than once if multiple lesions in different categories developed. NA denotes not applicable.

† A 95.1% confidence interval (CI) is reported for AIN due to HPV-6, 11, 16, or 18 because of the alpha adjustment applied.

‡ The analysis population for AIN due to any HPV type consisted of study participants who were seronegative and HPV DNA–negative for HPV-6, 11, 16, and 18 and HPV DNA–negative for HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 at enrollment and who received at least one dose of the study drug and completed at least one follow-up visit.

EFFICACY IN PREVENTING ANAL INTRAEPITHELIAL NEOPLASIA IN PER-PROTOCOL POPULATION

Table 2 shows the primary efficacy data against anal intraepithelial neoplasia in the per-protocol efficacy population and efficacy according to HPV type and grade of anal intraepithelial neoplasia. HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia developed in 5 participants in the vaccine group and 24 in the placebo group, with an observed efficacy of 77.5% (95% CI, 39.6 to 93.3). The vaccine was efficacious against both anal intraepithelial neoplasia of grade 1 (including condyloma) (73.0%; 95% CI, 16.3 to 93.4) and anal intraepithelial neoplasia of grade 2 or 3 (74.9%; 95% CI, 8.8 to 95.4). A total of 4 anal intraepithelial neoplasia lesions of grade 1 and 3 lesions of grade 2 or 3 related to HPV-6, 11, 16, or 18 developed in the vaccine group, as compared with 16 and 13, respectively, in the placebo group. Efficacy ranged from 65.5 to 100% for anal intraepithelial neoplasia analyzed according to HPV type but was statistically significant only for HPV-11. No cases of anal cancer developed in either study group.

Table S3 in the Supplementary Appendix shows the detection of HPV in swabs and biopsy samples from participants in whom anal intraepithelial neoplasia developed in association with more than one HPV type. In a post hoc case-assignment

Table 3. Vaccine Efficacy against HPV-6, 11, 16, or 18–Related Persistent Anal Infection and HPV DNA Detection at Any Time in the Intention-to-Treat Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
Persistent infection									
HPV-6, 11, 16, or 18	275	51	581.0	8.8	276	113	522.8	21.6	59.4 (43.0–71.4)
HPV-16 or 18	275	29	627.7	4.6	276	65	597.6	10.9	57.5 (33.2–73.6)
HPV-6	275	22	638.8	3.4	276	56	610.3	9.2	62.5 (37.5–78.2)
HPV-11	275	13	655.5	2.0	276	28	654.2	4.3	53.7 (7.5–78.0)
HPV-16	275	24	636.6	3.8	276	51	622.3	8.2	54.0 (23.9–72.9)
HPV-18	275	7	668.4	1.0	276	26	656.3	4.0	73.6 (37.5–90.3)
DNA detection at any time									
HPV-6, 11, 16, or 18	275	85	533.8	15.9	276	147	475.1	30.9	48.5 (32.3–61.1)
HPV-16 or 18	275	52	596.9	8.7	276	92	565.0	16.3	46.5 (24.0–62.7)
HPV-6	275	35	620.5	5.6	276	84	573.1	14.7	61.5 (42.3–74.8)
HPV-11	275	21	643.5	3.3	276	46	638.2	7.2	54.7 (22.6–74.3)
HPV-16	275	40	615.7	6.5	276	71	599.9	11.8	45.1 (18.0–63.7)
HPV-18	275	20	651.2	3.1	276	39	641.3	6.1	49.5 (11.3–72.1)

* The intention-to-treat population consisted of study participants who received at least one dose of the study drug. A participant may have been counted more than once if multiple lesions in different categories developed. Persistent infection was defined as detection of the same HPV type (HPV-6, 11, 16, or 18) in an anogenital swab or biopsy specimen collected at two or more consecutive visits 4 months or more apart. DNA detection at any time was defined as detection of HPV-6, 11, 16, or 18 DNA in an anogenital swab or biopsy specimen at one or more visits.

analysis performed in the per-protocol efficacy population to ascertain which of multiple HPV types detected was most likely to have caused the lesion, three lesions in the vaccine group, but none in the placebo group, were reassigned to nonvaccine types. The resulting recalculated efficacies against HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia grade 1 and grade 2 or 3 were 91.1% (95% CI, 64.2 to 99.0) and 91.7% (95% CI, 44.6 to 99.8), respectively.

EFFICACY IN PREVENTING PERSISTENT ANAL HPV INFECTION

In the intention-to-treat population, use of the qHPV vaccine significantly reduced persistent infection with HPV-6, 11, 16, or 18, with an observed efficacy of 59.4% (95% CI, 43.0 to 71.4) (Table 3). The rate of infection with HPV-6, 11, 16, or 18 at any time was reduced by 48.5% (95% CI, 32.3 to 61.1). Significant reductions were found for persistent infection with each of the four HPV types, as well as detection of their DNA at any time.

Table 4 shows vaccine efficacy against persistent infection with HPV and detection of HPV DNA at any time in the per-protocol efficacy population. The reduction in persistent anal HPV-6, 11, 16, or 18 infection was 94.9% (95% CI, 80.4 to 99.4). Efficacy against all vaccine types was high, and for HPV-6, 16, and 18 it was significant. Efficacies against persistent HPV-16 and 18 infection were 93.8% (95% CI, 60.0 to 99.9) and 100% (95% CI, 51.5 to 100), respectively. Vaccinated participants had an 84.0% reduction (95% CI, 68.6 to 92.7) in detection of HPV-6, 11, 16, or 18 DNA at any time. Reductions in the rate of detection of DNA from each of the four HPV types were significant and ranged from 76.2 to 100%.

Vaccine efficacy against HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia lesions

Table 4. Efficacy against HPV-6, 11, 16, or 18–Related Persistent Anal Infection and HPV DNA Detection at Any Time in the Per-Protocol Efficacy Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
Persistent infection									
HPV-6, 11, 16, or 18	193	2	385.6	0.5	208	39	381.2	10.2	94.9 (80.4 to 99.4)
HPV-16 or 18	191	1	384.1	0.3	205	24	389.6	6.2	95.8 (74.1 to 99.9)
HPV-6	140	1	277.9	0.4	144	13	286.8	4.5	92.1 (47.2 to 99.8)
HPV-11	140	0	279.4	0.0	144	5	295.6	1.7	100 (–15.5 to 100)
HPV-16	166	1	331.5	0.3	170	16	329.9	4.9	93.8 (60.0 to 99.9)
HPV-18	172	0	346.3	0.0	193	10	376.2	2.7	100 (51.5 to 100)
DNA detection at any time									
HPV-6, 11, 16, or 18	193	10	375.8	2.7	208	61	366.3	16.7	84.0 (68.6 to 92.7)
HPV-16 or 18	191	6	378.7	1.6	205	39	381.4	10.2	84.5 (63.1 to 94.6)
HPV-6	140	5	273.6	1.8	144	24	278.1	8.6	78.8 (43.4 to 93.7)
HPV-11	140	0	279.4	0.0	144	10	292.0	3.4	100 (53.4 to 100)
HPV-16	166	6	326.0	1.8	170	25	322.8	7.7	76.2 (40.7 to 92.0)
HPV-18	172	0	346.3	0.0	193	16	375.1	4.3	100 (71.9 to 100)

* The per-protocol efficacy population consisted of study participants who were seronegative and had HPV DNA–negative swab and biopsy specimens on day 1 for relevant vaccine types, were negative for vaccine-type DNA through month 7, and did not have any protocol violations. Persistent infection was defined as detection of the same HPV type (HPV-6, 11, 16, or 18) in an anogenital swab or biopsy specimen collected at two or more consecutive visits 4 months or more apart. DNA detection at any time was defined as detection of HPV-6, 11, 16, or 18 in an anogenital swab or biopsy specimen at one or more visits.

among participants who were seropositive was 100% (95% CI, –26.2 to 100) in the subgroup without vaccine-type DNA on day 1 and 21.3% (95% CI, –94.2 to 69.1) in the subgroup with vaccine-type DNA on day 1 (Tables S5A and S5B in the Supplementary Appendix).

ADVERSE EVENTS

Table 5 presents the adverse events reported during the study period. The proportions of participants reporting adverse events were similar in the vaccine group and the placebo group. One or more adverse events were reported by 69.8% of qHPV-vaccine recipients and 70.6% of placebo recipients. The majority of events were local injection-site reactions, the rate of which was similar in the two groups. Few participants (1.3% in the vaccine group and 1.0% in the placebo group) reported having an injection-site adverse event that was "severe" (the worst possible classification). Approximately 18% of recipients in each group reported vaccine-related systemic adverse events. Details of systemic and injection-site adverse events are given in Table S4 in the Supplementary Appendix. No vaccine-related serious adverse events or deaths were reported in either group.

DISCUSSION

Our study shows efficacy of the qHPV vaccine against HPV-6, 11, 16, or 18–related anal intraepithelial neoplasia of grade 1 (including condyloma) or grade 2 or 3, against persistent anal infection with each of the four HPV strains, and against anal detection at any time of DNA of each of the four HPV types, in both the per-protocol efficacy population and the intention-to-treat population. The proportion of participants who reported seri-

Table 5. Clinical Adverse Events during the Study in the Participants in the Analysis Population Who Had Follow-up Data.

Adverse Event	qHPV Vaccine (N=288)	Placebo (N=289)
	number (percent)	
None	87 (30.2)	85 (29.4)
Any	201 (69.8)	204 (70.6)
At injection site*	167 (58.0)	171 (59.2)
Systemic†	112 (38.9)	125 (43.3)
Vaccine-related‡	183 (63.5)	185 (64.0)
At injection site	167 (58.0)	170 (58.8)
Systemic	52 (18.1)	54 (18.7)
Serious§‖	2 (0.7)	0
Death	0	0
Serious vaccine-related	0	0

* Adverse events at the injection site were those reported as having occurred 1 to 5 days after any dose.
† Systemic adverse events were those reported as having occurred 1 to 15 days after any dose.
‡ Vaccine-related adverse events were those determined by the investigator to be possibly, probably, or definitely related to the vaccine.
§ The two serious adverse events in the qHPV vaccine group were an allergic reaction to peanuts and seizure caused by varicella-related fever.

ous adverse events or who discontinued the study owing to an adverse event was relatively low and was similar in the two groups. Lower rates of adverse events were observed in this study, in both groups, than in earlier studies of female participants — particularly regarding injection-site–related and systemic adverse events.[10,11]

Strengths of this study include the study design, as well as inclusion of participants from several countries, resulting in a diverse study population. Limitations include the narrow range of ages of the participants and the relatively short follow-up time. The study participants had limited sexual activity (a maximum of five lifetime sexual partners) as compared with many boys and men who have sex with men of similar age or older,[15] and since the qHPV vaccine is preventive, the results may not be generalizable to boys and men in the general population of similar ages to those of our study population. Among men who have sex with men who have not yet initiated sexual activity, vaccination would most likely result in levels of efficacy similar to those in our per-protocol efficacy population.

HPV vaccination in men who have sex with men presents special challenges. Efficacy would be optimal if vaccination occurred before the initiation of sexual activity, but few boys identify themselves to parents or physicians as men who have sex with men by this time.[16] Programs designed to target persons for vaccination on the basis of sexual orientation at a time when they have had limited prior sexual exposure would probably fail. Furthermore, the "herd immunity" that may result from vaccinating only girls and women would not fully benefit men who have sex with men, since these men may become infected with HPV through sexual contact with girls, women, boys, or men. Consistent with this, the rate of genital warts declined among heterosexual men, but not among men who have sex with men, in a setting with high levels of vaccination of girls and women.[17]

Although our study only included men who have sex with men, our data suggest potential benefits of vaccination for women and heterosexual men, beyond the already demonstrated protection against cervical and vulvovaginal disease and external genital condyloma. Anal HPV infection, anal intraepithelial neoplasia, and anal cancer have been shown to occur in women and heterosexual men.[18-22] Given the biologic similarity between anal cancer in men and women, including the high proportion of anal-cancer cases associated with HPV-16 or 18 infection, we would expect the qHPV vaccine to protect against anal intraepithelial neoplasia in the female and heterosexual male populations to a degree similar to that among men who have sex with men.

Our study suggests that qHPV vaccination could be a tool for preventing anal HPV-related disease, potentially even cancer. There were no cases of anal cancer in this young population, as we expected. However, just as the prevention of cervical intraepithelial neoplasia of grade 2 or 3 is expected to reduce the risk of cervical cancer in vaccinated women, prevention of anal intraepithelial neoplasia of grade 2 or 3 is expected to reduce the risk of anal cancer among vaccinees. The qHPV vaccine also reduced the incidence of anal condyloma, a substantial added benefit of vaccination.

In summary, the qHPV vaccine is efficacious in reducing the incidences of persistent anal infection with HPV-6, 11, 16, or 18 and anal intraepithelial neoplasia associated with these HPV types. Unlike the screening and treatment of cervical intraepithelial neoplasia to reduce the risk of cervical cancer, there is currently no routine screening and treatment of anal intra-

epithelial neoplasia of grade 2 or 3 to reduce the risk of anal cancer. Vaccination may be the best long-term approach to reducing the risks of both anal cancer and anal condyloma.

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