Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial

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Summary

Background The quadrivalent human papillomavirus (HPV) vaccine was shown to prevent infections and lesions related to HPV6, 11, 16, and 18 in a randomised, placebo-controlled study in men aged 16–26 years. We assessed the incidences of external genital warts related to HPV6 or 11, and external genital lesions and anal dysplasia related to HPV6, 11, 16, or 18, over 10 years of follow-up.

Methods The 3-year base study was an international, multicentre, double-blind, randomised, placebo-controlled trial done at 71 sites in 18 countries. Eligible participants were heterosexual men (aged 16–23 years) or men who have sex with men (MSM; aged 16–26 years). Men who had clinically detectable anogenital warts or genital lesions at screening that were suggestive of infection with non-HPV sexually transmitted diseases, or who had a history of such findings, were excluded. Eligible participants were randomly assigned (1:1) to receive three doses of either quadrivalent HPV vaccine or placebo on day 1, month 2, and month 6, administered as a 0·5-mL injection into the deltoid muscle. The 7-year, open-label, long-term follow-up extension study was done at 46 centres in 16 countries. Participants who received one or more doses of the quadrivalent HPV vaccine in the base study were eligible for enrolment into the long-term follow-up study (early vaccination group). Placebo recipients were offered the three-dose quadrivalent HPV vaccine at the end of the base study; those who received one or more quadrivalent HPV vaccine doses were eligible for enrolment into the long-term follow-up study (catch-up vaccination group). The primary efficacy endpoints were the incidence of external genital warts related to HPV6 or 11 and the incidence of external genital lesions related to HPV6, 11, 16, or 18 in all participants and the incidence of anal intraepithelial neoplasia (including anal warts and flat lesions) or anal cancer related to HPV6, 11, 16, or 18 in MSM only. The primary efficacy analysis was done in the per-protocol population for the early vaccination group, which included participants who received all three vaccine doses, were seronegative at day 1 and PCR-negative from day 1 through month 7 of the base study for the HPV type being analysed, had no protocol violations that could affect evaluation of vaccine efficacy, and had attended at least one visit during the long-term follow-up study. For the catch-up vaccination group, efficacy was assessed in the modified intention-to-treat population, which included participants who had received at least one vaccine dose, were seronegative and PCR-negative for HPV types analysed from day 1 of the base study to the final follow-up visit before receiving the quadrivalent HPV vaccine, and had at least one long-term follow-up visit. Safety was assessed in all randomised participants who received at least one vaccine dose. This study is registered with ClinicalTrials.gov, NCT00090285.

Findings Between Aug 10, 2010, and April 3, 2017, 1803 participants were enrolled in the long-term follow-up study, of whom 936 (827 heterosexual men and 109 MSM) were included in the early vaccination group and 867 (739 heterosexual men and 128 MSM) were included in the catch-up vaccination group. Participants in the early vaccination group were followed up for a median of 9·5 years (range 0·1–11·5) after receiving the third dose of the quadrivalent HPV vaccine, and participants in the catch-up vaccination group were followed up for a median of 4·7 years (0·0–6·6) after receiving the third dose. In early vaccine group participants during long-term follow-up compared with the placebo group in the base study, the incidence per 10 000 person-years of external genital warts related to HPV6 or 11 was 0·0 (95% CI 0·0–8·7) versus 137·3 (83·9–212·1), of external genital lesions related to HPV6, 11, 16, or 18 was 0·0 (0·0–7·7) versus 140·4 (89·0–210·7), and of anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16, or 18 in MSM only was 20·5 (0·5–114·4) versus 906·2 (553·5–1399·5). Compared with during the base study (ie, before quadrivalent HPV vaccine administration), during the long-term follow-up period, participants in the catch-up vaccination group had no new reported cases of external genital warts related to HPV6 or 11 (149·6 cases per 10 000 person-years [95% CI 101·6–212·3] *vs* 0 cases per 10 000 person-years [0·0–13·5]) or external genital lesions related to HPV6, 11, 16, or 18 (155·1 cases per 10 000 person-years [108·0–215·7] *vs* 0 cases per 10 000 person-years [0·0–10·2]), and a lower incidence of anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16, or 18 (886·0 cases per 10 000 person-years [583·9–1289·1] *vs* 101·3 cases per 10 000 person-years [32·9–236·3]). No vaccine-related serious adverse events were reported.

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Interpretation The quadrivalent HPV vaccine provides durable protection against anogenital disease related to HPV6, 11, 16, and 18. The results support quadrivalent HPV vaccination in men, including catch-up vaccination.

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Introduction

Worldwide, approximately 70 000 cases of cancer attributable to the human papillomavirus (HPV), including penile, anal, oropharyngeal, and other head and neck cancers, occur annually in men.[1] Over 80% of these cancers are attributable to HPV16 and 18, with more than 90% attributable to HPV types 16, 18, 31, 33, 45, 52, and 58.[2] Based on surveillance studies in Europe, North America, and Australia, the annual incidence of external genital warts (condylomata acuminata) in men is 0·1–0·2%, and it could be higher in other countries.[3] Approximately 90% of external genital warts are caused by HPV6 and 11.[4]

Men remain susceptible to HPV infections throughout their lives.[5] The probability of acquiring a new genital HPV infection is similar for sexually active men and women.[6] The prevalence of anogenital HPV infection in men, however, remains consistent throughout their lifespan, whereas women generally show a decreased prevalence with age.[5,7–9] HPV infection is associated with higher seroconversion rates in women than in men.[10] Antibodies generated following natural HPV infection in women are associated with reduced risk of subsequent infection, whereas similar protection is not observed in men.[11] This diminished immune response to HPV infection and the continued acquisition of new HPV infections in men could contribute to their consistent prevalence of HPV with age.

In a randomised, placebo-controlled trial done in young men aged 16–26 years (herein referred to as the base study), a three-dose regimen of the quadrivalent HPV vaccine showed efficacy against external genital and intra-anal persistent infection, external genital lesions, and anal intraepithelial neoplasia related to HPV6, 11, 16, and 18.[12–14] The quadrivalent HPV vaccine induced robust antibody titres and had an acceptable safety profile.[15,16]

Durable vaccine protection would maximise benefit in men, given their lifelong risk of HPV infection. Despite this potential benefit, there is a notable deficiency of research into the long-term effectiveness of HPV vaccines in men, particularly among men who have sex with men (MSM), who are at high risk of HPV-associated external genital warts and anal cancer. A long-term follow-up extension of the base study[12–16] in young men was therefore implemented to assess the incidence of external genital warts related to HPV6 and 11 and external

Research in context

Evidence before this study

The quadrivalent human papillomavirus (HPV) vaccine was shown to prevent infections and lesions related to HPV6, 11, 16, and 18 in a 3-year randomised, placebo-controlled study in men aged 16–26 years that was initiated in 2004. To search for long-term follow-up studies after HPV vaccination, we searched PubMed without language restrictions using the search terms "HPV vaccine" and "long-term follow-up". We limited the search to articles published between Jan 1, 2000, and Oct 15, 2020. We identified several long-term follow-up studies showing sustained effectiveness of bivalent and quadrivalent HPV vaccines in adolescents for up to 10 years and in young women (aged 16–25 years) for up to 14 years. After limiting these search results to include the search terms "males" or "men", we identified one long-term follow-up study of the quadrivalent HPV vaccine that showed durable protection and sustained antibody titres in boys and girls vaccinated at the age of 9–15 years. No previous long-term follow-up studies of HPV vaccines in men aged 16 years or older were identified.

Added value of this study

This long-term follow-up study, which began in 2010, shows that young men vaccinated with the quadrivalent HPV vaccine remain protected from anogenital disease related to HPV6, 11, 16, and 18 for up to 10 years after vaccination. There were no new cases of external genital warts related to HPV6 or 11, external genital lesions related to HPV6, 11, 16, or 18, or high-grade anal lesions related to HPV6, 11, 16, or 18 during the long-term follow-up period among men vaccinated with the quadrivalent HPV vaccine at the start of the base study. Catch-up vaccination of placebo recipients with the quadrivalent HPV vaccine at the end of the 3-year base study resulted in no new cases of external genital warts related to HPV6 or 11 or external genital lesions related to HPV6, 11, 16, or 18 and diminished incidence of anal lesions during long-term follow-up.

Implications of all the available evidence

To our knowledge, this is the first study to show that the quadrivalent HPV vaccine can confer long-term protection from diseases related to HPV6, 11, 16, and 18 in young men for up to 10 years after vaccination, consistent with the durable efficacy observed in previous studies in adolescents and young women. The results support the implementation of gender-neutral vaccination and catch-up vaccination programmes.

genital lesions and anal dysplasia related to HPV6, 11, 16, and 18, as well as the immunogenicity and safety of the quadrivalent HPV vaccine, up to 10 years after the last dose. Herein, we report the final results of this long-term follow-up study.

Methods

Study design and participants

The base study[12–16] was an international, multicentre, double-blind, randomised, placebo-controlled trial done at 71 ambulatory care sites in 18 countries (Australia, Brazil, Canada, Costa Rica, Croatia, Finland, Germany, Mexico, the Netherlands, Norway, the Philippines, Peru, Portugal, South Africa, Spain, Sweden, Taiwan, and the USA). Eligible participants were heterosexual men (aged 16–23 years), with one to five female sexual partners during their lifetime, or MSM (aged 16–26 years), with one to five male or female partners during their lifetime. Men who had clinically detectable anogenital warts or genital lesions at screening that were suggestive of infection with non-HPV sexually transmitted diseases, or who had a history of such findings, were excluded. Participants were randomly assigned (1:1) to receive three doses administered as a 0·5-mL injection in the deltoid muscle of quadrivalent HPV vaccine or placebo on day 1, month 2, and month 6, and followed up for a median of 2·9 years (range 0·0–4·3) after the first dose for HPV-related disease, infection, and antibody levels. At the end of the follow-up period, once efficacy had been shown,[12] participants in the placebo group were offered catch-up vaccination with three doses of the quadrivalent HPV vaccine and participants in the quadrivalent HPV vaccine group who did not complete the vaccine series during the study period were offered their remaining vaccine doses.

All study sites from the base study were invited to join a 7-year, open-label extension of the base study. However, 25 sites could not commit to an additional 7 years of follow-up for various reasons and therefore did not participate. As such, the long-term follow-up study was done at 46 centres in 16 countries (Australia, Brazil, Canada, Costa Rica, Finland, Germany, Mexico, Norway, Peru, Philippines, South Africa, Spain, Sweden, Taiwan, the Netherlands, and the USA). Participants who received one or more doses of quadrivalent HPV vaccine in the base study were eligible for enrolment in the long-term follow-up study. Two cohorts were assessed in the long-term follow-up study: the early vaccination group, which included participants who received the quadrivalent HPV vaccine during the base study, and the catch-up vaccination group, which included placebo recipients in the base study who were offered catch-up vaccination with three doses of quadrivalent HPV vaccine. The only exclusion criterion for enrolment in the long-term follow-up study was enrolment in a study that involved or would interfere with the collection of anogenital samples. Detection of external genital or anal lesions before the long-term follow-up study was not a reason for exclusion.

The base study and study extension were done in accordance with Good Clinical Practice Guidelines and applicable country or local statutes and regulations regarding ethical committee review, informed consent, and the protection of the rights and welfare of human participants in biomedical research. Participants (or their legally authorised representatives) provided written informed consent at the start of the base study and again at the start of the long-term follow-up study. The protocol of the long-term follow-up study (V501–020–21) is available in the appendix (pp 9–74).

Procedures

Detailed anogenital examinations were done yearly during long-term follow-up (figure 1) to detect external genital lesions and intra-anal lesions using the same methods as in the base study.[12,13] Briefly, external genitalia (penile, scrotal, perineal, and perianal areas) were examined for skin abnormalities. New external genital lesions assessed by the investigator to be possibly, probably, or definitely related to HPV infection, or of unknown aetiology, were biopsied and processed by a central laboratory for HPV detection and diagnosis.

Additionally, MSM underwent yearly anal cytology sampling (ThinPrep, Cytyc, Boxborough, MA, USA) followed by digital anorectal examination and standard anoscopy. Participants with abnormal anal cytology (defined as atypical squamous cells of undetermined significance or worse), suspected HPV-related lesions during standard anoscopy, or histologically confirmed HPV-related lesions in the perianal region were referred to undergo high-resolution anoscopy, as described previously.[13] In addition, all MSM underwent routine high-resolution anoscopy at the first and final long-term follow-up visits. Biopsy samples were obtained during high-resolution anoscopy of HPV-related lesions. Anorectal swab samples were collected yearly for chlamydia and gonorrhoea culture. The number of new sexual partners was assessed with a sexual history questionnaire, which was completed by all participants at yearly visits.

The same approach and assays for disease endpoint evaluation in the base study were used during the long-term follow-up study, allowing consistent evaluation from day 1 of the base study to the end of the long-term follow-up study. Briefly, biopsy tissue was analysed by use of an in-house HPV Thinsection PCR assay.[17] HPV6, 11, 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, and 59 DNA was assessed by use of an in-house multiplex PCR assay.[18,19] A consensus diagnosis from a panel of four independent pathologists masked to vaccination and HPV PCR status was used for endpoint adjudication. Each member of the pathology panel reviewed slides independently to formulate a consensus diagnosis (by at least two pathologists) as previously described.[12]

Serum was collected for immunogenicity analyses at the first (between months 48 and 72) and last

(month 120 or year 10) long-term follow-up visits from participants in the early vaccination group (figure 1). Serum geometric mean titres (GMTs) and seropositivity to HPV types 6, 11, 16, and 18 were assessed by use of an in-house competitive Luminex immunoassay.[20–22] Additional immunogenicity analyses were done by use of the total IgG-Luminex immunoassay at the first and last visits of the long-term follow-up study.[23]

Outcomes

The primary efficacy endpoints in the long-term follow-up study were the incidence per 10 000 person-years of external genital warts related to HPV6 or 11 and the incidence per 10 000 person-years of external genital lesions (defined as external genital warts, penile, perianal, and perineal intraepithelial neoplasia, or penile, perianal, or perineal cancer) related to HPV6, 11, 16, or 18 in all participants, and the incidence per 10 000 person-years of anal intraepithelial neoplasia (including anal warts and flat lesions), or anal cancer related to HPV6, 11, 16, or 18 in MSM only. Immunogenicity was assessed as a secondary endpoint based on serum GMTs and seropositivity to HPV types 6, 11, 16, and 18, measured with the competitive Luminex immunoassay. GMTs and seropositivity, measured with the total IgG-Luminex immunoassay, were assessed as prespecified exploratory endpoints. Other exploratory endpoints included the incidence per 1 person-year of acquisition of new sexual partners and, among MSM only, the incidence per 10 000 person-years of anal chlamydia and gonorrhoea. Deaths from any cause and serious adverse events considered to be related to administration of the quadrivalent HPV vaccine or to a study procedure occurring at any time were reported during long-term follow-up.

Statistical analysis

In the absence of a concurrent placebo control group, efficacy could not be measured directly during the long-term follow-up period. Therefore, long-term vaccine efficacy was assessed based on the incidence of the primary endpoints and interpreted in the context of the incidence of the endpoints in the vaccine and placebo groups of the base study.

Efficacy data were summarised separately for the early vaccination group and the catch-up vaccination group during the base study and long-term follow-up study. For the early vaccination group, the per-protocol population was used for efficacy analyses, which included participants who received all three vaccine doses, were seronegative at day 1 and PCR-negative from day 1 through month 7 of the base study for the HPV type being analysed, had no protocol violations that could affect evaluation of vaccine efficacy, and had attended at least one visit during the long-term follow-up study. For the catch-up vaccination group, the modified intention-to-treat population was used for efficacy analyses, defined as those who had received at least one quadrivalent HPV vaccine dose, were seronegative and PCR-negative for HPV types analysed from day 1 of the base study to the final follow-up visit before vaccination with the quadrivalent HPV vaccine, and had at least one long-term follow-up visit. The efficacy analyses were done in the per-protocol population for the early vaccination group only because catch-up vaccination group participants' last PCR and serology testing was at their final base study visit. These participants received a quadrivalent HPV vaccine after a lag between the end of the base study and the start of long-term follow-up study, when they might have become PCR-positive or serology-positive to a new HPV type. Undetected HPV infection occurring between the final base study visit and the first dose of quadrivalent HPV vaccine (median duration 22 months [range 4–60]) could potentially have affected the measured vaccine efficacy in this population.

Prespecified supportive efficacy analyses were done in a modified intention-to-treat population of early vaccination group participants who received at least one vaccine dose, were seronegative and PCR-negative at day 1 of the base study for the HPV type analysed, and had at least one long-term follow-up visit.

Demographic and baseline characteristics of participants are summarised by descriptive statistics, including the mean (SD) and median (range) age and number of sexual partners, as well as the numbers and proportions of participants with one or more sexual partners or who were seropositive or PCR-positive for vaccine-targeted HPV types.

The incidence of efficacy endpoints per 10 000 person-years of follow-up and exact Poisson 95% CIs were reported based on: (1) total follow-up time within the long-term follow-up period (early vaccination and catch-up vaccination groups), and (2) total follow-up time from the beginning of the base study (early vaccination group only). The incidence (with nominal 95% CIs) for primary endpoints were also estimated by sexual orientation (MSM or heterosexual men) in a prespecified analysis, to assess whether the vaccination effect was consistent across these subgroups. When feasible, the percentage reduction in incidence in the early vaccination group relative to the catch-up vaccination group was assessed and calculated as 100 × (1–relative risk), where relative risk is the ratio of the incidence in the early vaccination group relative to the incidence in the catch-up vaccination group. The 95% CIs of the percent risk reduction or vaccine efficacy were calculated using the exact method, as described previously.[24] In exploratory analyses, the Kaplan-Meier method was used to generate cumulative incidence plots to illustrate accrual of cases of anal intraepithelial neoplasia or anal cancer over time since vaccination with the quadrivalent HPV vaccine.

Immunogenicity analyses were restricted to the early vaccination group. The per-protocol immunogenicity population included participants in the per-protocol efficacy population who had at least one immunogenicity

assessment during long-term follow-up. The results of the competitive Luminex immunoassay and IgG-Luminex immunoassay are reported in milliMerck units (mMUs) per mL. Although the same designation is used for the unit of measurement in both assays, competitive Luminex immunoassay mMU/mL and IgG-Luminex immunoassay mMU/mL are different units of measurement and cannot be directly compared between tests or for individual HPV types. GMTs and their associated 95% CIs were estimated on the basis of the assumption that log titres followed a normal distribution. The 95% CIs for the proportions of participants who were seropositive were calculated with the Clopper-Pearson exact method.

Safety analyses were done in all randomised participants who received at least one vaccine dose; participants were analysed according to treatment received. Vaccine-related or procedure-related serious adverse events and deaths were descriptively summarised as the number of events in each treatment group.

Statistical analyses were done using SAS software, version 9.4. This study is registered with ClinicalTrials.gov, NCT00090285.

Role of the funding source

In close collaboration with the external investigators, employees of Merck Sharp & Dohme, a subsidiary of Merck & Co (Kenilworth, NJ, USA), the sponsor and funder of the study, were involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Participants were enrolled in the base study from Sept 3, 2004, to Aug 29, 2008.[12] The long-term follow-up study was done between Aug 10, 2010 (ie, the first follow-up visit in the long-term follow-up study, corresponding to months 48–84 from the first follow-up visit in the base study), and April 3, 2017 (ie, the final follow-up visit at month 120). Of the 4065 participants in the base study, 1803 consented and were enrolled in the long-term follow-up study, of whom 936 (827 heterosexual men and 109 MSM) were included in the early vaccination group and 867 (739 heterosexual men and 128 MSM) were included in the catch-up vaccination group (figure 1). Overall, 1373 (76%) participants completed long-term follow-up, including 709 in the early vaccination group and 664 in the catch-up vaccination group. Most discontinuations were due to withdrawal of consent or loss to follow-up. Participants in the early vaccination group were followed up for analysis of vaccine efficacy for a maximum of 12·1 years (median 10 years [range 0·5–12·1]) after receiving the first dose of quadrivalent HPV vaccine or 11·5 years (median 9·5 years [0·1–11·5]) after receiving the third dose. Participants in the catch-up vaccination group were followed up for analysis of vaccine efficacy for a maximum of 7·2 years (median 5·2 years [0·6–7·2]) after

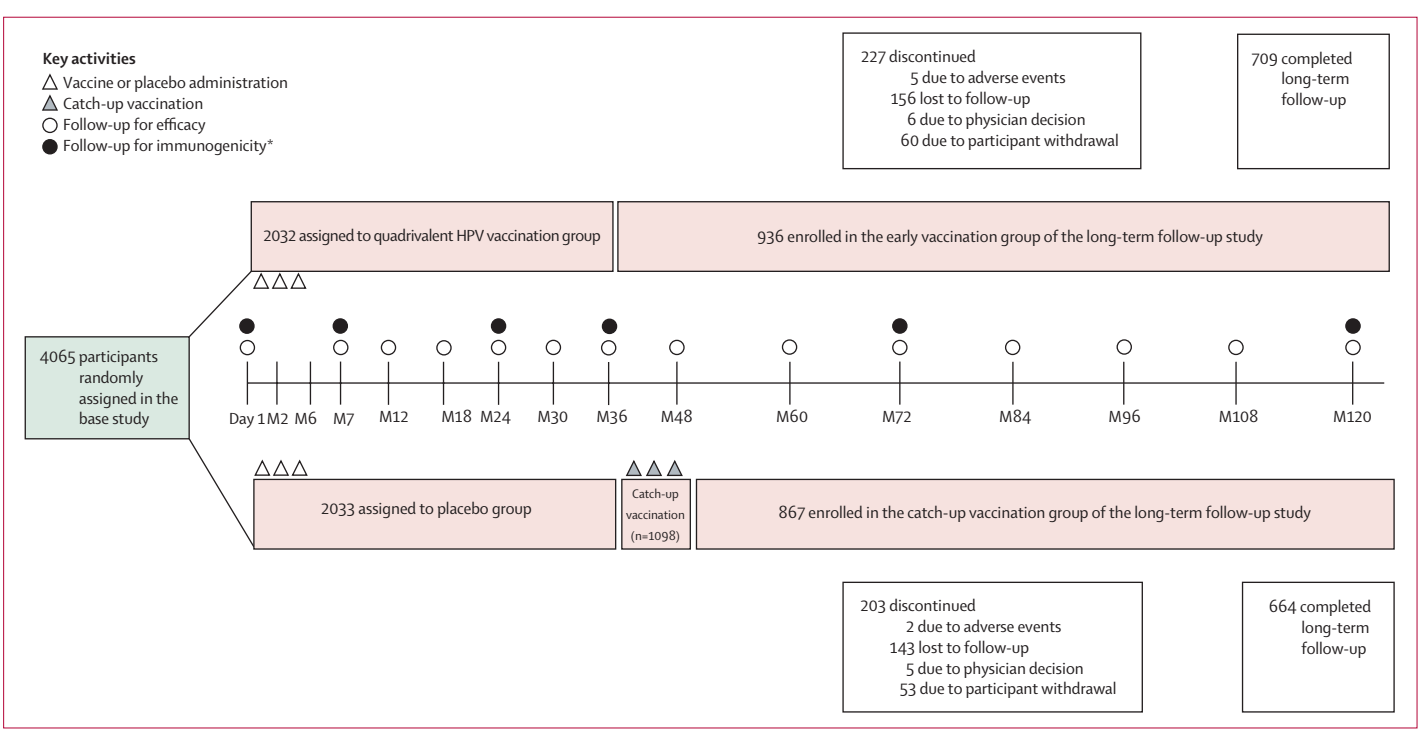


Figure 1: **Study design and participant flow**
HPV=human papillomavirus. *The first follow-up for immunogenicity in the long-term follow-up study occurred at any visit between months 48 and 84 (median follow-up was month 72).

	Early vaccination group, base study day 1 (n=936)	Catch-up vaccination group (n=867)	
		Base study day 1	Before catch-up vaccination*
Age, years			
Mean	21 (2·0)	20 (2·0)	25 (2·0)
Median	21 (16–26)	20 (16–26)	25 (20–30)
Lifetime number of sexual partners			
None	9 (1%)	9 (1%)	0
≥1	927 (99%)	856 (99%)	867 (100%)
No response	0	2 (<1%)	0
Lifetime number of sexual partners among participants who reported sex with one or more person			
All			
Mean	3 (1·4)	3 (1·4)	7 (7·1)
Median	3 (1–5)	3 (1–6)	5 (1–84)
Heterosexual men			
Mean	3 (1·4)	3 (1·4)	6 (4·7)
Median	3 (1–5)	3 (1–5)	5 (1–31)
MSM			
Mean	3 (1·3)	3 (1·4)	13 (13·4)
Median	3 (1–5)	3 (1–6)	9 (1–84)
Seropositive			
All			
HPV 6, 11, 16, or 18	75/935 (8%)	60/861 (7%)	128/867 (15%)
HPV 6	41/935 (4%)	35/861 (4%)	77/867 (9%)
HPV 11	17/935 (2%)	11/861 (1%)	30/867 (3%)
HPV 16	23/935 (2%)	23/861 (3%)	52/867 (6%)
HPV 18	11/935 (1%)	7/861 (1%)	15/867 (2%)
Heterosexual men			
HPV 6, 11, 16, or 18	46/826 (6%)	32/737 (4%)	78/739 (11%)
HPV 6	24/826 (3%)	16/737 (2%)	41/739 (6%)
HPV 11	8/826 (1%)	5/737 (1%)	15/739 (2%)
HPV 16	12/826 (1%)	12/737 (2%)	31/739 (4%)
HPV 18	7/826 (1%)	3/737 (<1%)	10/739 (1%)
MSM			
HPV 6, 11, 16, or 18	29/109 (27%)	28/124 (23%)	50/128 (39%)
HPV 6	17/109 (16%)	19/124 (15%)	36/128 (28%)
HPV 11	9/109 (8%)	6/124 (5%)	15/128 (12%)
HPV 16	11/109 (10%)	11/124 (9%)	21/128 (16%)
HPV 18	4/109 (4%)	4/124 (3%)	5/128 (4%)
PCR-positive			
All			
HPV 6, 11, 16, or 18	97/860 (11%)	103/809 (13%)	149/860 (17%)
HPV 6	42/859 (5%)	34/806 (4%)	57/860 (7%)
HPV 11	9/859 (1%)	11/804 (1%)	18/860 (2%)
HPV 16	42/860 (5%)	57/807 (7%)	70/860 (8%)
HPV 18	17/860 (2%)	25/804 (3%)	38/860 (4%)
Heterosexual men			
HPV 6, 11, 16, or 18	62/751 (8%)	66/682 (10%)	101/732 (14%)
HPV 6	24/750 (3%)	19/679 (3%)	34/732 (5%)
HPV 11	3/750 (<1%)	5/678 (1%)	11/732 (2%)
HPV 16	26/751 (3%)	35/681 (5%)	48/732 (7%)
HPV 18	12/751 (2%)	16/678 (2%)	26/732 (4%)

(Table 1 continues on next page)

the first quadrivalent HPV vaccine dose or 6·6 years (median 4·7 years [0·0–6·6]) after the third dose.

At the time of base study enrolment, baseline characteristics were generally similar between early vaccination group and catch-up vaccination group participants, and similar proportions of participants were seropositive and PCR-positive to HPV6, 11, 16, and 18 (table 1). At the end of the base study and before receiving their first quadrivalent HPV vaccination, participants in the catch-up vaccination group were older, had more lifetime sexual partners, and had a higher frequency of and PCR positivity to HPV 6, 11, 16, and 18 than those in the early vaccination group at the time they received their first dose of vaccine at the start of the base study (table 1). The baseline characteristics of participants in the base study who continued in the long-term follow-up study compared with those who did not were similar with respect to age, sexual history, and smoking status, and differed predominantly with respect to race and geographical region (appendix p 1). Hispanic American and Latin American had the highest racial and regional representations among long-term follow-up participants, whereas base study participants were most commonly White and North American.

Among participants in the per-protocol population of the early vaccination group, the incidence per 10 000 person-years of external genital warts related to HPV6 or 11 (0·0 [95% CI 0·0–8·7] *vs* 13·2 [1·6–47·6]), external genital lesions related to HPV6, 11, 16, or 18 (0·0 [0·0–7·7] *vs* 11·6 [1·4–41·8]), and of anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16 or 19 in MSM only (20·5 [0·5–114·4] *vs* 226·5 [61·7–580·0]) were lower during the long-term follow-up period than during the base study period (table 2). Corresponding incidences in unvaccinated controls (ie, the per-protocol population of the catch-up vaccination group during the base study) were 137·3 (83·9–212·1) for external genital warts related to HPV6 or 11, 140·4 (89·0–210·7) for external genital lesions related to HPV6, 11, 16, or 18, and 906·2 (553·5–1399·5) for anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16, or 18. Similar results were observed among early vaccination group participants in the modified intention-to-treat population (table 2). There were no new cases of high-grade anal intraepithelial neoplasia related to HPV6, 11, 16, and 18 during the long-term follow-up period in the per-protocol and modified intention-to-treat populations of the early vaccination group; however, one case of low-grade anal intraepithelial neoplasia was identified during year 8 of long-term follow-up. HPV6 and HPV58 were co-detected in the tissue sample and the causal HPV type could not be ascertained. This was the first time HPV6 had been detected in this participant, but the presence of this HPV type (regardless of whether it was transient or causal) in the lesion created an endpoint determination. Of note, a case of HPV51-related high-grade anal

intraepithelial lesion (grade 3) was observed in this participant during the base study (at month 36).

In catch-up vaccination group participants, the incidence per 10 000 person-years was lower during the long-term follow-up period (ie, after quadrivalent HPV vaccination) than during the base study period (ie, placebo group of the base study) for external genital warts related to HPV6 or 11 (0·0 [95% CI 0·0–13·5] *vs* 149·6 [101·6–212·3]), external genital lesions related to HPV6, 11, 16, or 18 (0·0 [0·0–10·2] *vs* 155·1 [108·1–215·7]), and anal intraepithelial neoplasia and anal cancer related to HPV6, 11, 16, or 18 (101·3 [32·9–236·3] *vs* 886·0 [583·9–1289·1]; table 2).

During the base study, the incidence of external genital lesions related to HPV6, 11, 16, or 18, and of anal intraepithelial neoplasia and anal cancer related to HPV6, 11, 16, or 18, in the per-protocol and modified intention-to-treat populations, were lower in the early vaccination group than in the respective populations of the catch-up vaccination group (table 2). The percentage risk reduction in the early vaccination versus the catch-up vaccination groups (91·8% [95% CI 69·4–98·6] for external genital lesions and 75·0% [27·7–92·2] for anal intraepithelial neoplasia in per-protocol analyses) was equivalent and consistent with the significant vaccine efficacy observed with quadrivalent HPV vaccine in the entire base study population.[12,13] After catch-up vaccination group participants received the quadrivalent HPV vaccine regimen, the incidence of external genital warts related to HPV6 or 11, of external genital lesions related to HPV6, 11, 16, or 18, and of anal intraepithelial neoplasia and anal cancer related to HPV6, 11, 16, or 18 was similar to the incidence in the early vaccination group (table 2). Five cases of anal intraepithelial neoplasia related to HPV6, 11, 16, or 18 were identified in the catch-up vaccination group during long-term follow-up: two participants had condyloma positive for HPV6 and 11 at year 5; one had condyloma positive for HPV11 and 52 at year 6 (causal type unknown); one developed flat HPV16-positive anal intraepithelial neoplasia grade 1 at year 6 and then developed HPV16-positive anal intraepithelial neoplasia grade 3 at year 8; and one developed anal intraepithelial neoplasia grade 3 positive for HPV18 and 59 at year 6, and subsequently developed anal intraepithelial neoplasia grade 2 positive for HPV59 and 39 at year 8 (the causal types were unknown for both lesions). The incidence of anal disease in both the early vaccination group and catch-up vaccination group during the long-term follow-up period was significantly lower than in placebo recipients during the base study (table 2). This observation indicates that, similar to the early vaccination group, the catch-up vaccination group derived protection against anal disease after quadrivalent HPV vaccination.

In exploratory analyses, the cumulative incidence over time of anal intraepithelial neoplasia and anal cancers related to HPV6, 11, 16, or 18 from quadrivalent HPV vaccination in early vaccination group and catch-up vaccination group participants were estimated using the Kaplan-Meier method (figure 2). The cumulative incidence of anal intraepithelial neoplasia in the catch-up vaccination group after quadrivalent HPV vaccination indicates that, similar to the early vaccination group, the catch-up vaccination group derived protection against anal disease after vaccination. Of note, most cases of anal lesions related to HPV6, 11, 16, or 18 occurred within 3 years after vaccination.

During the base study, the incidence of disease endpoints related to HPV6, 11, 16, or 18 was higher among participants who continued to the long-term follow-up study than in those who did not (appendix p 2). Vaccine efficacy against disease endpoints related to HPV6, 11, 16, or 18 infection was similar between the two groups (appendix p 2).

Anti-HPV6, 11, 16, and 18 antibodies persisted for up to 120 months after the first vaccine dose in the early vaccination group (figure 3; appendix pp 3–4). Anti-HPV GMTs peaked at month 7, declined sharply up to month 24 (base study), and then declined gradually thereafter up to month 120 (long-term follow-up study). At month 120, seropositivity to HPV6 was 79·1% (296/374), to HPV11 was 79·9% (299/374), to HPV16 was 94·9% (373/393), and to HPV18 was 40·2% (164/408; appendix pp 5–7). When the IgG-Luminex immunoassay, which is more sensitive than the competitive Luminex immunoassay, was used, seropositivity to HPV6 was 91·7% (255/278), to HPV11 was 92·0% (252/274), to HPV16 was 99·7% (290/291), and to HPV18 was 92·1% (281/305) at month 120 (appendix pp 5–6).

Similar results were observed in separate analyses for MSM and heterosexual men when both the competitive Luminex immunoassay and the IgG-Luminex immunoassay were used (appendix pp 3–6). GMTs tended to be lower in MSM than in heterosexual men for the four quadrivalent HPV-vaccine types at all timepoints, as previously observed in the base study.[15]

See Online for appendix

	Early vaccination group, base study day 1 (n=936)	Catch-up vaccination group (n=867)	
		Base study day 1	Before catch-up vaccination*
(Continued from previous page)			
MSM			
HPV 6, 11, 16, or 18	35/109 (32%)	37/127 (29%)	48/128 (38%)
HPV 6	18/109 (17%)	15/127 (12%)	23/128 (18%)
HPV 11	6/109 (6%)	6/126 (5%)	7/128 (5%)
HPV 16	16/109 (15%)	22/126 (17%)	22/128 (17%)
HPV 18	5/109 (5%)	9/126 (7%)	12/128 (9%)

Data are mean (SD), median (range), n (%), or n/N (%). HPV=human papillomavirus. MSM=men who have sex with men. *Before quadrivalent HPV catch-up vaccination encompasses approximately 4 years after base study day 1.

Table 1: **Characteristics of participants in the long-term follow-up study before quadrivalent HPV vaccination**

	Early vaccination group (n=936)			Catch-up vaccination group (n=867)			Early vaccination *vs* catch-up vaccination risk reduction estimate (95% CI)*
	Participants	Person-years follow-up	Incidence per 10 000 person-years (95% CI)	Participants	Person-years follow-up	Incidence per 10 000 person-years (95% CI)	
External genital warts related to HPV6 or 11							
Per-protocol population							
Base study	2/640	1518·9	13·2 (1·6–47·6)	20/623	1456·5	137·3 (83·9–212·1)	90·4% (62·3 to 98·4)
Long-term follow-up study	0/639	4225·4	0·0 (0·0–8·7)	..	..	..	..
mITT population							
Base study	6/763	2203·9	27·2 (10·0–59·3)	31/725	2072·2	149·6 (101·6–212·3)	81·8% (55·9 to 92·6)
Long-term follow-up study	0/763	5054·1	0·0 (0·0–7·3)	0/567	2737·2	0·0 (0·0–13·5)	..
External genital lesions† related to HPV6, 11, 16, or 18							
Per-protocol population							
Base study	2/731	1728·4	11·6 (1·4–41·8)	23/704	1638·1	140·4 (89·0–210·7)	91·8% (69·4 to 98·6)
Long-term follow-up study	0/730	4798·4	0·0 (0·0–7·7)	..	..	..	..
mITT population							
Base study	8/848	2444·5	32·7 (14·1–64·5)	35/791	2256·4	155·1 (108·0–215·7)	78·9% (53·9 to 91·2)
Long-term follow-up study	0/848	5603·0	0·0 (0·0–6·6)	0/740	3608·5	0·0 (0·0–10·2)	..
AIN and anal cancer related to HPV6, 11, 16, or 18 (MSM only)							
Per-protocol population							
Base study	4/88	176·6	226·5 (61·7–580·0)	20/109	220·7	906·2 (553·5–1399·5)	75·0% (27·7 to 92·2)
Long-term follow-up study	1/84‡	487·0	20·5 (0·5–114·4)	..	..	..	..
mITT population							
Base study	5/105	265·7	188·2 (61·1–439·2)	27/119	304·7	886·0 (583·9–1289·1)	78·8% (46·3 to 92·2)
Long-term follow-up study	1/101‡	579·7	17·2 (0·4–96·1)	5/96	493·7	101·3 (32·9–236·3)	83·0% (–26·8 to 99·3)

Unless otherwise indicated, data are n/N, where n is the number of endpoint cases and N is number of participants in the analysis population with follow-up in the indicated study period. AIN=anal intraepithelial neoplasia. HPV=human papillomavirus. mITT=modified intention to treat. MSM=men who have sex with men. *Refers to percentage reduction in incidence in the early vaccination group versus the catch-up vaccination group during the indicated period; during the long-term follow-up study, the comparison between these two groups represents a comparison between similarly quadrivalent HPV-vaccinated populations. †Includes external genital warts, penile, perianal, and perineal intraepithelial neoplasia, and penile, perianal, and perineal cancer. ‡There were no new cases of high-grade AIN related to HPV6, 11, 16, and 18 in per-protocol and mITT populations of the early vaccination group during long-term follow-up; one case of low-grade AIN was identified during long-term follow-up.

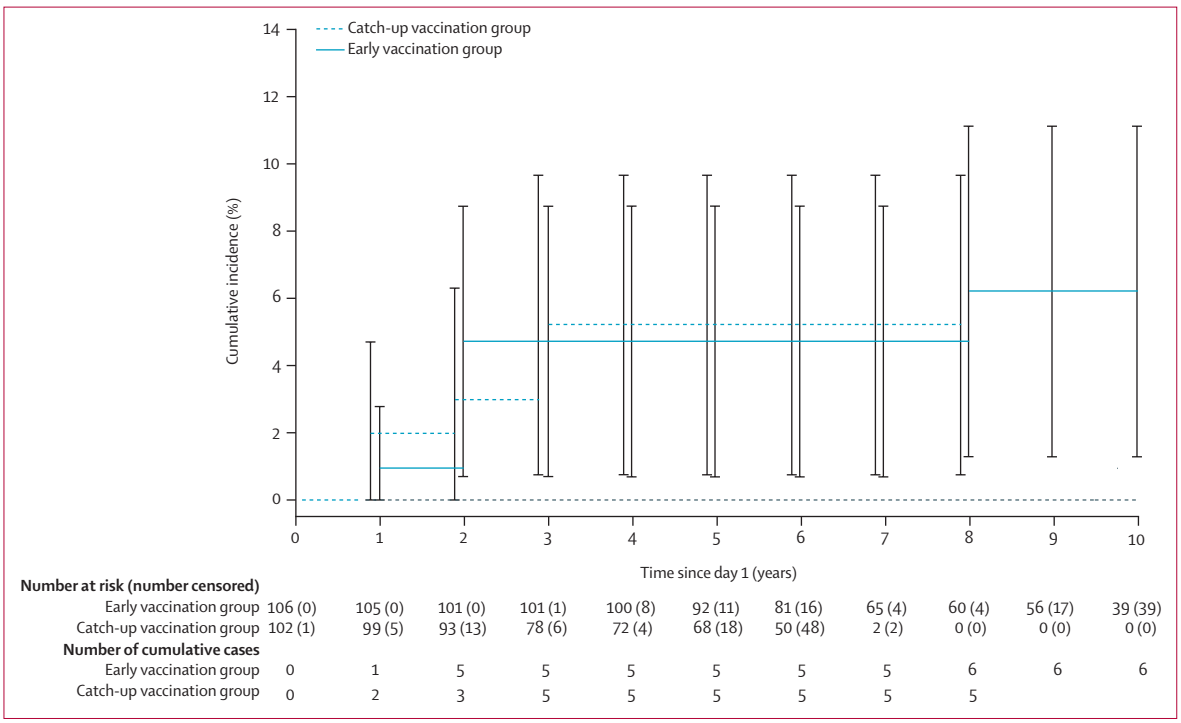
Table 2: **Reduction in the incidence of HPV-related external genital and anal disease in men vaccinated at age 16–26 years who participated in the long-term follow-up study**

There were no vaccine-related deaths during the long-term follow-up study (figure 1), and there were no serious adverse events considered by the investigator to be related to the vaccine or procedure during long-term follow-up. Five participants in the early vaccination group had serious adverse events resulting in death during the long-term follow-up study that were not considered by the investigator to be vaccine-related (one due to subarachnoid haemorrhage [2111 days after the third dose]; one due to pneumonia [2641 days after the third dose]; one due to a gunshot wound [2878 days after the third dose]; one due to a road traffic accident [3479 days after the third dose]; and one due to several serious adverse events including HIV infection [1582 days after the third dose], neuroma [2739 days after the third dose], and metabolic acidosis [2754 days after the third dose]). Two participants in the catch-up vaccination group had serious adverse events resulting in death during the long-term follow-up study that were not considered by the investigator to be vaccine-related (one due to myocardial infarction [230 days after the third dose] and one due to several serious adverse events including blast injury, second-degree burns, cerebral haemorrhage, and craniocerebral injury [all occurring 3393 days after the third dose]).

During long-term follow-up, the early vaccination and catch-up vaccination groups had similar rates (per person-year) of new sexual partner acquisition among heterosexual men (2·13 [95% CI 2·07–2·18] in the early vaccination group and 1·83 [1·78–1·88] in the catch-up vaccination group) and MSM (6·98 [6·72–7·24] and 5·51 [5·32–5·71]) cohorts (appendix p 7), which were similar to the rates observed during the base study. Similarly, the incidences of anal chlamydia and gonorrhoea infections during long-term follow-up among MSM were similar in the early vaccination and catch-up vaccination groups (appendix p 8).

Discussion

This study provides important data to show that HPV vaccination elicits long-term protection from HPV-related diseases in men, with durable efficacy against anogenital lesions, sustained immunogenicity, and a favourable safety profile in young men for up to



Number at risk (number censored)											
Early vaccination group	106 (0)	105 (0)	101 (0)	101 (1)	100 (8)	92 (11)	81 (16)	65 (4)	60 (4)	56 (17)	39 (39)
Catch-up vaccination group	102 (1)	99 (5)	93 (13)	78 (6)	72 (4)	68 (18)	50 (48)	2 (2)	0 (0)	0 (0)	0 (0)
Number of cumulative cases											
Early vaccination group	0	1	5	5	5	5	5	5	6	6	6
Catch-up vaccination group	0	2	3	5	5	5	5	5	5		

Figure 2: **Cumulative incidence of AIN and anal cancer related to HPV6, 11, 16, and 18 in MSM vaccinated with the quadrivalent HPV vaccine in the long-term follow-up study**

Error bars show 95% CIs. Data for the modified intention to treat populations of the early vaccination group and catch-up vaccination group are shown. AIN=anal intraepithelial neoplasia. HPV=human papillomavirus. MSM=men who have sex with men.

10 years of follow-up. There were no breakthrough cases of external genital warts related to HPV6 or 11, or external genital lesions, high-grade anal intraepithelial neoplasia, or anal cancer related to HPV6, 11, 16, or 18 in the per-protocol efficacy population of the early vaccination group during the long-term follow-up period. As placebo recipients in the base study received quadrivalent HPV vaccination before the start of the long-term follow-up period, no direct comparison with an unvaccinated population was possible. However, in the per-protocol analyses, the incidences of external genital warts related to HPV6 or 11, external genital lesions related to HPV6, 11, 16, or 18, and anal intraepithelial neoplasia or anal cancer related to HPV6, 11, 16, or 18 were lower in the early vaccination group during long-term follow-up than in the placebo group during the base study, suggesting that the quadrivalent HPV vaccine provides long-term protection.

Among catch-up vaccination group participants, the incidence of anal lesions was lower after vaccination with the quadrivalent HPV vaccine (ie, in the long-term follow-up period) than before vaccination (ie, during the base study). Before vaccination, catch-up vaccination group participants were exposed to HPV, leading to increased HPV prevalence and accumulation of disease endpoints. Although vaccination in the catch-up vaccination group was delayed by approximately 3 years, the vaccine still provided effective protection against additional vaccine HPV type-related disease to which participants remained susceptible. Analysis of the cumulative incidence of anal lesions over time after vaccination followed a similar trajectory in the early vaccination and catch-up vaccination groups, with disease generally emerging early (ie, within the first 3 years after vaccination), probably due to prevalent infections, followed by a plateau up to the end of the study, related to vaccine-induced immunity. This pattern was also observed among catch-up vaccination group participants, who were older, were more sexually experienced, and had a higher frequency of PCR positivity and seropositivity to HPV than those in the early vaccination group. Together, these results support the concept that, although early vaccination before HPV exposure is optimal, catch-up vaccination is also beneficial in protecting against new HPV infections and resultant disease. These findings are especially important for men, as they do not appear to develop effective immunity following natural infection and experience recurrent HPV infection and related disease throughout their lifetime, as shown in several analyses from the HPV Infection in Men study.[5,11,25,26] Although the vaccine does not provide a treatment effect, it likely prevents re-infection or development of disease related to additional HPV types. Two large retrospective studies found a greater than 80% reduction in recurrence of high-grade anal intraepithelial neoplasia at 7 years after treatment and a reduction in the recurrence of external genital warts of approximately 50% by 4 years after

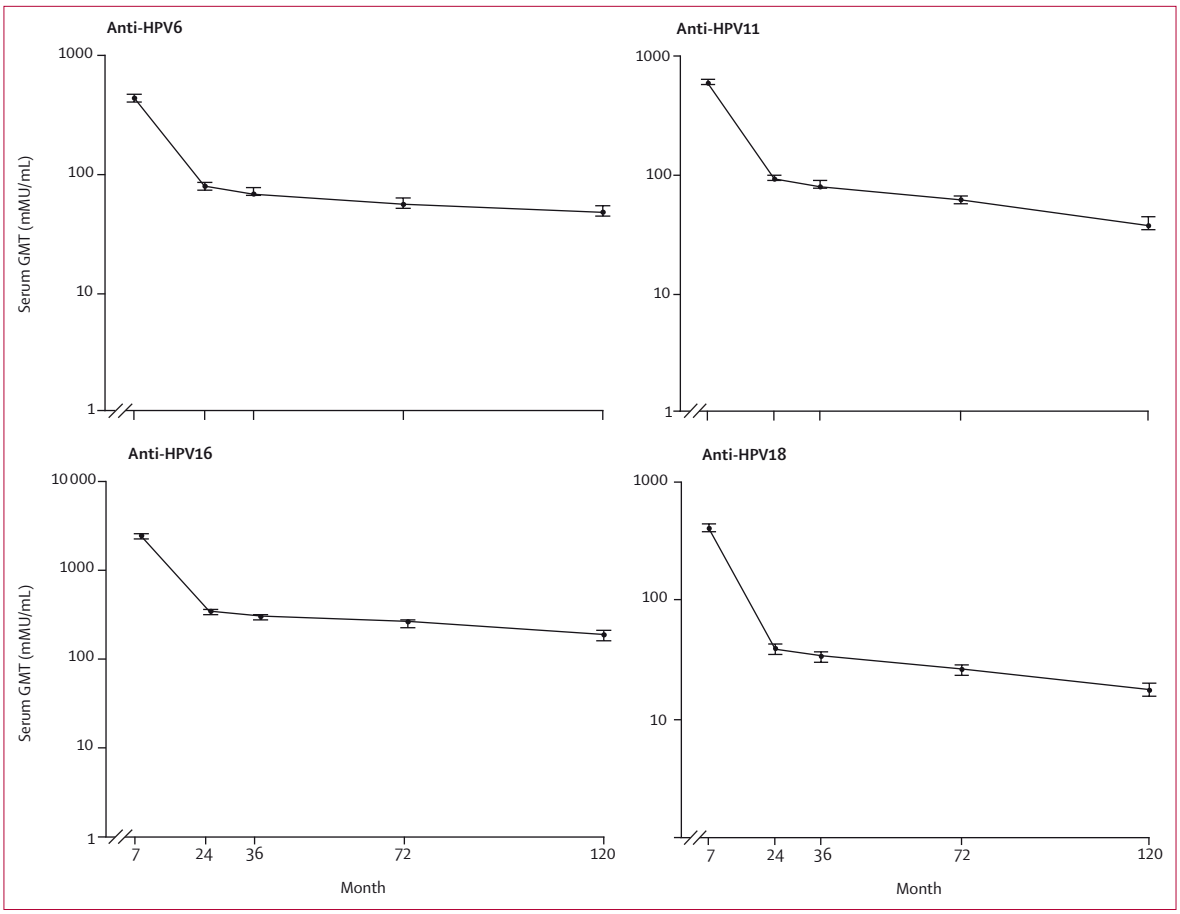


Figure 3: **Anti-HPV6, 11, 16, and 18 GMTs on the competitive Luminex immunoassay in early vaccine group participants from day 1 of the base study to year 10 of the long-term follow-up study (per-protocol population)**
Error bars show 95% CIs. GMT=geometric mean titre. HPV=human papillomavirus. mMU=milliMerck unit.

treatment in men who had been vaccinated with the quadrivalent HPV vaccine.[27,28] Similar findings of diminished recurrence post-vaccination were reported for anal intraepithelial neoplasia and warts in other retrospective analyses.[29]

The low incidence of lesions related to HPV6, 11, 16, or 18 during long-term follow-up is most likely due to vaccine protection, rather than an absence of exposure. Early vaccination group and catch-up vaccination group participants continued to acquire new sexual partners during long-term follow-up at a rate generally similar to or higher than that observed in the base study, when multiple new infections were identified in the placebo group. As further evidence of probable repeat HPV exposure, several long-term follow-up study participants acquired sexually transmitted infections (eg, chlamydia or gonorrhoea).

Sustained antibody responses to the quadrivalent HPV vaccine were observed up to month 120. Almost all (>97%) participants in the base study who received the quadrivalent HPV vaccine were seropositive to all four HPV types at 1 month after receiving the third dose and, in early vaccination group participants, seropositivity (assessed with the competitive Luminex immunoassay) remained high throughout the 10-year study for HPV6, 11, and 16, but decreased over time for HPV18. However, seropositivity at month 120, assessed with the more sensitive IgG-Luminex immunoassay,[30] was more than 90% for all four HPV types, including HPV18. Even with a decline in seropositivity, according to the competitive Luminex immunoassay, over time, we did not observe breakthrough lesions in early vaccination group participants during the long-term follow-up study. A similar observation was made in a long-term follow-up study of the quadrivalent HPV vaccine in young women aged 16–26 years, in which HPV18 seropositivity after 14 years was 52% when assessed with the competitive Luminex immunoassay and 94% when assessed with the IgG-Luminex immunoassay.[31] Despite the lower HPV18 seropositivity with the competitive Luminex immunoassay relative to other HPV types and timepoints in this previous study, no breakthrough cases of high-grade cervical lesions related to HPV16 and 18 during 14 years of follow-up were observed.[31]

This study was done with strict guidelines for case endpoint assignment. Any lesion that contained multiple HPV types, with one of the types being HPV6, 11, 16, or 18, was considered to be an endpoint, even if the quadrivalent HPV vaccine type was only present at a single timepoint. The causative HPV type could not be ascertained when multiple types were present. An HPV vaccine type could have represented transient infection without causation. Of five anal intraepithelial neoplasia endpoint lesions in the quadrivalent HPV group during the base study, three were positive for a quadrivalent HPV vaccine type only at lesion diagnosis, whereas other high-risk types not present in the vaccine were present in lesions on multiple visits.[13] Accordingly, it is possible that the single case of low-grade anal intraepithelial neoplasia observed during long-term follow-up in the early vaccination group, which was positive for both HPV6 and 58, might not have represented a breakthrough lesion at all.

Limitations of this study include the high proportion of participants who discontinued the study (430 [24%] of 1803), which could introduce selection bias in the remaining participants. A high discontinuation rate was expected, given the age of participants and the long study duration. The proportion of participants who discontinued was consistent between the long-term follow-up study (approximately 3·4% annually) and base study (approximately 6·6% annually) periods, and was predominantly due to loss to follow-up or withdrawn consent. Another limitation of the study is that all placebo recipients who entered long-term follow-up received quadrivalent HPV vaccination at the end of the base study, thereby preventing comparison with a control group. However, the absence of breakthrough cases of external genital warts related to HPV6 or 11, external genital lesions related to HPV6, 11, 16, or 18, and high-grade anal intraepithelial neoplasia and anal cancer related to HPV6, 11, 16, or 18, despite continued sexual activity and presumed exposure, provides strong evidence of sustained quadrivalent HPV vaccine efficacy. The results also support the value of catch-up vaccination, even in participants already infected or in those who develop disease related to other HPV types.

A major strength of this study is that it provides up to 10 years of follow-up using a common rigorous protocol implemented in the base study, allowing consistent, continuous evaluation of participants up to 120 months. The study was done at multiple sites worldwide, increasing the likelihood that the results are generalisable. The higher incidence of disease endpoints related to HPV6, 11, 16, or 18 during the base study in participants who continued to the long-term follow-up study compared with those who did not most likely reflects differences in HPV infection rates in the ethnic group or region that predominates in each group. No substantive difference in vaccine efficacy was observed between the two groups. Therefore, inferences relating to the long-term efficacy of the quadrivalent HPV vaccine derived from long-term follow-up study participants are generalisable to the entire population of men aged 16–26 years in the base study.

The results of this long-term follow-up study in young men, together with a previously published long-term follow-up study of quadrivalent HPV vaccine in boys aged 9–15 years of age,[32] indicate that the quadrivalent HPV vaccine provides durable protection and sustained immunogenicity for at least 10 years in both heterosexual men and MSM vaccinated at 9–26 years of age. Although HPV vaccination programmes primarily target pre-adolescents and young adolescents, these data indicate that unvaccinated adult men with previous exposure to one or more HPV types can also benefit from vaccination. Ultimately, implementation of both gender-neutral and catch-up vaccination programmes maximises the opportunity to prevent the disproportionately high incidence of vaccine-preventable disease in MSM, who would otherwise have limited protection from female-only vaccination strategies.[33–36]

Contributors

SEG acquired data, analysed data, interpreted the results, provided study materials or patients, and drafted the manuscript. ARG, JMP, MHS, RD, and AS contributed to study conception, design or planning, data acquisition or analysis, and interpretation of the results. MEP acquired data, provided study materials or patients, and provided administrative, logistical, and technical support. REC interpreted the results. EDM acquired data and interpreted the results. EL-P, EB, HJ, AF, RK, and BMR acquired data. OB and HJZ analysed data, interpreted the results, and provided statistical expertise. TG analysed data, acquired data, interpreted the results, and provided administrative, logistical, and technical support. AL interpreted the results and drafted the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content and reviewed and approved the final version of the manuscript. OB and HJZ accessed and verified the study data. All authors had access to the study data and related analyses and vouch for the completeness and accuracy of the data presented. The decision to submit the manuscript for publication was made by the corresponding author in conjunction with the sponsor and coauthors. The sponsor did not have the potential to prevent submission of the manuscript. The manuscript also underwent formal review by the sponsor, which resulted in no major change in the manuscript. The sponsor did not have the potential to prevent submission of the manuscript for publication.

Declaration of interests

SEG reports speaker honoraria from, and being an investigator for, Merck Sharp & Dohme (MSD) Corp, a subsidiary of Merck & Co (Kenilworth, NJ, USA); being an investigator for Inovio; receiving research support from Medtronic; and being a consultant for THD America. ARG reports receiving grants from MSD paid to her institution and being a member of the scientific advisory board for MSD. JMP reports grants and travel support from MSD during the conduct of the study; grants and personal fees from, and stock options in, Vir Biotechnology; stock options in Virion Therapeutics; and personal fees from Vaccitech, outside the submitted work. MEP reports funding from MSD relating to the conduct of the vaccine trials. EDM has been an investigator for HPV vaccine studies sponsored by MSD and is a member of the scientific advisory board for MSD. EB reports clinical investigator fees for this trial. HJ reports grants and non-financial support from Klinisches Studienzentrum für Infektiologie; personal fees from Hormosan Pharma, GlaxoSmithKline, Ifi-Medizin, and CIP Clinic; grants from Sanofi-Aventis Deutschland, CROMSOURCE, Centre Hospitalier Universitaire de Nantes, and the US Military HIV Research Program (MHRP); grants, personal fees, and non-financial support from, and board membership for,

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Data sharing

MSD, a subsidiary of Merck & Co (Kenilworth, NJ, USA) is committed to providing qualified scientific researchers access to anonymised patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research by qualified scientific researchers. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data sharing website at: http://engagezone.msd.com/ds_documentation.php. Data will be made available on request after product approval in the USA and the EU, or after product development is discontinued. There are circumstances that might prevent MSD from sharing the requested data.

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