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Research Paper

Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries

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ABSTRACT

Background: The quadrivalent human papillomavirus (qHPV) vaccine prevented vaccine HPV type-related infection and disease in young women in the 4-year FUTURE II efficacy study (NCT00092534). We report long-term effectiveness and immunogenicity at the end of 14 years of follow-up after enrollment in FUTURE II.

Methods: Young women (16–23 years of age) from Denmark, Iceland, Norway, and Sweden who received three qHPV vaccine doses during the randomized, double-blind, placebo-controlled FUTURE II base study were followed for effectiveness for an additional ≥10 years through national registries. Tissue samples including but not limited to those collected during organized cervical cancer screening programs were obtained from regional biobanks to be adjudicated for histopathology diagnosis and tested for HPV DNA. The observed incidence of HPV16/18-related high-grade cervical dysplasia (primary outcome) was compared with recent historical background incidence rates in an unvaccinated population. Serum was collected at years 9 and 14 to assess antibody responses.

Findings: No cases of HPV16/18-related high-grade cervical dysplasia were observed in the per-protocol effectiveness population ($N = 2121$; 24,099·0 person-years of follow-up) during the entire study. Vaccine effectiveness of 100% (95% CI 94·7–100) was demonstrated for ≥12 years, with a trend toward continued protection through 14 years post-vaccination. Seropositivity rates at study conclusion were >90% (HPV6/11/16) and 52% (HPV18) using competitive Luminex immunoassay, and >90% (all four HPV types) using the more sensitive IgG Luminex immunoassay.

Interpretation: Vaccination of young women with qHPV vaccine offers durable protection against HPV16/18-related high-grade cervical dysplasia for ≥12 years, with a trend toward continued protection through 14 years post-vaccination, and induces sustained HPV6/11/16/18 antibody responses for up to 14 years post-vaccination. There was no evidence of waning immunity, suggesting no need for a booster dose during that period.

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Research in context

Evidence before this study

LTFU studies of the bivalent and qHPV vaccines with up to 10 years of follow-up, as well as a previous interim analysis of the study reported herein with up to 12 years of follow-up, have generally supported the continued effectiveness of the vaccines for clinical trial participants vaccinated as adolescents or young adults.

Added value of this study

The study demonstrated no breakthrough cases of high-grade cervical dysplasia related to HPV types 16 and 18 based on a maximum follow-up of 14·0 years (median 11·9 years) following vaccination Dose 3. Vaccine effectiveness against high-grade cervical dysplasia was maintained at 100% compared with a similar, unvaccinated population through the entire study. This suggests that vaccination with a three-dose regimen of qHPV vaccine elicits continued protection against disease caused by HPV types covered by the vaccine for up to 14 years.

Implications of all the available evidence

Because the risk of HPV infection can be lifelong, the full benefit of HPV vaccination programs will only be realized if the protective efficacy of HPV vaccination is long lasting. This study reports long-term effectiveness in a sentinel cohort with an observed follow-up that is at least 5 years in advance of the first individuals who received qHPV vaccine post-licensure, providing sufficient lead time for identifying potential breakthroughs and making relevant public health decisions. Since no waning immunity was observed, implementation of booster vaccination as public health policy is so far unnecessary.

1. Introduction

Human papillomavirus (HPV) causes 690,000 new cancer cases per year worldwide, including nearly all the more than 560,000 cases of cervical cancers that occur globally each year (based on 2018 estimates) [1], as well as a significant proportion of vulvar, vaginal, anal, penile, and oropharyngeal cancers [1,2]. Indeed, approximately 4.5% of all cancers (8.6% in women) are attributable to HPV [2]. The quadrivalent HPV (qHPV) vaccine was developed to protect against HPV types 16 and 18, which are responsible for approximately 70% of cervical cancers and most cases of HPV-related vulvar, vaginal, and anal cancers based on epidemiological studies [2–5], as well as HPV6 and 11 which cause approximately 90% of genital warts [6]. In clinical trials, the qHPV vaccine prevented HPV6/11/16/18-related cervical and anogenital dysplasia and genital warts, and elicited robust antibody responses [7,8]; the vaccine was initially licensed in 2006 and is now widely used in national immunization programs [9]. Post-licensure studies conducted in the decade following initial approval of qHPV vaccine have supported the favorable effectiveness and safety profile observed in the clinical program [10,11].

The average length of follow-up in the pivotal efficacy studies, Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II, was approximately 4 years [12,13]. The qHPV vaccine demonstrated efficacy against HPV16/18-related cervical intraepithelial neoplasia (CIN) grade 2 or 3 and adenocarcinoma in situ (AIS) in the FUTURE II base study in more than 12,000 young women globally [13,14]. As the risk for HPV exposure can be lifelong [15], protective efficacy of the vaccine lasting decades is required to achieve the full benefit of vaccination. Ten additional years' extension of the follow-up time of the FUTURE II base study in Nordic countries was feasible and a long-term follow-up (LTFU) study was implemented to assess effectiveness and immunogenicity of the qHPV vaccine after completion of the base study; ie, up to 14 years post-vaccination. This extension was a post-licensure requirement from the United States Food and Drug Administration and the European Medicines Agency [16,17]. The final qHPV vaccine effectiveness and immunogenicity results of the LTFU study through 14 years post-vaccination are reported here.

2. Methods

2.1. Study design and participants

In the double-blind base study (FUTURE II; NCT00092534), 12,167 participants were enrolled at 90 sites in 13 countries [14]. Base-study participants were assessed for efficacy, immunogenicity, and safety for approximately 4 years in the base study, and the results have been reported [13,14,18].

The LTFU study is an extension of the base study among study participants from the Nordic countries of Denmark, Iceland, Norway, and Sweden. Participants from these countries were 16 to 23 years of age at the start of the base study. These countries have established organized cervical cancer screening programs with routine centralized administration and registration, with close to 100% completeness and accuracy [19–25]. During the base study, participants were not screened in the national programs (since they were screened within the study); they resumed participation in the national programs after the end of the base study. The LTFU study used registry-based follow-up to assess effectiveness and active follow-up with serum collection to assess immunogenicity.

Nordic participants who agreed to long-term passive registry follow-up, re-analysis of biopsy specimens, future contact with LTFU study investigators, and/or serum collection for the LTFU study by providing written consent (as needed per local requirements) were eligible for the LTFU study. The LTFU study was conducted in accordance with principles of Good Clinical Practice, and was approved by the appropriate scientific ethics committees and regulatory agencies.

2.2. Randomization and masking

The base-study participants were equally randomized to receive three doses of qHPV vaccine or placebo, administered intramuscularly at day 1, month 2, and month 6. Randomization and masking procedures for the base study have been described in detail previously [14]. Vaccination assignments were unblinded at the end of the base study, and placebo recipients were offered qHPV vaccination.

In this report, we present follow-up results of the base-study participants who were randomized to receive qHPV vaccine at the start of the base study; no vaccinations were administered during the LTFU study.

2.3. Procedures

A National Registry Study Center (NRSC) was established in each of the four Nordic countries to obtain nation-wide registry-based follow-up data, access biological specimens, and manage blood collections. At enrollment in the base study, participants received a unique allocation number (AN). Each resident in Nordic countries also has a unique personal identification number (PIN), which is used universally in the society of the individual countries. The NRSCs established a link between the AN and PIN to obtain study participant information from the relevant data stored in the national registries.

For long-term effectiveness, LTFU-study participants were followed through linkages with national cancer registries and organized screening programs for cervical, vulvar, and vaginal abnormalities. The NRSCs conducted retrospective searches of the national registries to acquire data for effectiveness evaluation, including cervical cancer screening-related biopsy and treatment specimens and reports; acquired results from screening and follow-up visits (including cervical cytology test results, cervical biopsy and cervical surgery results, and diagnoses of vulvar and vaginal precancers and cancers); retrieved clinical histological specimens from the clinical biobanks/archives existing in all Nordic countries (including hematoxylin and eosin [H&E]-stained slides and formalin fixed paraffin-embedded tissue blocks); and routed specimens to the Nordic Coordinating Center (NCC). The NCC was responsible for the administrative processes related to the Pathology Panel and routing tissue blocks and pathology reports to the designated central laboratories for processing. The central laboratories created the histology slides, which were routed back to the NCC for Pathology Panel circulation and thin-section samples. These samples were routed to the testing laboratory for polymerase chain reaction (PCR) analysis.

For long-term immunogenicity, the participants were requested to visit a designated blood collection center to provide serum samples for immunogenicity assessments at years 5 and 10 of the LTFU study, corresponding to approximately 9 and 14 years (or 108 and 168 months) of total follow-up post-vaccination. These results were coupled with the serum samples collected at months 7, 24, and 48 for immunogenicity assessment in the base study.

2.4. Outcomes

The primary outcome of the LTFU study was the combined incidence of CIN grade 2 or 3 (CIN2, CIN3), AIS, and cervical cancer (referred to as CIN2 or worse) related to HPV16 and 18. Secondary outcomes included (1) the combined incidence of HPV6/11/16/18-related CIN (any grade), AIS, and cervical, vulvar, and/or vaginal cancer; (2) the combined incidence of CIN2 or worse related to 10 non-vaccine HPV types (HPV31/33/35/39/45/51/52/56/58/59); and (3) the geometric mean titres (GMTs) and seropositivity rates for HPV6, 11, 16, and 18 at years 5 and 10 of the LTFU study. An exploratory outcome was the incidence of HPV6/11/16/18-related cervical, vaginal, and vulvar disease in participants who were previously infected with these types (ie, baseline HPV DNA PCR negative/seropositive).

A case of the primary outcome related to a given HPV type occurred if a participant developed a lesion with a consensus diagnosis by the Nordic Pathology Panel of CIN2, CIN3, AIS, or cervical cancer, and PCR testing detected the relevant HPV type in an adjacent section from the same tissue block, as described previously [26]. If multiple HPV types were detected, the lesion was classified as related to each of the HPV types detected. For all efficacy endpoints, HPV DNA detection by PCR was considered a surrogate marker of HPV infection.

The methodology for PCR testing for 14 HPV types [27,28] and pathology diagnosis adjudication on thin sections of tissue samples [14,26] was the same as in the base study, except the composition of the Nordic Pathology Panel in the LTFU study, which was distinct from the pathology panel that adjudicated the histology samples during the base study (see appendix for details). The base study and LTFU study used the same validation and adjudication processes to ensure consistency throughout the entire duration of the study.

GMTs and seropositivity to HPV types 6, 11, 16, and 18 were measured using the competitive Luminex immunoassay (cLIA) [29–31], which was also the primary immunoassay in the base study, and the immunoglobulin G Luminex immunoassay (IgG-LIA) [32]. Results of the cLIA and IgG-LIA are reported as antibody concentrations in arbitrary milli-Merck units per milliliter; however, the measurements represent different outputs and the two assays are not directly comparable.

2.5. Statistical analyses

The primary hypothesis was that the qHPV vaccine will remain ≥90% effective compared with an unvaccinated population for at least 14 years after the start of vaccination in preventing HPV 16/18-related CIN2, CIN3, AIS, and cervical cancer (ie, CIN2 or worse). qHPV vaccine effectiveness was calculated as 100 x (1 − relative risk), where relative risk is the ratio of the incidence of HPV16/18-related CIN2 or worse observed in participants followed in the LTFU and the expected incidence in an unvaccinated Nordic population. The incidence of HPV16/18-related CIN2 or worse in an unvaccinated Nordic population was estimated as 0·287/100 person-years based on data from Nordic national registries and a questionnaire study (the Concomitant Cohort Study [33]) (see appendix). To demonstrate the hypothesis of vaccine effectiveness ≥90%, the incidence rate observed in participants of the LTFU study should not have exceeded 0·0287/100 person-years, which is 10% of the 0·287/100 person-years incidence in an unvaccinated population.

An adapted Poisson Shewhart-based control chart method was used for the primary analysis of monitoring breakthrough disease and waning vaccine effectiveness. The use of a control chart method for monitoring disease incidence was an innovative and unique aspect of this study and allowed for prospective monitoring and rapid detection of rises in incidence rates. A full description of the methodology can be found in the appendix. Briefly, incidence of HPV16/18-related CIN2 or worse was evaluated at 2-year intervals during the LTFU period, starting at approximately year 4 post-vaccination and plotted in the control chart. If the plotted incidences at 2-year intervals conformed to a pre-specified pattern of crossing the 2- and 3-sigma upper control limits of the control chart, an inference would be made that the accumulating data were indicative of waning effectiveness.

The primary effectiveness analysis was conducted in the per-protocol effectiveness (PPE) population consisting of participants who (1) received three doses of qHPV vaccine within 1 year; (2) had no protocol violations that could impact vaccine effectiveness; (3) were PCR-negative and seronegative at baseline and PCR-negative through month 7 of the base study for the appropriate HPV type(s); and (4) consented to effectiveness follow-up. Some supportive effectiveness analyses were conducted in the HPV-naïve to relevant type (HNRT) population of participants who (1) received at least one vaccination; (2) had any follow-up visit in the LTFU study; and (3) were PCR-negative and seronegative to the appropriate HPV type(s) prior to vaccination. In addition, exploratory analyses were conducted in participants with evidence of prior exposure to HPV at day 1 of the base study.

Immunogenicity was analyzed in the per-protocol immunogenicity (PPI) population, which comprised participants who (1) were sero- and PCR-negative at baseline and PCR-negative through month 7 of the base study to the appropriate HPV type(s, 2) received three doses of qHPV vaccine within specified day ranges; (3) did not violate the protocol in ways that could affect the evaluation of immunogenicity; and (4) consented to immunogenicity follow-up and provided a serum sample for immunogenicity analysis during the LTFU period.

Long-term immunogenicity with respect to HPV types 6, 11, 16, and 18 was assessed by computing: (1) point estimates of GMTs and corresponding 95% confidence intervals (CI); and (2) point estimates of seropositivity percentages and corresponding 95% CI, based on both the cLIA and the IgG-LIA.

2.6. Role of the funding source

In close collaboration with the external investigators, employees of Merck Sharpe & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, the sponsor and funder of the study, were directly involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation and review of the manuscript. Each author had access to all study results, critically contributed to manuscript development, and approved the final version of the paper. The presentation also underwent formal review by the sponsor. The decision to submit the manuscript for publication was made by the corresponding author in conjunction with the sponsor and co-authors. The sponsor did not have the potential to prevent submission of the manuscript. The opinions expressed in the manuscript represent the collective views of the authors and do not necessarily reflect the official position of the sponsor.

3. Results

Participants were enrolled in the FUTURE II base study beginning in June 2002. The base study included 5493 women from Denmark, Iceland, Norway, and Sweden who were vaccinated with either qHPV vaccine or placebo, including 2750 women who received at least one dose of qHPV vaccine during the base-study vaccination phase (Fig. 1). Of these, 2650 participants consented to be included in registry searches for effectiveness information, and 2385 consented to provide serum samples for immunogenicity analyses (supplementary Table 1). Numbers of participants contributing to the primary and secondary effectiveness analyses are presented in supplementary Table 2. The data cut-off date for registry analyses in the LTFU extension was March 1, 2017; the last participant visit for blood collection was March 31, 2017.

At enrollment in the base study, the median age of the LTFU-study participants who received qHPV vaccine at the start of the base study was 21 years (range: 16–23 years; supplementary Table 3). The majority of participants were from Denmark and Norway (40·8% and 30·9%, respectively).

For the primary effectiveness analysis, the PPE population involved 2121 participants contributing a total follow-up of 24,099·0 person-years since month 7 of the base study (ie, one month after the last qHPV vaccine dose administration). PPE analyses are based on a maximum follow-up of 14·0 years (median 11·9 years) post-vaccine Dose 3, or 14·4 years (median 12·4 years) post-vaccine Dose 1. Overall, 96·9% of participants had at least one cervical cytology screening during the LTFU period; the proportion by country was: Denmark, 97·4%; Iceland, 97·1%; Norway, 97·6%; and Sweden, 94·2%.

Under the hypothesis of vaccine effectiveness ≥90%, the anticipated incidence rate of HPV16/18-related CIN2 or worse in the PPE population should not exceed 0·0287/100 person-years. Based on the 24,099·0 person-years of follow-up time accrued through the end of the LTFU study, ≤7 cases of HPV16/18-related CIN2 or worse were expected if vaccine effectiveness was maintained at ≥90%. However, in the actual study, there were no cases of HPV16/18-related CIN2 or worse in the PPE population at any time during the base study or LTFU, indicating a vaccine effectiveness of 100% (95% CI 94·7–100) (table 1). Given the number of eligible participants for this analysis, a minimum of 2634 person-years of follow-up time is necessary in any given time interval since year 4 to draw firm conclusions from the results of this analysis based on the statistical method (see appendix).

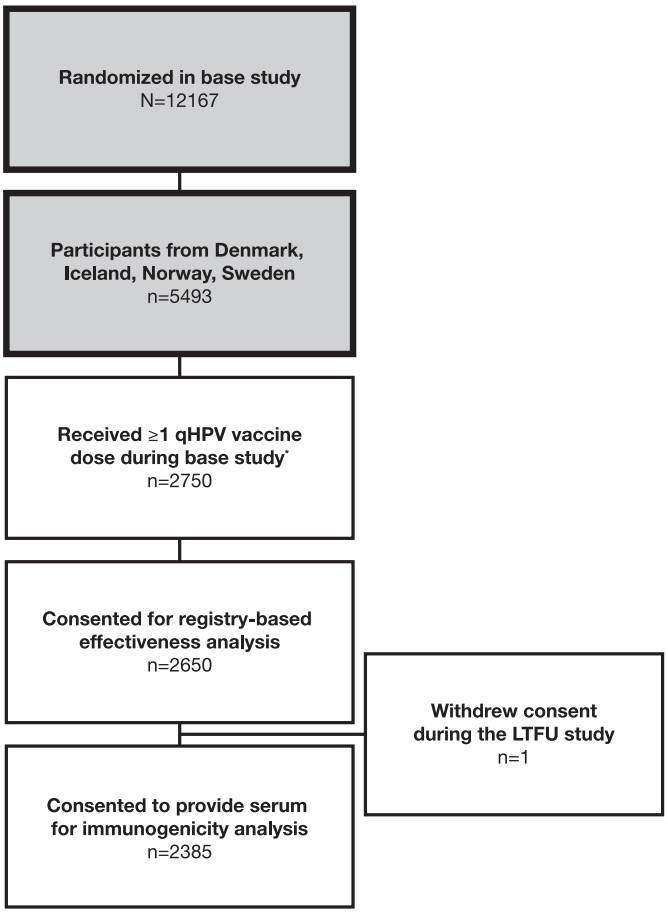

Fig. 1. Participant disposition. LTFU=long-term follow-up. qHPV=quadrivalent human papillomavirus. *Nordic participants who received placebo in the base study are not included in this report.

A total of 3197·6 person-years have accrued over the period from 10 to 12 years following vaccination, which is sufficient time to conclude that the qHPV vaccine continued to be effective through 12 years (table 1). The same pattern was seen in the interval up to 14 years, indicating a trend of continued effectiveness through 14 years. However, there is insufficient follow-up time in the 12 to 14 years interval to make a conclusive claim of effectiveness beyond 12 years.

Fig. 2 shows the control chart monitoring of observed vaccine effectiveness. Shaded time intervals represent time periods for which the follow-up time is insufficient for attributing statistical significance to the plotted incidences crossing or not crossing the 2- or 3-sigma limits. None of the points on the graph, which represent the number of cases observed during each 2-year interval, crossed the 2- or 3-sigma control limits during the evaluable time intervals (unshaded intervals in Fig. 2). Neither of the two criteria pre-specified as indicative of waning vaccine effectiveness were met. Thus, there was no evidence of decreased vaccine effectiveness in the PPE population through at least 12 years after the first vaccine dose.

Pre-specified supportive analyses were conducted in the HNRT population, which comprised susceptible participants and did not exclude protocol violators. Based on the 27,395·3 person-years of follow-up time accrued in the LTFU study, ≤8 cases of HPV16/18-related CIN2 or worse were expected if vaccine effectiveness was maintained at ≥90%. There was one case of HPV16/18-related CIN2 or worse in this population throughout the base and LTFU study (table 1), indicating a vaccine effectiveness of 98·7% (95% CI 92·9–100). The single participant with a case of the primary endpoint had positive PCR results at month 7 for HPV16 (suggesting early infection occurring before full vaccination) and was diagnosed with a CIN3 lesion which

Table 1
Analysis of qHPV vaccine effectiveness against HPV16/18-related CIN2 or worse by time since qHPV vaccination, HPV type, and lesion type

	Young women 16–23 years of age (N=2650)			
	Cases/n	Person-years' follow-up	Rate per 100 person-years (95% CI)	Vaccine effectiveness,* % (95% CI)
PPE population†				
HPV16/18-related CIN2 or worse	0/2121	24099·0	0·0 (0·0–<0·1)	100 (94·7–100·0)
By time since qHPV vaccine Dose 1				
≤4 years	0/2121	7246·8	0·0 (0·0–0·1)	
>4 to 6 years	0/2121	4220·4	0·0 (0·0–0·1)	
>6 to 8 years	0/2089	4121·8	0·0 (0·0–0·1)	
>8 to 10 years	0/2022	3901·0	0·0 (0·0–0·1)	
>10 to 12 years	0/1855	3197·6	0·0 (0·0–0·1)	
>12 to 14 years	0/1211	1393·4	0·0 (0·0–0·3)	
>14 to 16 years	0/122	18·0	0·0 (0·0–20·5)	
By HPV type				
HPV16-related	0/1814	20583·9	0·0 (0·0–<0·1)	
HPV18-related	0/2018	22940·6	0·0 (0·0–<0·1)	
By lesion type				
CIN2	0/2121	24099·0	0·0 (0·0–<0·1)	
CIN3	0/2121	24099·0	0·0 (0·0–<0·1)	
AIS	0/2121	24099·0	0·0 (0·0–<0·1)	
Cervical cancer	0/2121	24099·0	0·0 (0·0–<0·1)	
HNRT population‡				
HPV16/18-related CIN2 or worse	1/2292	27395·3	<0·1 (<0·1–<0·1)	98·7 (92·9–100)
By time since qHPV vaccine Dose 1				
≤4 years	0/2292	9168·0	0·0 (0·0–<0·1)	
>4 to 6 years	0/2292	4558·4	0·0 (0·0–0·1)	
>6 to 8 years	0/2254	4452·2	0·0 (0·0–0·1)	
>8 to 10 years	1/2186	4223·6	<0·1 (<0·1–0·1)	
>10 to 12 years	0/2013	3465·0	0·0 (0·0–0·1)	
>12 to 14 years	0/1303	1509·5	0·0 (0·0–0·2)	
>14 to 16 years	0/127	18·6	0·0 (0·0–19·9)	
By HPV type				
HPV16-related	1/1978	23624·9	<0·1 (<0·1–<0·1)	
HPV18-related	0/2189	26166·0	0·0 (0·0–<0·1)	
By lesion type				
CIN2	0/2292	27395·3	0·0 (0·0–<0·1)	
CIN3	1/2292	27395·3	<0·1 (<0·1–<0·1)	
AIS	0/2292	27395·3	0·0 (0·0–<0·1)	
Cervical cancer	0/2292	27395·3	0·0 (0·0–<0·1)	

AIS=adenocarcinoma in situ. CI=confidence interval. CIN=cervical intraepithelial neoplasia. HNRT= HPV-naïve to relevant type. HPV=human papillomavirus. N=number of participants who received at least one dose of the qHPV vaccine at the start of the base study and consented to effectiveness follow-up. n=number of participants who had at least one follow-up visit. PPE=per-protocol effectiveness. qHPV=quadrivalent human papillomavirus.

* Vaccine effectiveness measures the relative reduction of the disease incidence in vaccine recipients compared with the baseline incidence rate of 0·287/100 person-years established from the incidence rate in an unvaccinated cohort.

† Person-years' follow-up for the PPE population was calculated starting from month 7 of the base study, the case counting start time in the PPE population.

‡ Person-years' follow-up for the HNRT population was calculated starting from day 1 of the base study, the case counting start time in the HNRT population.

was positive for HPV16 during the 8–10 years' follow-up interval of the LTFU study (see appendix for details). Similar to the PPE population, this analysis showed that the qHPV vaccine continued to be effective through 12 years, with a trend of continued effectiveness up to 14 years. Based on the control chart analysis, significant vaccine effectiveness was demonstrated through 12 years post-vaccine Dose 1 (Fig. 2).

There was one case of the secondary endpoint of HPV6/11/16/18-related CIN of any grade, AIS, cervical cancer, vulvar cancer, and vaginal cancer (HPV16-related CIN1) in the PPE population during 26,513·3 total person-years of follow-up (table 2). The single PPE-eligible participant who developed this endpoint had positive PCR results for HPV45 and 51 at baseline and was diagnosed with a CIN1 lesion which was positive for HPV16, 45, and 52 during the 6–8-year follow-up interval in the LTFU study; HPV16 was detected only at the time of the CIN1 diagnosis, and was therefore unlikely to have caused the lesion (see appendix for details). There were no HPV6/11/16/18-related cases of vulvar or vaginal cancer in the PPE population.

There were 47 cases of CIN2 or worse related to 10 non-qHPV vaccine types (31/33/35/39/45/51/52/56/58/59) in the HNRT population over 28,032·2 person-years' follow-up, representing an incidence of 0·2 (95% CI 0·1–0·2)/100 person-years at risk (supplementary Table 4). Assuming that an estimated 36% of cases of CIN2 or worse were caused by these 10 non-vaccine types, the expected incidence in a non-vaccinated population would be 0·187/100 person-years. Based on the person-years at risk for the HNRT population, approximately 52 cases of CIN2 or worse related to the non-vaccine types would be expected. The observation that non-vaccine HPV type-related isease cases continued to accrue over the study duration suggests that the population continued to be exposed to these HPV types during the study.

An exploratory analysis of vaccine effectiveness was conducted in women with serologic evidence of prior HPV infection (ie, positive by serology), but without active infection as assessed by negative PCR on day 1 of the base study. No cases of HPV6/11/16/18-related CIN, vulvar, or vaginal cancer were observed in this population over 4064·6 person-years of follow-up (supplementary Table 5). While the sample size was limited ($n = 337$) and the study was not powered to assess effectiveness in this subgroup, this finding suggests that HPV

Table 2
Incidence of HPV6/11/16/18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, and vaginal cancer by time since qHPV vaccination, HPV type, and lesion type

	Young women 16–23 years of age (N=2650)		
	Cases/n	Person-years' follow-up	Rate per 100 person-years (95% CI)
PPE population*			
HPV6/11/16/18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, and vaginal cancer	1/2312	26513·3	<0·1 (<0·1–<0·1)
By time since qHPV vaccine Dose 1			
≤4 years	0/2312	7899·3	0·0 (0·0–<0·1)
>4 to 6 years	0/2312	4610·0	0·0 (0·0–0·1)
>6 to 8 years	1/2286	4519·7	<0·1 (<0·1–0·1)
>8 to 10 years	0/2228	4306·7	0·0 (0·0–0·1)
>10 to 12 years	0/2054	3565·4	0·0 (0·0–0·1)
>12 to 14 years	0/1367	1591·8	0·0 (0·0–0·2)
>14 to 16 years	0/143	20·3	0·0 (0·0–18·1)
By HPV type			
HPV6-related	0/2005	23002·7	0·0 (0·0–<0·1)
HPV11-related	0/2005	23002·7	0·0 (0·0–<0·1)
HPV16-related	1/1903	21769·1	<0·1 (<0·1–<0·1)
HPV18-related	0/2148	24656·8	0·0 (0·0–<0·1)
By lesion type			
CIN1	1/2164	24571·9	<0·1 (<0·1–<0·1)
CIN2 or worse	0/2164	24571·9	0·0 (0·0–<0·1)
CIN2	0/2,164	24571·9	0·0 (0·0–<0·1)
CIN3 or worse	0/2,164	24571·9	0·0 (0·0–<0·1)
CIN3	0/2,164	24571·9	0·0 (0·0–<0·1)
AIS	0/2,164	24571·9	0·0 (0·0–<0·1)
Cervical cancer	0/2,164	24571·9	0·0 (0·0–<0·1)
Vulvar cancer	0/2,312	26509·0	0·0 (0·0–<0·1)
Vaginal cancer	0/2,312	26509·0	0·0 (0·0–<0·1)
HNRT population†			
HPV6/11/16/18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, and vaginal cancer	2/2488	29984·4	<0·1 (<0·1–<0·1)
By time since qHPV vaccine Dose 1			
≤4 years	0/2488	9952·0	0·0 (0·0–<0·1)
>4 to 6 years	0/2488	4959·7	0·0 (0·0–0·1)
>6 to 8 years	1/2457	4862·1	<0·1 (<0·1–0·1)
>8 to 10 years	1/2397	4640·5	<0·1 (<0·1–0·1)
>10 to 12 years	0/2218	3843·6	0·0 (0·0–0·1)
>12 to 14 years	0/1461	1706·3	0·0 (0·0–0·2)
>14 to 16 years	0/146	20·2	0·0 (0·0–18·3)
By HPV type			
HPV6-related	0/2177	26252·2	0·0 (0·0–<0·1)
HPV11-related	0/2177	26252·2	0·0 (0·0–<0·1)
HPV16-related	2/2074	24961·1	<0·1 (<0·1–<0·1)
HPV18-related	0/2328	28078·6	0·0 (0·0–<0·1)
By lesion type			
CIN1	1/2328	27805·2	<0·1 (<0·1–<0·1)
CIN2 or worse	1/2328	27805·1	<0·1 (<0·1–<0·1)
CIN2	0/2328	27805·2	0·0 (0·0–<0·1)
CIN3 or worse	1/2328	27805·1	<0·1 (<0·1–<0·1)
CIN3	1/2328	27805·1	<0·1 (<0·1–<0·1)
AIS	0/2328	27805·2	0·0 (0·0–<0·1)
Cervical cancer	0/2328	27805·2	0·0 (0·0–<0·1)
Vulvar cancer	0/2487	29976·6	0·0 (0·0–<0·1)
Vaginal cancer	0/2487	29976·6	0·0 (0·0–<0·1)

AIS=adenocarcinoma in situ. CI=confidence interval. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. HNRT=HPV-naïve to relevant type. N=number of participants who received at least one dose of the qHPV vaccine at the start of the base study and consented to effectiveness follow-up. n=number of participants who had at least one follow-up visit, PPE=per-protocol effectiveness. qHPV=quadrivalent human papillomavirus.

* Person-years' follow-up was calculated starting from month 7 of the base study, the case counting start time in the PPE population.

† Person-years' follow-up was calculated starting from day 1 of the base study, the case counting start time in the HNRT population.

vaccination may be effective in preventing lesions in people with serologic evidence of a prior infection.

Anti-HPV6/11/16/18 cLIA GMTs were highest at month 7, declined most sharply between months 7 and 24, and were generally stable between month 24 through month 168 (table 3; supplementary figure 1).

After 14 years of follow-up (month 168), >90% of participants in the PPI population remained seropositive for HPV types 6, 11, and 16 and 52·4% of participants remained seropositive for HPV18 based on the cLIA (table 3). The decrease in seropositivity for HPV18 as assessed by cLIA cannot be interpreted as decrease in protection. In analyses using the more sensitive IgG-LIA, >90% of participants

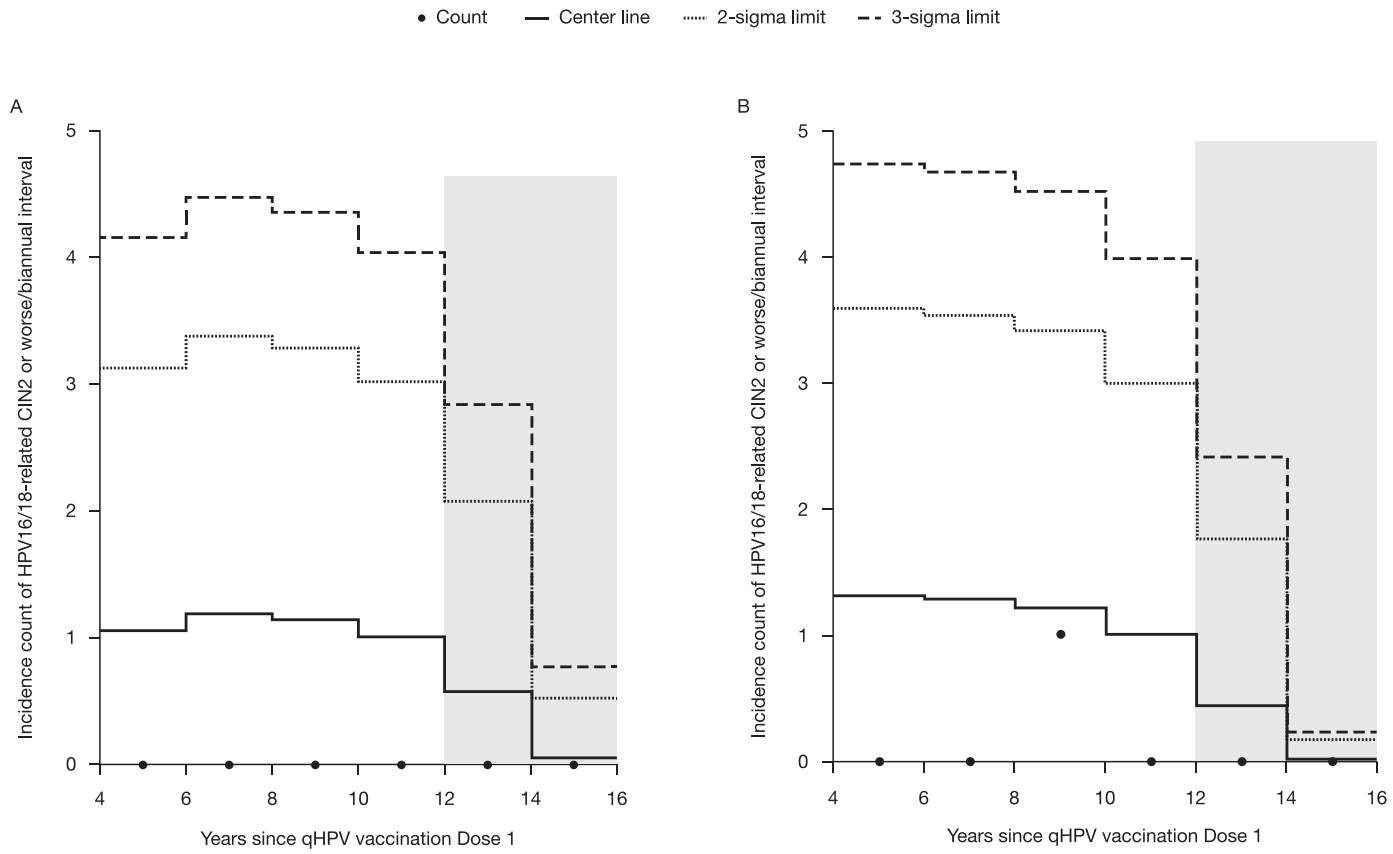

Fig. 2. Control chart analysis of effectiveness of qHPV vaccine against HPV16/18-related CIN2 or worse in the PPE population (A) and HNRT population (B). Shaded areas are intervals with insufficient follow-up time to declare statistical significance. CIN=cervical intraepithelial neoplasia. HNRT=HPV-naïve to relevant type. HPV=human papillomavirus. PPE=per-protocol effectiveness. qHPV=quadrivalent human papillomavirus.

remained seropositive for all vaccine types, including HPV18, at month 168 (table 3). Moreover, if being seronegative by cLIA for HPV18 would indicate being susceptible to HPV18-related infection and disease, at least 33% of participants in the LTFU study would be susceptible (since the seropositivity rate at Month 48, before the start of the LTFU study, was 67%). Considering that the incidence of HPV16/18-related CIN2 or worse in an unvaccinated Nordic population is estimated as 0·287/100 person-years, 80% and 20% of such lesions are estimated to be caused by HPV16 and HPV18, respectively (based on results of the efficacy studies of the qHPV vaccine) [13,14]. There were 17,526.6 person-years at risk in PPE analyses during the LTFU study for the primary endpoint of HPV16/18-related CIN2 or worse (supplementary Table 6); 33% of participants being susceptible to HPV18-related infection and disease would result in three to four cases of HPV18-related CIN2 or worse during the LTFU study. As seen in Table 1, no case was observed.

4. Discussion

The qHPV vaccine demonstrated 100% effectiveness against HPV16/18-related CIN2 or worse in the PPE population through 12 years after the first vaccine dose, with a continuing trend of effectiveness observed through 14 years. Continued effectiveness was observed when evaluating the secondary endpoint of combined incidence of HPV6/11/16/18-related CIN (any grade), AIS, cervical, vulvar, and vaginal cancer as well. In supportive analyses conducted in the HNRT population, there was one case of HPV16-related CIN3. Further examination of the course of events for this case indicated that the participant may have been infected with HPV16 prior to completion of the vaccine series in the base study, preceding development of the CIN3 lesion 8–10 years later during the LTFU period. This case underlines the fact that the vaccine is prophylactic and does not have therapeutic efficacy.

Sustained antibody responses to the vaccine HPV types were observed through 14 years post-vaccination. While the seropositivity rates remained high (>90%) for HPV types 6, 11, and 16 through year 14 post-vaccination using both the cLIA and IgG-LIA, the proportion of participants who were seropositive for HPV18 by cLIA declined to 52·4% at 14 years post-vaccination. However, when the same serum samples were tested using the IgG-LIA, a more sensitive assay that measures all IgG antibodies produced in response to vaccination, >90% of participants were seropositive for HPV18 at this timepoint. While the minimum antibody titres necessary for protection are unknown, results from animal studies suggest very low titres (up to 100-fold lower than the threshold of detection of a standard pseudovirion-based neutralization assay) may be protective [34]. As there were no observed cases of HPV18-related CIN2 or worse among women vaccinated with qHPV in this study, results suggest protective efficacy via immune memory or lower than cLIA-detectible HPV18 antibody levels. Therefore, the low seropositivity rate observed for HPV18 by cLIA appears to be of limited clinical significance.

The antibody levels assessed by cLIA and IgG-LIA are expressed in mMU/mL, which is consistent with the previous published literature and global regulatory documents. World Health Organization international antibody units (IU) have only been established for HPV16 and HPV18, but are not available for other HPV types. A conversion factor from mMU/mL in cLIA and IgG-LIA to IU/mL has been proposed in a previous publication [35].

The study had a unique design: while the LTFU study was an extension of a randomized, placebo-controlled Phase 3 study (FUTURE II), the LTFU study in Nordic participants incorporated elements of a population-based epidemiological study with minimal

Table 3
Summary of cLIA and IgG-LIA GMTs and seropositivity through month 168 in the PPI population

cLIA	Time since Dose 1	Young women 16–23 years of age (N=2750) n	cLIA GMT (95% CI), mMu/mL	cLIA seropositivity* (95% CI)‡, %
Anti-HPV6	Day 1	1380	<8 (<8, <8)	0·0 (0·0, 0·3)
	Month 7	272	521·5 (473·8, 574·0)	99·6 (98·0, 100)
	Month 24	280	133·4 (119·5, 149·0)	97·9 (95·4, 99·2)
	Month 48	1253	97·8 (92·7, 103·2)	94·1 (92·6, 95·3)
	Month 108	1234	89·2 (84·7, 94·0)	94·4 (93·0, 95·6)
	Month 168	1058	78·4 (73·8, 83·2)	90·6 (88·7, 92·3)
Anti-HPV11	Day 1	1380	<8 (<8, <8)	0·0 (0·0, 0·3)
	Month 7	273	738·8 (665·4, 820·4)	99·6 (98·0, 100)
	Month 24	280	174·2 (157·0, 193·2)	98·6 (96·4, 99·6)
	Month 48	1253	123·5 (117·2, 130·1)	97·4 (96·4, 98·2)
	Month 108	1234	85·2 (80·7, 90·0)	95·5 (94·1, 96·6)
	Month 168	1058	66·8 (62·6, 71·3)	91·1 (89·2, 92·8)
Anti-HPV16	Day 1	1319	<12 (<12, <12)	0·0 (0·0, 0·3)
	Month 7	263	2233·8 (1917·7, 2602·0)	100 (98·6, 100)
	Month 24	271	546·9 (486·5, 614·7)	98·9 (96·8, 99·8)
	Month 48	1194	493·4 (464·8, 523·7)	98·9 (98·1, 99·4)
	Month 108	1179	348·6 (328·3, 370·2)	99·1 (98·3, 99·5)
	Month 168	1005	291·2 (272·1, 311·5)	98·3 (97·3, 99·0)
Anti-HPV18	Day 1	1483	<8 (<8, <8)	0·0 (0·0, 0·2)
	Month 7	297	433·7 (383·1, 491·0)	98·3 (96·1, 99·5)
	Month 24	306	59·8 (51·0, 70·2)	74·5 (69·2, 79·3)
	Month 48	1343	43·8 (40·5, 47·4)	67·0 (64·4, 69·5)
	Month 108	1332	32·5 (30·2, 34·9)	59·9 (57·2, 62·6)
	Month 168	1131	26·1 (24·1, 28·2)	52·4 (49·5, 55·4)

IgG-LIA	Time since Dose 1	Young women 16–23 years of age (N=2750) n	IgG-LIA GMT (95% CI), mMu/mL	IgG-LIA Seropositivity† (95% CI)‡, %
Anti-HPV6	Month 108	1235	95·2 (90·5, 100·1)	97·6 (96·6, 98·4)
	Month 168	1054	81·2 (76·1, 86·5)	98·1 (97·1, 98·8)
Anti-HPV11	Month 108	1235	67·4 (64·3, 70·8)	96·3 (95·1, 97·3)
	Month 168	1055	53·5 (50·2, 57·0)	98·0 (97·0, 98·8)
Anti-HPV16	Month 108	1181	346·1 (327·3, 365·9)	100 (99·7, 100)
	Month 168	1000	290·2 (271·0, 310·8)	100 (99·6, 100)
Anti-HPV18	Month 108	1333	46·1 (43·3, 49·2)	91·4 (89·7, 92·8)
	Month 168	1036	36·5 (33·7, 39·5)	93·8 (92·2, 95·2)

CI=confidence interval. cLIA=competitive Luminex immunoassay. GMT=geometric mean titre. HPV=human papillomavirus. IgG-LIA=immunoglobulin G Luminex immunoassay. mMU=milli Merck units. N=number of participants who have received at least one dose of the qHPV vaccine at the start of the base study. n=number of participants contributing to the analysis. PPI=per-protocol immunogenicity.

* The serostatus cut-offs for anti-HPV6, 11, 16, and 18 serum cLIA were 20, 16, 20, and 24 mMU/mL, respectively.

† Percent represents proportion of participants with IgG-LIA anti-HPV serum levels ≥15, 15, 7, and 10 mMU/mL for HPV types 6, 11, 16, and 18, respectively, for month 108. For month 168, anti-HPV serum levels ≥9, 6, 5, and 5 mMU/mL for HPV types 6, 11, 16, and 18, respectively, were used as cut-off values. The original version of the IgG LIA was used for testing month 108 samples. A new version of the IgG LIA was used for testing month 168 samples. The newer version of the assay was bridged to the earlier version to ensure comparable antibody measurements between the two versions.

‡ The CIs are computed based on exact methods.

loss to follow-up (ie, passive and comprehensive surveillance based on health registry data; endpoints based on standard clinical practice; possibility to estimate expected incidence of endpoints among non-vaccinated women with the initial same level of sexual activity). Cervical cancer screening is widely implemented in national programs in Nordic countries, and records are available in virtually complete nationwide registries. As anticipated, retention rates in the LTFU study were high with favorable adherence (ie, 97·1% of the participants who consented for effectiveness follow-up had at least one cervical cytology screening during the LTFU period), supporting the robustness of the analyses presented. The same rigorous methodology (eg, pathological diagnosis adjudication; PCR testing for HPV DNA) as in the base study was also used to assess outcomes in the LTFU study, ensuring consistency throughout the 14 years of total follow-up and a continuous level of rigor.

The participants in this cohort represent a sentinel cohort with an observed follow-up time of approximately 5 years more than the first cohort which received qHPV vaccine post-licensure. This provides sufficient lead time for identifying vaccine breakthrough cases. Threshold levels for incidence of breakthrough cases were established to define a point where vaccine effectiveness may have waned by a moderate amount, and where there may exist a need for a booster vaccine dose. This was evaluated using control chart methods, an innovative aspect of this study, which had the advantage of monitoring disease incidence in real time during the LTFU study. This real-time monitoring is conducive to prompt detection of a decrease in vaccine effectiveness, should any such decline occur [36]. As no waning of immunity was observed in this cohort since the first vaccine dose, implementation of booster vaccination in this population is not warranted. Also, as the study participants were vaccinated in the base study at 16 to 23 years of age, they reached approximately 30 to 37 years of age by the end of the LTFU study after 14 years of total follow-up. This covers the age range for peak incidence of

HPV16/18-related CIN2/3, as well as the beginning of the period of highest cervical cancer risk [37].

The accrual of non-vaccine HPV type-related disease during the LTFU study is consistent with previous observations that the qHPV vaccine provides only limited cross-protection against non-vaccine HPV types (ie, partial protection against HPV31-related infection and disease) [38,39]. In addition, these data highlight that the women included in the cohort remained sexually active and continued to acquire cervical dysplasia as they approached mid-adulthood during the study.

Limitations of this study include the lack of a control arm in the LTFU study, as participants who received placebo in the base study were offered the intervention, ie, qHPV vaccination upon base-study completion for ethical reasons and to be in compliance with the Helsinki declaration of clinical trial conduct. Therefore, effectiveness was determined relative to estimated incidence in an unvaccinated population. In fact, the strong adherence to routine cervical screening programs in Nordic countries, the ability to compare cervical disease incidence rates in the study population, together with the robustness of the statistical methods and analyses used in the study, supported the design and conduct of a hypothesis-driven LTFU study and allowed rigorous conclusions to be drawn. Because the effectiveness assessment in the LTFU was based on passive surveillance of routine clinical practice, endpoints were limited to HPV-related cervical precancers and cancers and vulvar and vaginal cancers, as diagnoses of other HPV-related disease endpoints (eg, vulvar/vaginal/anal intraepithelial neoplasia) assessed during the base study would not have been systematically collected in registry data in all the Nordic countries. Given that the natural history, pathophysiology, and mechanisms of protection elicited by HPV vaccination are similar at different anatomic sites, it is reasonable to assume that results for cervical endpoints would be applicable to other HPV-related disease endpoints.

In summary, the study results demonstrate significant qHPV vaccine effectiveness of 100% through 12 years after the first dose of qHPV vaccine, with a continuing trend of protection up to 14 years post-vaccination in the population of Nordic women. There was no evidence of waning immunity over this time period, suggesting that there is no need for a booster dose. Thus, the effectiveness results were consistent with prolonged and sustained immunity against the vaccine-related HPV types. A 9-valent HPV (9vHPV) vaccine has been developed and licensed in 2014 to protect against infection and disease caused by the four HPV types covered by the qHPV vaccination and the five HPV types which are most commonly associated with cervical cancer after HPV16 and 18 [9]. Based on epidemiological studies, the 9vHPV vaccine has the potential to prevent approximately 90% cervical cancer cases, 70–85% high-grade cervical dysplasia, 85–95% of HPV-related vulvar, vaginal, and anal cancers, and 90% of genital warts [9]. The long-term effectiveness that was demonstrated for the qHPV vaccine is likely to be applicable to the 9vHPV vaccine since the two vaccines are manufactured similarly, share antigens for four HPV types, and have similar efficacy and immunogenicity profiles for HPV6, 11, 16, and 18 [9]. A long-term effectiveness study of the 9vHPV vaccine is ongoing in Nordic countries to confirm this expectation [36].

Author contributions

SKK contributed to conception, design, or planning the study, acquisition of the data, interpretation of the results, drafting the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

MN contributed to conception, design, or planning the study, acquisition of the data, analysis of the data, interpretation of the results, drafting the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

KS contributed to acquisition of the data, analysis of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

JD contributed to conception, design, or planning the study, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

LT contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

CM contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

SB contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

EE contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

MH contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

ÁIÁ contributed to interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

KB contributed to acquisition of the data, analysis of the data, and critically reviewing or revising the manuscript for important intellectual content.

KF contributed to acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content.

IG contributed to analysis of the data, provision of study materials/patients, and drafting of the manuscript.

SWS contributed to acquisition of the data, analysis of the data, and critically reviewing or revising the manuscript for important intellectual content.

OB provided statistical expertise and contributed to analysis of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

TG contributed to acquisition of the data, analysis of the data, interpretation of the results, drafting of the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

AL contributed to interpretation of the results, drafting of the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

JBM provided statistical expertise and contributed to conception, design, or planning the study, analysis of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

DR provided statistical expertise and contributed to conception, design, or planning the study, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

YSY provided statistical expertise and contributed to analysis of the data and critically reviewing or revising the manuscript for important intellectual content.

CB contributed to conception, design, or planning the study, acquisition of the data, analysis of the data, interpretation of the results, drafting the manuscript, and critically reviewing or revising the manuscript for important intellectual content.

AS contributed to conception, design, or planning the study, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

All authors have reviewed the version of the manuscript to be submitted and agree with its content and submission. All authors had access to all relevant study data and related analyses, vouch for the completeness and accuracy of the data presented, and are accountable for all aspects of the work.

Declaration of interests

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SKK reports research grants from MSD during the conduct of the study through her affiliating institute and personal fees from MSD outside the submitted work.

MN reports research grants from MSD Norway through her affiliating institute during the conduct of the study and outside the scope of this study.

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LT reports that her affiliating institution (ICS) received research grants from MSD Denmark ApS during the conduct of the study.

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MH reports working on clinical trials sponsored by MSD during the conduct of the study.

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KB, KF, and IG have nothing to disclose.

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OB, TG, AL, JBM, DR, YSY, CB, and AS are current or former employees of MSD and may own stock or stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

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Data sharing

The data-sharing policy, including restrictions, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Supplementary materials

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References

[1] de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020;8(2):e180–90.
[2] de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer 2017;141(4):664–70.
[3] Alemany L, Saunier M, Alvarado-Cabrero I, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer 2015;136(1):98–107.
[4] de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11(11):1048–56.
[5] Serrano B, de Sanjosé S, Tous S, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer 2015;51(13):1732–41.
[6] Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis 2009;199(6):805–14.
[7] Barr E, Tamms G. Quadrivalent human papillomavirus vaccine. Clin Infect Dis 2007;45(5):607–9.
[8] Haupt RM, Sings HL. The efficacy and safety of the quadrivalent human papillomavirus 6/11/16/18 vaccine gardasil. J Adolesc Health 2011;49(5):467–75.
[9] Luxembourg A, Moeller E. 9-Valent human papillomavirus vaccine: a review of the clinical development program. Expert Rev Vaccines 2017;16(11):1119–39.
[10] Garland SM, Kjaer SK, Munoz N, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin Infect Dis 2016;63(4):519–27.
[11] Vichnin M, Bonanni P, Klein NP, et al. An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. Pediatr Infect Dis J 2015;34(9):983–91.
[12] Muñoz N, Kjaer SK, Sigurdsson K, et al. Impact of human papillomavirus (HPV)–6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102(5):325–39.
[13] Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila) 2009;2(10):868–78.
[14] The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356(19):1915–27.
[15] Moscicki A-B, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine 2012;30(Suppl 5):F24–33.
[16] US Food and Drug Administration. Approval Letter - Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant 6/08/2006, 2006. http://wayback.archive-it.org/7993/20170722145339/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm111283.htm (accessed November 11, 2019).
[17] European Medicines Agency (EMA). Gardasil: EPAR - Scientific discussion 2006, 2006. https://www.ema.europa.eu/en/documents/scientific-discussion/gardasil-epar-scientific-discussion_en.pdf (accessed November 11, 2019).
[18] The FUTURE I/II Study Group. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010;340:c3493.
[19] Bilet EF, Langseth H, Thoresen SØ, Bray F. Completeness of invasive cervical cancer at the Cancer Registry of Norway. Acta Oncol 2009;48(7):1070–3.
[20] Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45(7):1218–31.
[21] Leinonen MK, Hansen SA, Skare GB, et al. Low proportion of unreported cervical treatments in the cancer registry of Norway between 1998 and 2013. Acta Oncol 2018;57(12):1663–70.
[22] Elfström KM, Sparén P, Olausson P, Almstedt P, Strander B, Dillner J. Registry-based assessment of the status of cervical screening in Sweden. J Med Screen 2016;23(4):217–26.
[23] Sigurdsson K. Cervical cancer: cytological cervical screening in Iceland and implications of HPV vaccines. Cytopathology 2010;21(4):213–22.
[24] Sigurdsson K, Sigvaldason H. Effectiveness of cervical cancer screening in Iceland, 1964–2002: a study on trends in incidence and mortality and the effect of risk factors. Acta Obstet Gynecol Scand 2006;85(3):343–9.
[25] Von Euler-Chelpin M, Lynge E, Rebolj M. Register-based studies of cancer screening effects. Scand J Public Health 2011;39(Suppl 7):158–64.
[26] Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356(19):1928–43.
[27] Else EA, Swoyer R, Zhang Y, et al. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with INNO-LiPA HPV genotyping extra assay. J Clin Microbiol 2011;49(5):1907–12.
[28] Roberts CC, Swoyer R, Bryan JT, Taddeo FJ. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with the linear array HPV genotyping PCR assay and influence of DNA extraction method on HPV detection. J Clin Microbiol 2011;49(5):1899–906.
[29] Dias D, Van Doren J, Schlottmann S, et al. Optimization and validation of a multiplexed luminex assay to quantify antibodies to neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. Clin Diagn Lab Immunol 2005;12(8):959–69.

[30] Opalka D, Lachman CE, MacMullen SA, et al. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed luminex assay. Clin Diagn Lab Immunol 2003;10(1):108–15.
[31] Smith JF, Kowalski R, Esser MT, Brown MJ, Bryan JT. Evolution of type-specific immunoassays to evaluate the functional immune response to Gardasil: a vaccine for human papillomavirus types 16, 18, 6 and 11. Hum Vaccin 2008;4(2):134–42.
[32] Opalka D, Matys K, Bojczuk P, et al. Multiplexed serologic assay for nine anogenital human papillomavirus types. Clin Vaccine Immunol 2010;17(5):818–27.
[33] Kjaer SK, Tran TN, Sparen P, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. J Infect Dis 2007;196(10):1447–54.
[34] Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines–immune responses. Vaccine 2012;30(Suppl 5):F83–7.
[35] Brown D, Müller M, Sehr P, et al. Concordance assessment between a multiplexed competitive Luminex immunoassay, a multiplexed IgG Luminex immunoassay, and a pseudovirion-based neutralization assay for detection of human papillomaviruse types 16 and 18. Vaccine 2014;32(44):5880–7.
[36] Luxembourg A, Kjaer SK, Nygard M, et al. Design of a long-term follow-up effectiveness, immunogenicity and safety study of women who received the 9-valent human papillomavirus vaccine. Contemp Clin Trials 2017;52:54–61.
[37] Bosch FX, Tsu V, Vorsters A, Van Damme P, Kane MA. Reframing cervical cancer prevention. Expanding the field towards prevention of human papillomavirus infections and related diseases. Vaccine 2012;30(Suppl 5):F1–11.
[38] Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years. J Infect Dis 2009;199(7):926–35.
[39] Wheeler CM, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. J Infect Dis 2009;199(7):936–44.