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Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population☆,☆☆

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HIGHLIGHTS

- The 9vHPV vaccine prevents 98% of high-grade cervical dysplasia related to the 9 HPV types covered by the vaccine.
- The 9vHPV vaccine prevents 98% of cervical surgeries related to the 9 HPV types covered by the vaccine.
- Vaccine did not prevent diseases related to HPV types detected at baseline but reduced diseases related to other HPV types.
- While early vaccination in HPV naïve persons is best, sexually active persons may benefit from catch-up vaccination programs.
- These data will be important to inform future public health vaccination recommendations.

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ABSTRACT

Objective. Nine-valent human papillomavirus (9vHPV) vaccine efficacy against disease and cervical surgeries related to all nine vaccine components was assessed compared with a historic placebo population. This was not assessed in the 9vHPV vaccine efficacy trial since the trial was quadrivalent HPV (qHPV) vaccine-controlled, efficacy was measured for the five HPV types covered only by 9vHPV vaccine (HPV31/33/45/52/58), but not the four types covered by both vaccines (HPV6/11/16/18).

Methods. Three international, randomized, double-blind studies were conducted using the same methodology. In the 9vHPV vaccine study (NCT00543543), 7106 and 7109 women received 9vHPV or qHPV vaccine, respectively. In the historic qHPV vaccine studies (FUTURE I [NCT00092521] and II [NCT00092534]), 8810 and 8812 women received qHPV vaccine or placebo, respectively, based on the same eligibility criteria. Cervical cytological testing was performed regularly. Biopsy or definitive therapy specimens were assessed for HPV DNA.

Results. Among women negative for 14 HPV types prior to vaccination, incidence of high-grade cervical disease (9vHPV, $n = 2$ cases; placebo, $n = 141$ cases) and cervical surgery (9vHPV, $n = 3$ cases; placebo, $n =$

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170 cases) related to the nine HPV types was reduced by 98.2% (95% confidence interval [CI], 93.6–99.7) and 97.8% (95% CI, 93.4–99.4), respectively. The 9vHPV vaccine did not prevent disease related to vaccine HPV types detected at baseline, but significantly reduced cervical, vulvar, and vaginal diseases related to other vaccine HPV types.

Conclusions. Effective implementation of the 9vHPV vaccine may substantially reduce the burden of HPV-related diseases and related medical procedures.

Trial registrations: clinicaltrials.gov: NCT00543543, NCT00092521, NCT00092534.

1. Introduction

A nine-valent human papillomavirus (9vHPV) vaccine was developed to provide protection against HPV types 6, 11, 16, and 18 already covered by the quadrivalent HPV (qHPV) vaccine and the next five most common oncogenic types associated with cervical cancer worldwide (types 31, 33, 45, 52, and 58) [1]. Based on the prevalence of the 9vHPV vaccine types in worldwide studies, the 9vHPV vaccine is expected to prevent approximately 90% of all cervical cancers; 70–85% of high-grade cervical disease; and 90% of HPV-related vulvar, vaginal, and anal cancers and genital warts worldwide [2–5]. Based on the worldwide HPV prevalence and type distribution, the 9vHPV vaccine is expected to provide an additional 19%, 13%, and 20% reduction in cervical, vulvar, and vaginal cancers compared with the qHPV vaccine [5], and an additional 30% reduction in high-grade cervical intraepithelial neoplasia [4]. As such, the 9vHPV vaccine compared with the qHPV vaccine provides additional protection against a substantial proportion of disease in women [6]. This additional protection, conferred by the 9vHPV vaccine, has implications for cervical cancer screening guidelines and cancer reduction expectations in countries that do not have screening programs but have HPV vaccination programs.

In a clinical trial in women, the 9vHPV vaccine prevented ~97% of high-grade cervical, vulvar, and vaginal disease associated with HPV 31, 33, 45, 52, and 58, elicited non-inferior antibody responses to HPV 6, 11, 16, and 18 compared with qHPV vaccine, and was generally well tolerated [7,8]. For ethical reasons, the clinical trial did not have a placebo arm [9]. Since the trial was controlled with qHPV vaccine, a direct comparison with an unvaccinated population was not possible. Thus, the reduction in disease and procedures related to all nine vaccine components among pre- and young-adolescent females, as well as sexually experienced women, is not known. The lack of formal assessment of efficacy compared with an unvaccinated group has been highlighted in prior publications as a limitation of previous analyses. These data are needed to inform public health vaccination recommendations and future revisions to cervical cancer screening algorithms in vaccinated populations.

Here, we present efficacy estimates against cervical, vulvar, and vaginal disease caused by all nine vaccine HPV types and prevention of related cervical surgeries compared with a historic placebo population (the placebo arm of the qHPV vaccine efficacy trials, FUTURE I, and FUTURE II [10,11]). Efficacy was assessed in females naïve to 14 HPV types (i.e. the nine vaccine types and the five next most common known oncogenic types) at baseline—a population that resembles a pre-adolescent/adolescent population. In addition, we present 9vHPV vaccine efficacy estimates among all trial participants, stratified by baseline HPV status.

2. Methods

2.1. Clinical studies used in the analyses

Protocol V503-001 (NCT00543543) was a double-blind, qHPV-vaccine-controlled, dose-ranging, efficacy, immunogenicity, and safety study of the 9vHPV vaccine in approximately 14,000 women aged 16–26 years. Protocols V501-013 (FUTURE I; NCT00092521) and V501-015 (FUTURE II; NCT00092534) were double-blind, placebo-controlled, efficacy, immunogenicity, and safety studies of the qHPV vaccine in approximately 17,600 women aged 16–26 years (see Supplementary Appendix). Eligibility criteria were consistent across the three studies; design details and key primary results have been reported [7–12].

2.2. Ethics approval

All trials were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies [7,8,10,11]. All participants provided written informed consent prior to study participation in accordance with local laws and regulations.

2.3. Vaccination and follow-up

Participants received a three-dose regimen of 9vHPV vaccine, qHPV vaccine, or placebo at Day 1, Month 2, and Month 6. Pap tests for assessment of cervical abnormalities were collected at Day 1, Month 7, and at 6- to 12-month intervals thereafter for the entire study duration for laboratory analysis. Participants with abnormal Pap test results came for additional visits and underwent meticulous examination of the cervix (colposcopy) and collection of tissue samples (biopsy, excision) for pathological examination to detect potential HPV-related disease. During the collection of cervical cytology samples, an inspection for non-cervical lesions was performed. Examinations of the entire external genitalia (including the periurethral, perineal, perianal, and vulvar regions) were conducted at Day 1, Month 7, and each subsequent study visit. If a lesion suspected to be HPV-related was observed, it was biopsied. Several measures were taken to minimize the risk of missing a lesion: participants were screened frequently (every 6 to 12 months) and were required to receive all of their gynecological care in the context of the study, including collection of all cytology and tissue samples mandated per the study protocol. In the very rare cases, when cytology or tissue samples were collected outside of the context of the study, all efforts were made to obtain relevant cytology, colposcopy/operative, and pathology reports; biopsy diagnostic slides; and tissue blocks if available. As a result, it is very unlikely that any high-grade dysplasia or cancer occurring during the study would have been missed. Histologic sections were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories), who were unaware of treatment-group assignment and HPV status, and were then read for endpoint determination by a blinded adjudication panel of four pathologists. Tissue samples were tested by polymerase chain reaction (PCR) [13,14] for the 12 HPV types identified as oncogenic by the International Agency for Research on Cancer (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) [15], plus HPV 6 and 11, which are responsible for 90% of genital warts [3]. HPV DNA detection by PCR was considered as a surrogate of HPV infection and used to identify participants with active HPV infection at enrollment and determine HPV infection endpoints, as previously described [9,11].

Analyses presented here are based on end-of-study data for the 9vHPV vaccine (through the last visit that occurred on March 10, 2014), representing up to 6.0 years of follow-up post-Dose 1 (median:

Table 1
Baseline HPV DNA positivity by trial and vaccine allocation.

	9vHPV vaccine program				qHPV vaccine program			
	9vHPV vaccine group (*N* = 7106)		qHPV vaccine group (*N* = 7109)		qHPV vaccine group (*N* = 8810)		Placebo group (*N* = 8812)	
	%	(m/n)	%	(m/n)	%	(m/n)	%	(m/n)
Any of 14 HPV types tested[a]	37.2	(2529/6807)	36.8	(2504/6811)	32.5	(2776/8541)	32.2	(2757/8566)
HPV 6	4.3	(296/6961)	3.9	(270/6970)	4.2	(368/8691)	4.0	(349/8708)
HPV 11	0.5	(38/6959)	0.7	(46/6974)	0.7	(64/8703)	0.6	(55/8720)
HPV 16	10.5	(729/6960)	9.9	(689/6969)	9.0	(781/8681)	8.9	(772/8706)
HPV 18	4.5	(313/6954)	4.4	(303/6960)	3.6	(316/8697)	3.7	(325/8717)
HPV 31	5.4	(374/6962)	5.3	(370/6982)	4.5	(394/8687)	4.4	(387/8712)
HPV 33	2.5	(173/6964)	2.4	(167/6968)	2.1	(183/8698)	2.0	(175/8710)
HPV 35	1.7	(120/6967)	1.5	(105/6975)	1.6	(137/8696)	1.5	(133/8715)
HPV 39	6.1	(425/6962)	4.9	(342/6963)	4.6	(396/8690)	4.6	(402/8709)
HPV 45	2.9	(198/6944)	2.8	(198/6962)	2.2	(192/8694)	2.6	(226/8706)
HPV 51	7.9	(552/6956)	8.2	(568/6956)	7.6	(655/8664)	7.1	(614/8693)
HPV 52	7.0	(484/6960)	6.9	(481/6979)	5.8	(505/8687)	5.5	(481/8714)
HPV 56	10.9	(761/6952)	10.6	(741/6958)	7.8	(674/8685)	7.6	(661/8688)
HPV 58	3.9	(273/6964)	3.8	(267/6967)	3.5	(301/8695)	3.9	(342/8715)
HPV 59	4.5	(316/6953)	4.3	(296/6955)	3.6	(315/8694)	3.7	(326/8705)

HPV, human papillomavirus; m, number of subjects positive by PCR to the indicated HPV type; N, number of subjects randomized to the indicated vaccination group; n, number of subjects with non-missing PCR results for all of the indicated HPV types; PCR, polymerase chain reaction; qHPV, quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine; 9vHPV, nine-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine. Percent was calculated as 100 × (m/n).
[a] HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

4.0 years) [8]. End-of-study data for the FUTURE I and FUTURE II studies include up to 4.9 years of follow-up post-Dose 1 (average: 3.6 years; 25th and 75th percentiles: 3.5 and 3.9 years, respectively) [16].

2.4. Individual study characteristics

The included trials were identical in most parameters, as they used the same eligibility criteria and methods to assess study endpoints (i.e. pathology panel and PCR assay) [17]. However, the following differences should be noted: FUTURE II required Pap screening every 12 months, whereas the two other trials (V503-001 and FUTURE I) required Pap screening every 6 months; in V503-001 and FUTURE I (but not FUTURE II), participants with histologically confirmed, HPV-related, external genital or vaginal lesions were referred to colposcopy if the external genital or vaginal biopsies were not obtained during colposcopy.

2.5. Statistical analysis

Efficacy analyses were conducted on the modified intention-to-treat (mITT) population (identical to the population referred to as the ITT population in some HPV vaccine clinical trial publications [10,11,16,18]), which comprised participants who received at least one vaccination and had at least one measurement of efficacy for the

Table 2
Effect of 9vHPV vaccine on the reduction in incidence of cervical disease (subjects PCR-negative to 14 HPV types at baseline).

Endpoint Causal HPV type	**9vHPV vaccine (*N* = 4365)**		**Historic placebo (*N* = 5887)**		
	Observed cases	Incidence per 10,000 person-years cases (95% CI)	Observed cases	Incidence per 10,000 person-years cases (95% CI)	Reduction in incidence % (95% CI)
Subjects contributing to the analysis	4229		5756		
Cervical disease, any grade					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	4	2.5 (0.7–6.4)	315	159.7 (142.5–178.3)	98.4 (96.0–99.5)
HPV 6	1	0.6 (0.0–3.5)	40	20.1 (14.4–27.4)	96.9 (82.5–99.8)
HPV 11	0	0.0 (0.0–2.3)	14	7.0 (3.9–11.8)	100 (62.8–100)
HPV 16	0	0.0 (0.0–2.3)	128	64.5 (53.8–76.7)	100 (96.5–100)
HPV 18	0	0.0 (0.0–2.3)	44	22.1 (16.1–29.7)	100 (90.4–100)
HPV 31	3	1.9 (0.4–5.5)	67	33.7 (26.1–42.8)	94.4 (84.0–98.5)
HPV 33	0	0.0 (0.0–2.3)	35	17.6 (12.3–24.5)	100 (88.1–100)
HPV 45	1	0.6 (0.0–3.5)	13	6.5 (3.5–11.2)	90.4 (43.5–99.5)
HPV 52	0	0.0 (0.0–2.3)	62	31.2 (23.9–40.0)	100 (92.4–100)
HPV 58	0	0.0 (0.0–2.3)	52	26.2 (19.5–34.3)	100 (91.8–100)
High-grade cervical disease					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	2	1.3 (0.2–4.5)	141	71.0 (59.7–83.7)	98.2 (93.6–99.7)
HPV 6	0	0.0 (0.0–2.3)	10	5.0 (2.4–9.2)	100 (54.7–100)
HPV 11	0	0.0 (0.0–2.3)	1	0.5 (0.0–2.8)	100 (≤ − 999–100)
HPV 16	0	0.0 (0.0–2.3)	73	36.7 (28.8–46.2)	100 (93.7–100)
HPV 18	0	0.0 (0.0–2.3)	18	9.0 (5.4–14.3)	100 (74.0–100)
HPV 31	2	1.3 (0.2–4.5)	32	16.1 (11.0–22.7)	92.2 (71.1–98.7)
HPV 33	0	0.0 (0.0–2.3)	17	8.5 (5.0–13.7)	100 (71.9–100)
HPV 45	0	0.0 (0.0–2.3)	3	1.5 (0.3–4.4)	100 (−113.3–100)
HPV 52	0	0.0 (0.0–2.3)	28	14.1 (9.4–20.4)	100 (85.1–100)
HPV 58	0	0.0 (0.0–2.3)	23	11.6 (7.3–17.4)	100 (81.1–100)

CI, confidence interval; HPV, human papillomavirus; N, number of subjects in the analysis population; PCR, polymerase chain reaction; 9vHPV, nine-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

endpoint being analyzed (9vHPV, $N = 6997$; placebo, $N = 8748$). The mITT population included participants independent of their HPV DNA test result at the time of vaccination. Analyses were conducted among women who were negative to 14 HPV types at baseline (9vHPV, $N = 4365$; placebo, $N = 5887$) and among all mITT participants stratified by baseline HPV positivity.

The efficacy of the 9vHPV vaccine relative to historic placebo was estimated by direct comparison, where vaccine efficacy was defined as 100% (1 – [incidence rate in 9vHPV vaccine group/incidence rate in historic placebo]). The 95% confidence interval (CI) for vaccine efficacy was estimated using an exact method as described by Chen et al. [12]. The V503-001, FUTURE I, and FUTURE II trials were similarly designed, and incidence rates of efficacy endpoints were similar between the qHPV vaccine groups contributed by these studies (Supplementary Table S1), providing support for the direct comparison of 9vHPV vaccine with historic placebo.

3. Results

Participant characteristics were similar with respect to sociodemographic and sexual characteristics across the included trials [7,10,11]. The mean age (years) was 21.9 in the 9vHPV and 21.8 in the qHPV vaccine arms of the 9vHPV vaccine trial, and 20.0 in both the qHPV vaccine and placebo arms of the qHPV vaccine trials (Supplementary Table S2).

Baseline HPV DNA positivity in each arm (9vHPV, qHPV, placebo) of the included trials was comparable (Table 1). HPV 16 positivity ranged from 8.9% in the placebo group to 10.5% in the 9vHPV vaccine group. Similar proportions of trial participants were positive for two or more vaccine HPV types across trial groups (Supplementary Table S3); most participants were negative to all four qHPV vaccine types (83.5–85.2%), all five newly included HPV types (82.8–85.4%), and all 9vHPV vaccine types (72.6–75.7%). Only two participants were positive for all qHPV vaccine types (one in the 9vHPV vaccine arm, and one in the qHPV vaccine arm), and none were positive for all 9vHPV vaccine types.

The incidence and percentage reduction of HPV-related disease and procedures with 9vHPV vaccine versus placebo were initially assessed among women negative at baseline for 14 HPV types. Cervical disease of any grade related to the 9vHPV vaccine types was reduced by 98.4% (95% CI, 96.0–99.5), and high-grade cervical intraepithelial neoplasia (CIN) by 98.2% (95% CI 93.6–99.7) compared with placebo (Table 2). Similarly, large reductions in disease related to each of the individual nine HPV types were observed. In general, no clinically or statistically significant efficacy against lesions related to non-vaccine HPV types (HPV 35, 39, 51, 56, and 59) was observed (data not shown). The overall reduction in vulvar and vaginal disease of any grade was 94.9% (95% CI, 90.4–97.5; Table 3). High efficacy against vulvar and vaginal condylomas was also observed (94.3%; 95% CI, 89.0–97.6). Reduction in high-grade vulvar and vaginal disease was 100% (95% CI, 85.7–100). Vaccine

Table 3
Effect of 9vHPV vaccine on the reduction in incidence of vulvar and vaginal disease (subjects PCR-negative to 14 HPV types at baseline).

Endpoint Causal HPV type	9vHPV vaccine ($N = 4365$)		Historic placebo ($N = 5887$)		
	Observed cases	Incidence per 10,000 person-years cases (95% CI)	Observed cases	Incidence per 10,000 person-years cases (95% CI)	Reduction in incidence % (95% CI)
Subjects contributing to the analysis	4320		5827		–
Vulvar and vaginal disease, any grade					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	9	5.6 (2.6–10.6)	218	110.3 (96.1–125.9)	94.9 (90.4–97.5)
HPV 6	8	5.0 (2.1–9.8)	154	77.5 (65.8–90.8)	93.6 (87.5–97.3)
HPV 11	1	0.6 (0.0–3.5)	33	16.5 (11.4–23.2)	96.2 (78.0–99.8)
HPV 16	1	0.6 (0.0–3.5)	49	24.5 (18.1–32.4)	97.5 (86.2–99.9)
HPV 18	0	0.0 (0.0–2.3)	17	8.5 (4.9–13.6)	100 (72.0–100)
HPV 31	0	0.0 (0.0–2.3)	26	13.0 (8.5–19.0)	100 (83.8–100)
HPV 33	0	0.0 (0.0–2.3)	4	2.0 (0.5–5.1)	100 (−38.4–100)
HPV 45	0	0.0 (0.0–2.3)	5	2.5 (0.8–5.8)	100 (−24.1–100)
HPV 52	0	0.0 (0.0–2.3)	21	10.5 (6.5–16.0)	100 (78.8–100)
HPV 58	0	0.0 (0.0–2.3)	9	4.5 (2.1–8.5)	100 (47.0–100)
Vulvar and vaginal condyloma					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	8	5.0 (2.1–9.8)	174	87.7 (75.2–101.8)	94.3 (89.0–97.6)
HPV 6	7	4.3 (1.7–8.9)	144	72.4 (61.1–85.3)	94.0 (87.8–97.2)
HPV 11	1	0.6 (0.0–3.5)	31	15.5 (10.5–22.0)	96.0 (76.2–99.8)
HPV 16	0	0.0 (0.0–2.3)	19	9.5 (5.7–14.8)	100 (75.9–100)
HPV 18	0	0.0 (0.0–2.3)	14	7.0 (3.8–11.7)	100 (62.9–100)
HPV 31	0	0.0 (0.0–2.3)	15	7.5 (4.2–12.4)	100 (66.5–100)
HPV 33	0	0.0 (0.0–2.3)	4	2.0 (0.5–5.1)	100 (−38.4–100)
HPV 45	0	0.0 (0.0–2.3)	3	1.5 (0.3–4.4)	100 (−112.8–100)
HPV 52	0	0.0 (0.0–2.3)	16	8.0 (4.6–13.0)	100 (69.4–100)
HPV 58	0	0.0 (0.0–2.3)	7	3.5 (1.4–7.2)	100 (24.9–100)
High-grade vulvar and vaginal disease					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	0	0.0 (0.0–2.3)	29	14.5 (9.7–20.8)	100 (85.7–100)
HPV 6	0	0.0 (0.0–2.3)	5	2.5 (0.8–5.8)	100 (−24.1–100)
HPV 11	0	0.0 (0.0–2.3)	1	0.5 (0.0–2.8)	100 (−∞–100)
HPV 16	0	0.0 (0.0–2.3)	24	12.0 (7.7–17.8)	100 (82.1–100)
HPV 18	0	0.0 (0.0–2.3)	1	0.5 (0.0–2.8)	100 (−∞–100)
HPV 31	0	0.0 (0.0–2.3)	5	2.5 (0.8–5.8)	100 (−24.1–100)
HPV 33	0	0.0 (0.0–2.3)	0	0.0 (0.0–1.8)	–
HPV 45	0	0.0 (0.0–2.3)	0	0.0 (0.0–1.8)	–
HPV 52	0	0.0 (0.0–2.3)	0	0.0 (0.0–1.8)	–
HPV 58	0	0.0 (0.0–2.3)	2	1.0 (0.1–3.6)	100 (−331.1–100)

CI, confidence interval; HPV, human papillomavirus; N, number of subjects in the analysis population; PCR, polymerase chain reaction; 9vHPV, nine-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

efficacy against disease caused by each of the individual vaccine types was similar. Cervical biopsy related to the 9vHPV vaccine types was reduced by 95.1% (95% CI, 92.6–97.0) and cervical definitive therapy (loop electrosurgical excision procedure, conization) by 97.8% (95% CI, 93.4–99.4) (Table 4), with reductions of 91.3–100% and 91.5–100%, respectively, across the individual vaccine types.

Vaccine efficacy and incidence rates compared with placebo were also assessed by baseline HPV status (Table 5, Supplementary Table S4). Among women who were negative for all 9vHPV vaccine types, cervical disease of any grade and high grade related to HPV 6, 11, 16, or 18 was significantly reduced by 99.0% (1.1 versus 106.4/10,000 person-years) and 100% (0.0 versus 49.4/10,000 person-years), respectively; cervical disease related to HPV 31, 33, 45, 52, or 58 was reduced by 96.9% (3.2 versus 104.3/10,000 person-years; 9vHPV versus placebo) and 95.3% (2.1 versus 45.8/10,000 person-years; 9vHPV versus placebo), respectively. The incidence of cervical disease related to HPV 31, 33, 45, 52, or 58 was markedly reduced among women positive at baseline for HPV 6, 11, 16, or 18 but negative for HPV 31, 33, 45, 52, and 58 (any grade: 95.1%, 8.3 versus 168.3/10,000 person-years; high grade, 91.1%; 8.3 versus 93.4/10,000 person-years). Similarly, cervical disease incidence related to HPV 6, 11, 16, or 18 was significantly reduced compared with placebo among women negative at baseline for HPV 6, 11, 16, and 18 but positive for HPV 31, 33, 45, 52, or 58 (any grade: 97.4%, 3.9 versus 154.4/10,000 person-years; high grade: 95.8%, 3.9 versus 93.7/10,000 person-years).

Efficacy against vulvar and vaginal disease of any grade was primarily restricted to participants who were HPV 6-, 11-, 16-, and 18-negative at baseline (Table 5). A significant reduction in the incidence of vulvar and vaginal disease was observed among women negative at baseline to all nine HPV types for lesions related to HPV 6, 11, 16, or 18 (any grade: 94.9%, 5.3 versus 103.1/10,000 person-years; condyloma: 95.0%, 4.2 versus 85.7/10,000 person-years) and HPV 31, 33, 45, 52, or 58 (any grade: 98.2%, 0.5 versus 29.4/10,000 person-years; condyloma: 100%, 0.0 versus 20.0/10,000 person-years).

Reductions in the incidence of biopsy (95.8%) and definitive therapy (100%) were observed for HPV 6-, 11-, 16-, or 18-related lesions as well as HPV 31-, 33-, 45-, 52-, or 58-related lesions (94.7% and 93.9%, respectively) among women negative for the respective HPV types at baseline (Table 5). Likewise, reductions in biopsy (94.5%) and definitive therapy (96.2%) related to HPV 6, 11, 16, or 18 lesions were observed among women negative for these types at baseline but positive for HPV 31, 33, 45, 52, or 58. Reductions in biopsy (93.5%) and definitive therapy (93.0%) related to HPV 31-, 33-, 45-, 52-, or 58-positive lesions were observed among females positive at baseline for HPV 6, 11, 16, or 18.

4. Discussion

The 9vHPV vaccine demonstrated robust (>94%) direct protection against cervical disease of any grade and, specifically, high-grade cervical disease, vulvar, and vaginal disease of any grade, condyloma, cervical biopsy, and cervical definitive therapy procedures compared with the historic placebo population among females negative for 14 HPV types. This confirms the efficacy estimate previously published for the five new vaccine types [7,8] and provides an estimate of 94.9–100% efficacy, with respect to HPV 6, 11, 16, and 18, compared with an unvaccinated population when the vaccine is delivered to young adolescent females.

The 9vHPV vaccine reduced the risk of therapeutic procedures (97.8%) following detection of cervical abnormalities associated with vaccine HPV types compared with unvaccinated women. This reduction is similar to the decrease in high-grade cervical disease observed with 9vHPV vaccination, suggesting that widespread 9vHPV vaccine dissemination may substantially reduce surgical procedures and healthcare utilization.

Among women positive for one or more HPV types at trial enrollment, efficacy against other targeted HPV types was maintained. Robust efficacy (95.8–100%) was observed against cervical lesions (any grade and high grade) and procedures caused by HPV 6, 11, 16, or 18 among women negative for those types at baseline, regardless of baseline HPV 31, 33, 45, 52, and 58 status. Similar results were observed among women negative for HPV 31, 33, 45, 52, and 58, regardless of HPV 6, 11, 16, or 18 status (91.1–95.1% efficacy against HPV 31-, 33-, 45-, 52-, and 58-related endpoints). These data support the potential

Table 4
Effect of 9vHPV vaccine on the reduction in incidence of cervical biopsy and definitive therapy procedures (subjects PCR-negative to 14 HPV types at baseline).

Endpoint Causal HPV type	**9vHPV vaccine (N = 4365)**		**Historic placebo (N = 5887)**		
	Observed Cases	Incidence per 10,000 person-years cases (95% CI)	Observed cases	Incidence per 10,000 person-years cases (95% CI)	Reduction in incidence % (95% CI)
Subjects contributing to the analysis	4229		5759		
Biopsy					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	21	13.1 (8.1–20.0)	540	269.2 (246.9–292.8)	95.1 (92.6–97.0)
HPV 6	4	2.5 (0.7–6.4)	63	30.7 (23.6–39.3)	91.9 (78.7–97.3)
HPV 11	0	0.0 (0.0–2.3)	17	8.3 (4.8–13.2)	100 (71.1–100)
HPV 16	4	2.5 (0.7–6.4)	204	100.1 (86.8–114.8)	97.5 (93.6–99.2)
HPV 18	4	2.5 (0.7–6.4)	79	38.5 (30.5–48.0)	93.5 (83.5–97.8)
HPV 31	7	4.4 (1.8–9.0)	103	50.3 (41.0–61.0)	91.3 (82.3–96.0)
HPV 33	0	0.0 (0.0–2.3)	49	23.9 (17.7–31.6)	100 (91.1–100)
HPV 45	2	1.2 (0.2–4.5)	30	14.6 (9.9–20.8)	91.5 (68.9–98.6)
HPV 52	3	1.9 (0.4–5.5)	117	57.2 (47.3–68.5)	96.7 (90.7–99.1)
HPV 58	0	0.0 (0.0–2.3)	77	37.5 (29.6–46.9)	100 (93.9–100)
Definitive therapy					
Any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	3	1.9 (0.4–5.5)	170	83.2 (71.1–96.6)	97.8 (93.4–99.4)
HPV 6	0	0.0 (0.0–2.3)	11	5.3 (2.7–9.6)	100 (57.5–100)
HPV 11	0	0.0 (0.0–2.3)	2	1.0 (0.1–3.5)	100 (−344.0–100)
HPV 16	0	0.0 (0.0–2.3)	91	44.4 (35.8–54.5)	100 (94.9–100)
HPV 18	0	0.0 (0.0–2.3)	25	12.2 (7.9–18.0)	100 (82.5–100)
HPV 31	2	1.2 (0.2–4.5)	39	19.0 (13.5–26.0)	93.4 (75.4–98.9)
HPV 33	1	0.6 (0.0–3.5)	15	7.3 (4.1–12.0)	91.5 (45.5–99.6)
HPV 45	0	0.0 (0.0–2.3)	7	3.4 (1.4–7.0)	100 (22.6–100)
HPV 52	0	0.0 (0.0–2.3)	37	18.0 (12.7–24.8)	100 (88.4–100)
HPV 58	0	0.0 (0.0–2.3)	27	13.1 (8.7–19.1)	100 (84.0–100)

CI, confidence interval; HPV, human papillomavirus; N, number of subjects in the analysis population; PCR, polymerase chain reaction; 9vHPV, nine-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

for the 9vHPV vaccine to prevent disease among sexually active, HPV-infected women.

The qHPV vaccine [10,11,19] and 9vHPV vaccine [7] are preventative, with no demonstrated efficacy against disease caused by an HPV type present at the time of vaccination. Most prevalent HPV infections in women aged 16–26 years (Supplementary Table S3) or 24–45 years [20] contain only one or two high-risk HPV types. Thus, HPV-infected, sexually active women remain susceptible to new vaccine-preventable HPV infections, as shown here and in previous analyses from qHPV vaccine trials [21]. Moreover, long-term follow-up studies of vaccinated cohorts demonstrate efficacy against disease occurrence following treatment of dysplastic lesions, presumably through protection against

Table 5
Effect of 9vHPV vaccine on the reduction in incidence of cervical, vulvar, and vaginal disease; cervical biopsy; and definitive therapy procedures stratified by baseline HPV status (mITT population).

Endpoint	Day 1 PCR-positive to ≥1 of the indicated HPV types		Percent risk reduction[a] (95% CI) [incidence rate (95% CI)[b] 9vHPV (N = 6997): historic placebo (N = 8748)]	
	HPV 6, 11, 16, or 18	HPV 31, 33, 45, 52, or 58	Related to HPV 6, 11, 16, or 18	Related to HPV 31, 33, 45, 52, or 58
Cervical disease, any grade	No	No	99.0 (96.4–99.8) [1.1 (0.1–3.9): 106.4 (93.3–120.9)]	96.9 (93.4–98.7) [3.2 (1.2–7.0): 104.3 (91.3–118.6)]
		Yes	97.4 (85.6–99.9) [3.9 (0.1–22.0): 154.4 (110.8–209.5)]	18.9 (−4.8–37.7) [420.9 (342.8–511.4): 519.1 (434.3–615.6)]
	Yes	No	−2.2 (−32.7–20.7) [511.9 (423.0–614.0): 501.0 (416.7–597.3)]	95.1 (81.9–99.1) [8.3 (1.0–30.0): 168.3 (121.8–226.7)]
		Yes	24.5 (−0.6–43.4) [663.4 (534.8–813.6): 879.1 (721.1–1061.3)]	13.3 (−15.0–35.4) [682.3 (551.4–835.0): 787.0 (638.9–959.1)]
High-grade cervical disease	No	No	100 (96.1–100) [0.0 (0.0–2.0): 49.4 (40.6–59.6)]	95.3 (88.4–98.4) [2.1 (0.6–5.5): 45.8 (37.4–55.6)]
		Yes	95.8 (76.9–99.8) [3.9 (0.1–22.0): 93.7 (60.6–138.3)]	6.8 (−32.6–34.6) [254.2 (195.3–325.2): 272.7 (213.4–343.4)]
	Yes	No	−2.3 (−40.9–25.8) [333.6 (264.1–415.8): 326.2 (259.8–404.3)]	91.1 (67.5–98.5) [8.3 (1.0–30.0): 93.4 (59.9–139.0)]
		Yes	12.7 (−24.3–38.7) [455.2 (352.0–579.1): 521.4 (404.9–661.0)]	−14.4 (−67.3–21.4) [462.9 (358.7–587.9): 404.5 (303.0–529.1)]
Vulvar and vaginal disease, any grade	No	No	94.9 (90.6–97.4) [5.3 (2.5–9.8): 103.1 (90.2–117.3)]	98.2 (90.5–99.9) [0.5 (0.0–3.0): 29.4 (22.7–37.4)]
		Yes	92.4 (76.4–98.0) [11.1 (2.3–32.4): 146.7 (105.3–199.0)]	51.1 (−27.5–83.1) [26.1 (10.5–53.7): 53.3 (29.8–87.8)]
	Yes	No	49.0 (18.6–69.3) [102.6 (67.0–150.3): 201.3 (151.2–262.6)]	76.3 (−6.4–96.3) [7.7 (0.9–27.7): 32.4 (14.8–61.4)]
		Yes	43.1 (2.8–67.8) [140.6 (89.2–211.0): 247.4 (173.3–342.5)]	9.7 (−156.7–68.2) [53.4 (24.4–101.5): 59.2 (27.1–112.4)]
Vulvar and vaginal condyloma	No	No	95.0 (90.5–97.9) [4.2 (1.8–8.4): 85.7 (74.0–98.8)]	100 (91.0–100) [0.0 (0.0–2.0): 20.0 (14.6–26.8)]
		Yes	93.5 (75.9–98.9) [7.4 (0.9–26.7): 113.9 (77.9–160.7)]	82.5 (−30.4–99.2) [3.7 (0.1–20.6): 21.1 (7.8–46.0)]
	Yes	No	61.4 (34.9–78.2) [70.1 (41.6–110.9): 181.7 (134.4–240.2)]	82.3 (−32.4–99.2) [3.8 (0.1–21.3): 21.5 (7.9–46.9)]
		Yes	51.5 (11.6–74.8) [102.4 (59.7–163.9): 211.3 (143.5–299.9)]	−5.3 (−212.8–68.2) [41.3 (16.6–85.2): 39.3 (14.4–85.4)]
High-grade vulvar and vaginal disease	No	No	100 (86.7–100) [0.0 (0.0–2.0): 13.3 (9.0–19.0)]	100 (36.0–100) [0.0 (0.0–2.0): 3.6 (1.5–7.0)]
		Yes	79.0 (−56.3–99.1) [3.7 (0.1–20.6): 17.6 (5.7–41.0)]	65.0 (−217.8–98.6) [3.7 (0.1–20.6): 10.5 (2.2–30.8)]
	Yes	No	−544.6 (−∞–13.6) [23.1 (8.5–50.3): 3.6 (0.1–20.0)]	– [3.8 (0.1–21.3): 0.0 (0.0–13.2)]
		Yes	40.0 (−147.0–84.1) [23.5 (6.4–60.1): 39.1 (14.4–85.2)]	9.9 (−398.1–83.7) [17.6 (3.6–51.4): 19.5 (4.0–57.1)]
Cervical biopsy	No	No	95.8 (92.9–97.8) [6.9 (3.7–11.8): 164.5 (148.2–182.0)]	94.7 (91.6–97.0) [9.1 (5.3–14.5): 172.4 (155.8–190.3)]
		Yes	94.5 (84.0–98.6) [11.1 (2.3–32.4): 203.5 (154.5–263.1)]	−5.5 (−31.1–14.7) [738.8 (630.4–860.5): 700.1 (601.6–810.2)]
	Yes	No	−18.1 (−46.6–4.9) [817.5 (700.6–948.5): 692.5 (592.9–804.1)]	93.5 (83.1–97.8) [15.3 (4.2–39.2): 236.3 (182.8–300.6)]
		Yes	0.4 (−27.1–21.7) [1051.1 (881.3–1244.1): 1054.9 (883.9–1249.4)]	4.4 (−21.6–24.8) [1083.2 (910.7–1279.0): 1132.9 (954.8–1334.5)]
Cervical definitive therapy	No	No	100 (96.8–100) [0.0 (0.0–2.0): 60.4 (50.8–71.4)]	93.9 (86.4–97.4) [3.2 (1.2–7.0): 52.1 (43.2–62.3)]
		Yes	96.2 (78.7–99.8) [3.7 (0.1–20.6): 96.8 (64.3–139.9)]	28.8 (−2.2–50.7) [185.1 (136.5–245.4): 259.8 (203.6–326.7)]
	Yes	No	7.2 (−28.4–33.6) [279.3 (217.3–353.4): 301.0 (239.4–373.6)]	93.0 (74.3–98.8) [7.6 (0.9–27.6): 109.3 (74.3–155.1)]
		Yes	44.4 (18.1–62.7) [276.4 (200.9–371.1): 497.0 (388.9–625.9)]	34.2 (4.0–55.1) [316.3 (234.8–417.0): 480.6 (374.6–607.2)]

CI, confidence interval; HPV, human papillomavirus; mITT, modified intention-to-treat; N, number of subjects in the analysis population; PCR, polymerase chain reaction; 9vHPV, nine-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

[a] The percentage risk reduction in the 9vHPV vaccine group relative to historic placebo was calculated as 100% × (1 − incidence rate in 9vHPV vaccine group/incidence rate in historic placebo group).

[b] Estimated number of cases per 10,000 person-years of follow-up.

subsequent infection with a vaccine-related HPV type [22–25]. True long-term protection against disease in sexually active women (including women >26 years of age [20]) may be greater than originally estimated from trials, where cases were censored after the first disease occurrence. Effectiveness studies conducted among populations where vaccine uptake is high (e.g. >80%) are needed to assess the full population impact of the vaccine.

The 9vHPV vaccine protects against disease related to the HPV types most commonly associated with high-grade intraepithelial neoplasia and cancer. In contrast, no efficacy was observed against non-vaccine HPV types 35, 39, 51, 56, and 59 [7]. Although these HPV types can cause high-grade cervical disease, they are not commonly found in cervical cancer [1,4,26,27]. However, as they cause ~10% of cervical cancers worldwide, which may develop later in life than HPV 16- and 18-related cancers [1], screening algorithms to prevent these cancers are needed.

Recent publications have raised the prospect of changing screening procedures and guidelines in HPV-vaccinated populations [28]. Our results indicate the 9vHPV vaccine can reduce rates of cervical abnormalities. As shown in the ATHENA trial [26] and prospective studies [29], the absolute risk of developing CIN 3 is highest among women positive for HPV 16, 18, 31, 33, 45, and 52-types against which the 9vHPV vaccine offers direct protection. Among populations vaccinated with 9vHPV vaccine, the expected reduction in circulating HPV types that cause the majority of anogenital disease and associated procedures should bolster the argument to reconsider current screening. The 9vHPV vaccine efficacy estimates presented here may be useful in modeling the age at screening initiation and the screening interval, informing development of simplified cervical cancer screening policies.

This study included a diverse population across world regions and demographic characteristics. The trials utilized common protocols, eligibility criteria, case definition, pathology panel adjudication, PCR assays, and colposcopy standardization, minimizing variability in exposure and endpoint assessment. All participants were intensively screened throughout several years, with rigorous assessment of disease endpoints and procedures. Although there is much strength to this analysis, there are limitations that should be noted. Ethical considerations precluded use of a placebo group in the 9vHPV program, hence the reliance on historic placebo populations. Given the similar eligibility criteria across the qHPV and 9vHPV vaccine trials, placebo and vaccinated cohorts were similar on key characteristics; thus, biases due to differences in sexual history and baseline HPV status were minimized. A comparison of Pap test abnormalities with historic placebo could not be rigorously performed, as HPV-type attribution, which is based on HPV typing of cervical swab samples, in the historic placebo groups for HPV 31, 33, 45, 52, and 58 in FUTURE I and II were performed only in a limited fashion. Prior reports indicate the qHPV vaccine reduces HPV 16- and 18-related Pap test abnormalities by >90% [16], and the 9vHPV vaccine reduces abnormalities due to HPV 31, 33, 45, 52, and 58 by >90% (versus qHPV vaccine) [8].

Overall, 9vHPV vaccination significantly reduces genital disease caused by the targeted HPV types compared with a population of unvaccinated women. If the 9vHPV vaccine is broadly disseminated, the burden of genital diseases is likely to dramatically decrease. While early vaccination in HPV-naïve persons is optimal, adult and sexually active persons may benefit from vaccination, supporting broad catch-up vaccination programs.

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Conflicts of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf *and declare the following.* A.R.G.'s institution has received grants from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ) on her behalf for her research; she is a member of the Scientific Advisory Board for MSD. E.A.J. has received grants and personal fees from MSD and Sanofi Pasteur MSD. S.M.G. has received institutional grants to perform HPV studies from MSD, GSK, CSL, and the Commonwealth Department of Health, has received scientific advisory board support from MSD and speaking fees from MSD for work performed in her private time. W.K.H. has received fees as a consultant for MSD. O-E.I. has received personal fees from MSD for conducting clinical HPV vaccine trials and for scientific advisory committee meetings, and has received lecture fees from Sanofi Pasteur MSD. S.K.K. has received scientific advisory board fees from MSD, Sanofi Pasteur MSD, and BD; unrestricted research grants have been obtained through her affiliating institute from MSD. A.F. has acted as pathologist consultant for MSD in HPV vaccine clinical trials. R.J.K. has acted as a consultant as part of the central pathology panel for MSD. B.M.R. is part of the central pathology panel for the HPV vaccine trials and has a consulting agreement with MSD, paid to Johns Hopkins University. M.H.S. is part of the central pathology panel and a consultant on this clinical trial, and the University of Virginia received support from MSD for this activity. O.M.B., E.M., M.R., C.S., and A.L. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

Authors' contributions

A.R.G. contributed to study conception, design, and planning, acquired data, and interpreted the results; she is guarantor of the study and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. E.A.J. contributed to study conception, design, and planning, and acquired and analyzed the data. S.M.G. contributed to study conception, design, and planning, acquired data (FUTURE 1 study), and interpreted the results. W.K.H. analyzed the data and interpreted the results. O-E.I. and S.K.K. acquired the data and interpreted the results. A.F. interpreted the results. R.J.K. and B.M.R. acquired data. M.H.S. contributed to study conception, design, and planning, acquired and analyzed data, and interpreted the results.

O.M.B. analyzed data, interpreted results, and provided statistical expertise. E.M. contributed to study conception, design, and planning, and analyzed the data. M.R. and A.L. contributed to study conception, design, and planning, and interpreted the results. C.S. contributed to study conception, design, and planning. A.R.G., E.A.J., O.M.B., and A.L. drafted the manuscript; all other authors critically reviewed or revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Data statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.253.

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