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Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up

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ABSTRACT

Background: A quadrivalent human papillomavirus vaccine (qHPV; HPV6/11/16/18) has demonstrated efficacy and effectiveness worldwide. We report qHPV vaccine efficacy for up to 6.5 years after first administration among Chinese women 20–45 years of age.

Methods: In this randomized, double-blind, placebo-controlled, multicenter, Phase 3 study (NCT00834106), women were randomized 1:1 to receive 3 doses of qHPV vaccine or placebo (Day 1, Month 2, Month 6). Endo-ecto-cervical and external genital swabs were collected for HPV testing and gynecologic examinations, and cervical cytology testing were performed at Day 1 and Months 7, 12, 18, 24, 30, 42, 54, 66, and 78. Any abnormality in cytology testing would trigger colposcopy examination and cervical biopsy, if necessary. Efficacy against genital disease, persistent infection, and the composite endpoint was assessed. Primary efficacy analyses were conducted in the per-protocol efficacy (PPE) population.

Results: Of 3006 participants randomized, 2759 (91.8%) and 2374 (79%) completed the Month 30 and Month 78 visits, respectively. At Month 78, efficacy among women aged 20–45 years was 100% (95% CI: 32.3, 100; 0 vs 7 cases) and 100% (95% CI: 70.9, 100; 0 vs 14 cases) against HPV16/18-related cervical intraepithelial neoplasia Grade 2 or 3, adenocarcinoma in situ, and cervical cancer (CIN 2+) and HPV6/11/16/18-related CIN 1+, respectively, in the PPE population. The efficacy against cervical 6-month and 12-month persistent infection was 91.6% (95% CI: 66.0, 99.0) and 97.5% (95% CI: 85.1, 99.9) at Month 30 and Month 78, respectively, in the PPE population. The vaccine also reduced the rate of cervical cytology abnormalities associated with HPV6/11/16/18, with an efficacy of 94.0% (95% CI: 81.5, 98.8). The vaccine was generally well tolerated (reported separately).

Conclusion: The qHPV vaccine is efficacious against endpoints of persistent infection and genital precancerous lesions in Chinese women aged 20–45 years.

Abbreviations: 6-M PI, 6-month persistent infection; 12-M PI, 12-month persistent infection; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells-cannot exclude HSIL; CI, confidence interval; CIN, cervical intraepithelial neoplasia; cLIA, competitive Luminex immunoassay; EEC, endo/ecto-cervical; EGL, external genital lesion; FAS, full analysis set; GW, genital warts; HNRT, naïve to relevant HPV type; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IPP, Independent Pathology Panel; LEEP, loop electrosurgical excision procedure; LVPP, labial/vulvar/perineal/perianal; mMU, milli-Merck unit; Pap, Papanicolaou; PCR, polymerase chain reaction; PI, persistent infection; PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

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1. Introduction

Human papillomavirus (HPV) is a primary cause of cervical and other cancers, as well as genital warts. Cervical cancer represents a significant public health burden in China; with >60,000 new cases and >29,000 deaths annually, it is the third leading cause of cancer deaths among Chinese women aged 15–44 years (per 2012 data) [1–3]. An additional >13,000 cases of other HPV-related cancers (anal, penile, vulvar/vaginal, head, and neck) occur in China annually [1].

Prophylactic bivalent, quadrivalent (qHPV) and nine-valent vaccines protect against oncogenic HPV types [4,5], including HPV16/18, which are responsible for approximately 70% of cervical cancers worldwide [6]. In China, HPV16/18 account for approximately 69% of cervical cancers and 44% of high-grade cervical lesions (high-grade squamous intraepithelial lesions [HSIL]/cervical intraepithelial neoplasia [CIN] 2/CIN 3/carcinoma in situ [CIS]) [3]. The qHPV and nine-valent HPV vaccines also protect against HPV6/11, which are responsible for >90% of the genital warts cases associated with HPV globally [7]. HPV vaccination programs have been implemented in >60 countries worldwide [8,9], and real-world data from the decade since vaccine introduction support effectiveness in preventing HPV infections and disease [8–10].

The incidence of HPV infection peaks in sexually active women <25 years of age; however, a high disease burden is observed in mid-adult women up to 45 years of age [11]. In rural China, along with the first peak of HPV prevalence in young women (aged 15–24 years), prevalence increased again among mid-adult women (aged 35–39 years) and remained stable thereafter [12]. The qHPV vaccine has demonstrated efficacy in young [13,14] and mid-adult women [15] (aged 15–26 and 24–45 years, respectively) in global clinical trials. Prior international studies did not include participants from mainland China; thus, efficacy of the qHPV vaccine needed to be demonstrated in Chinese women to be licensed in China.

We assessed qHPV vaccine efficacy and safety in Chinese women aged 20–45 years, fulfilling the Chinese regulatory requirement to demonstrate efficacy and safety among young and adult Chinese women in clinical trials. The lower age bound was based on the youngest legal marriage age in China (20 years). We report an analysis of efficacy at end of study, representing up to 6.5 years of follow-up. Safety endpoints are reported separately (manuscript in preparation). Chiefly based on these results, the qHPV vaccine was approved in China in May 2017 for vaccination of females 20–45 years of age.

2. Methods

2.1. Study design and participants

Study V501-041 (NCT00834106) was a randomized, double-blind, placebo-controlled, safety and efficacy study that included a base study (30 months) and an extension stage (up to 78 months).

Beginning January 3, 2009, women aged 20–45 years were enrolled at 6 sites in China. The end-of-study results from the extension are based on cumulative data through September 30, 2016. Eligible participants had 1–4 male or female lifetime sexual partners or no prior partners but planned to become sexually active within 3 months of study initiation. Pregnant women and those with a history of genital warts or significant cervical disease, active cervical disease, or prior HPV vaccine recipients were excluded. Participants who received ≥1 vaccination were eligible for the extension.

Participants were randomized separately at each site to qHPV vaccine or placebo (1:1) using a block randomization scheme provided by the sponsor with appropriate blocking factors to maintain balance among treatment groups. Participants were stratified by age at enrollment (20–26 years [planned n = 1800 participants] or 27–45 years [planned n = 1200]). All investigators and study site personnel, laboratory personnel, independent pathology panel, study participants, and sponsor personnel were blinded to the treatment allocation during the entire study.

The base study primary efficacy endpoint was HPV6/11/16/18-related 6-month persistent infection (PI), external genital lesions (EGLs), and cervical disease (abbreviated "6-month PI+") among women aged 20–45 years and the subgroup aged 20–26 years. EGL is defined as genital warts (GW), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), vulvar cancer, and vaginal cancer. Cervical disease (referred to as "CIN 1+") is defined as CIN Grade 1, 2, 3 (CIN 1, 2, 3), adenocarcinoma in situ (AIS), and cervical cancer. The primary extension study efficacy endpoint was HPV16/18-related CIN 2/3, AIS, and cervical cancer (referred to as "CIN 2+") among women aged 20–45 years. Safety was also a primary objective and will be reported separately.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent.

2.2. Vaccination and follow-up

The qHPV vaccine is manufactured by Merck & Co., Inc., Kenilworth, NJ, USA. Each 0.5-mL dose contains 20, 40, 40, and 20 μg HPV6, 11, 16, and 18 L1 VLPs, respectively, and 225 μg amorphous aluminum hydroxyphosphate sulfate. Each placebo dose contained adjuvant (225 μg) in normal saline. Vaccinations were administered as intramuscular injections on Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks). Pregnancy tests were administered prior to each vaccination. Participants who became pregnant after receiving 1 or 2 vaccine doses did not return for subsequent vaccinations until pregnancy resolution; they could complete the vaccination series ≥6 weeks after pregnancy resolution and normalization of β-hCG levels.

Complete physical gynecological examinations were performed, and labial/vulvar/perineal/perianal (LVPP) and endo-ecto-cervical (EEC) swabs for HPV DNA analysis (by polymerase chain reaction [PCR]) and cytology samples for Papanicolaou (Pap) testing (ThinPrep™, Cytyc, Boxborough, MA, USA) were collected at Day 1 and Months 7, 12, 18, 24, 30, 42, and every 12 months thereafter.

After the Month 30 visit, the study was extended twice (initially to Month 66, then a further extension with annual follow-up and without a planned terminal follow-up) to accrue sufficient numbers of cases of HPV16/18-related CIN 2+ to demonstrate qHPV vaccine efficacy. However, in analyses conducted in response to the Chinese regulatory agency request, the primary efficacy hypothesis for the extension study was successfully demonstrated when the 78-month follow-up was ongoing. Therefore, the efficacy follow-up was terminated at the Month 78 visit. The safety follow-up was continuous, and an additional close-out visit (phone) was conducted.

2.3. Laboratory assessments and case adjudication

Cytology tests were assessed by a central laboratory using the Bethesda System-2001 [16]. In cases of abnormal Pap test results, participants were referred to colposcopy based on a protocol-specified triage algorithm. In cases where abnormalities were detected in colposcopy or physical gynecological examinations, biopsy material was obtained. Participants may have been subject

to loop electrosurgical excision procedure (LEEP) or conization therapy per predefined criteria. Biopsy, LEEP, and conization samples were reviewed by the blinded Independent Pathology Panel (IPP) of up to 4 pathologists for endpoint adjudication.

The presence of vaccine HPV types and non-vaccine HPV types in LVPP and EEC swabs, biopsy tissue, and LEEP or conization specimens was detected using the INNO-LiPA HPV v2 Genotyping PCR assay (Innogenetics, Ghent, Belgium).

HPV6/11/16/18-related, 6- or 12-month PI was defined as either: (A) detection of the same HPV type on 2 or more consecutive LVPP or EEC or biopsy samples obtained at least 6 or 12 months (±1 month) apart; or (B) presence of genital disease (as determined by the IPP) and detection of HPV6, 11, 16, or 18 in an adjacent section from the same tissue block and detection of the same HPV type in a LVPP or EEC swab or biopsy sample obtained at the visit immediately before or after the biopsy showing genital disease, following the Month 7 visit. Cervical PI refers to infection at the cervix while non-cervical PI refers to infection at LVPP regions. Overall PI takes into account infection all these regions and includes cases with an infection at the cervix and another at LVPP regions.

Cases of GW, VIN, VaIN, CIN, AIS, and vulvar/vaginal/cervical cancers as adjudicated by the IPP were considered HPV6/11/16/18-related if the relevant type was detected in the same tissue block.

2.4. Statistical analyses

The primary efficacy analyses were conducted in the per-protocol efficacy (PPE) population who: (1) were seronegative on Day 1 and PCR-negative from Day 1 through Month 7 for the HPV type being analyzed; (2) received all 3 doses of the correct clinical material within 1 year; (3) had ≥1 follow-up after Month 7; and (4) had no protocol deviations that could affect efficacy evaluation. The primary base study efficacy hypothesis was tested using 2-sided, exact, confidence intervals (CIs) constructed for efficacy in (A) 20–45-year-old and (B) 20–26-year-old women. Sequential testing was performed to control overall Type I error at the 1-sided 2.5% level. The statistical criterion for success was defined by the lower bound of the CI excluding 0%. Similarly, the extension study primary efficacy hypothesis was tested using a 2-sided exact CI, at the 1-sided 2.5% level. Testing of the extension study hypothesis was contingent upon success of the base study primary efficacy hypothesis. Efficacy was defined as 100% x (1 – qHPV vaccine incidence rate/placebo incidence rate).

Supportive efficacy analyses were conducted without formal hypothesis testing in: (A) the naïve to relevant HPV-type (HNRT) population, who received ≥1 dose of correct clinical material and were seronegative and PCR-negative at Day 1 for the HPV type being analyzed; and (B) the full analysis set (FAS) of participants who received ≥1 dose of correct clinical material and had any follow-up data after the first vaccination.

The correlation between 12-month PI and CIN 2+ was analyzed in the HNRT placebo group. The positive (negative) likelihood ratios were calculated by dividing the percentage of participants with positive (negative) HPV testing result in all CIN 2+ cases by the percentage with positive (negative) HPV testing results in all non-CIN 2+ cases, as described [17].

3. Results

3.1. Participants

Baseline characteristics were generally similar between groups (Table 1 and Supplementary Table 1). More than 25% of participants were positive for HPV6, 11, 16, or 18 before enrollment by either serology or PCR (~7% by PCR alone) (Table 1).

Table 1
Baseline characteristics.

Characteristic	qHPV vaccine (N = 1503)	Placebo (N = 1503)
Age (years), mean (SD)	28.7 (6.4)	28.7 (6.4)
20–26 years, n (%)	923 (61.4)	917 (61.0)
27–45 years, n (%)	580 (38.6)	586 (39.0)
Age at first sexual intercourse (years), mean (SD)	21.6 (2.3)	21.5 (2.5)
Number of sexual partners, n (%)		
1	1240 (82.5)	1248 (83.0)
≥2	263 (17.5)	255 (17.0)
Abnormality on cervical cytology, n (%)	104 (7.4)[a]	93 (6.6)
Positive to HPV6, 11, 16, or 18; n/m (%)		
By serology[b]	367/1502 (24.4)	336/1503 (22.4)
HPV6	199/1502 (13.2)	190/1503 (12.6)
HPV11	77/1503 (5.1)	75/1503 (5.0)
HPV16	162/1503 (10.8)	126/1503 (8.4)
HPV18	46/1503 (3.1)	52/1503 (3.5)
By PCR[c]	107/1492 (7.2)	102/1476 (6.9)
HPV6	13/1503 (0.9)	10/1502 (0.7)
HPV11	10/1503 (0.7)	3/1502 (0.2)
HPV16	68/1503 (4.5)	66/1502 (4.4)
HPV18	21/1503 (1.4)	26/1502 (1.7)
By serology or PCR	405/1493 (27.1)	389/1481 (26.3)

N, number of participants randomized; m, number participants with non-missing data; n, number of participants in the respective category.
cLIA, competitive Luminex immunoassay; EEC, endo/ecto-cervical; HPV, human papillomavirus; LVPP, labial/vulvar/perineal/perianal; mMU, milli-Merck unit; PCR, polymerase chain reaction; qHPV, quadrivalent human papillomavirus; SD, standard deviation.
[a] N = 1502.
[b] Positive by serology is defined as having an anti-HPV cLIA titer ≥ the cutoff values of 20, 16, 20, or 24 mMU/mL, respectively, for HPV6, 11, 16, or 18.
[c] Positive by PCR is defined as having a positive PCR result at Day 1 on ≥1 of the following: LVPP swabs, EEC swabs, or (if obtained) external genital biopsy specimens, or cervical biopsy specimens.

Of 3006 participants randomized, 2936 received all 3 vaccinations, and 2759 and 2374 completed the Month 30 and 78 visits, respectively (Fig. 1). The mean (median) duration of efficacy follow-up was 6.07 (6.48) years after the first vaccination. Numbers in each analysis population by vaccination group are presented in Supplementary Table 2.

3.2. Efficacy against cervical disease and external genital lesions

At the end of Month 78, efficacy in the PPE population against HPV16/18-related CIN 2+ was 100% (95% CI: 32.3, 100; 0 vs 7 cases) among women aged 20–45 years (Table 2). The primary efficacy objective in the extension study was met. Efficacy was also 100% (95% CI: 65.2, 100; 0 vs 12 cases) against HPV16/18-related CIN 1+. When all 4 vaccine HPV types (6/11/16/18) were taken into account, efficacy against any grade (CIN 1+) and high-grade (CIN 2+) cervical disease was also 100% (95% CI: 70.9, 100; 0 vs 14 cases) and 100% (95% CI: 32.2, 100; 0 vs 7 cases), respectively (Table 2).

In supportive analyses in the HNRT population, the qHPV vaccine demonstrated 100% (95% CI: 64.9, 100; 0 vs 12 cases) efficacy against both HPV16/18-related CIN 2+ and HPV6/11/16/18-related CIN 2+, and high efficacy (≥90.8%) against CIN 1+ (Table 2 and Supplementary Table 3). As expected in a population that included baseline HPV-positive women, efficacy was lower in the FAS (Table 2).

There were no cases of HPV6/11/16/18-related EGL in the PPE population. One case of HPV6-related genital warts was observed at Month 18 in the qHPV vaccine group in the HNRT population. The participant was 26 years old at enrollment, negative for all 4 HPV types at Day 1, but positive for HPV 6 at Month 7.

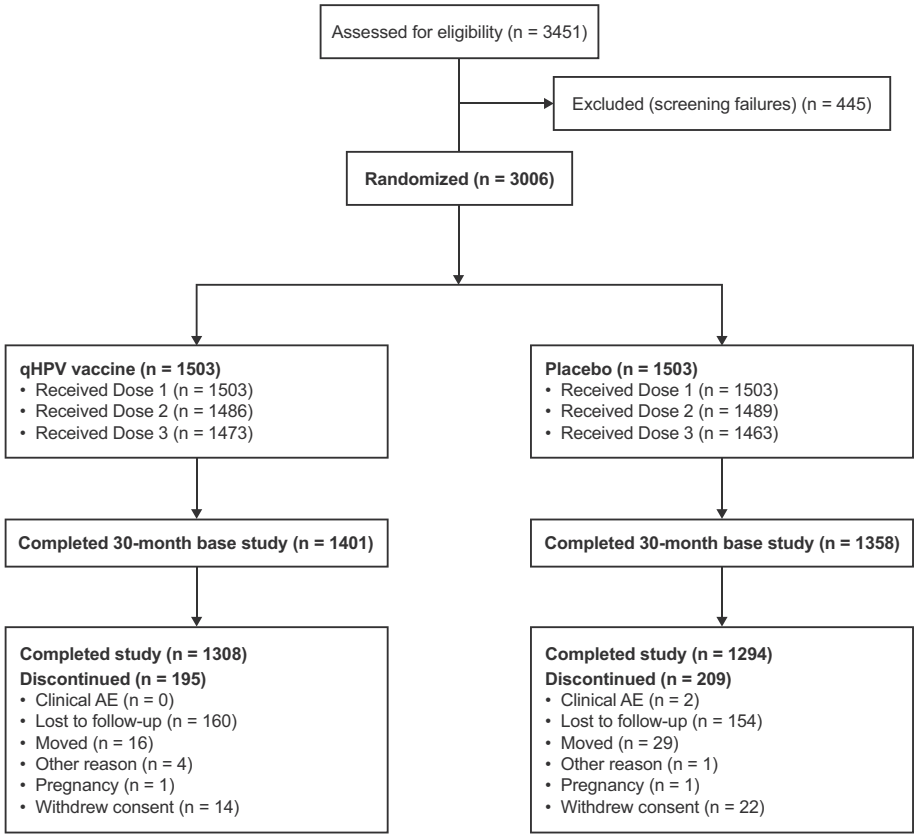

Fig. 1. Participant disposition. AE, adverse event; qHPV, quadrivalent human papillomavirus.

Table 2
Efficacy of qHPV vaccine against HPV6/11/16/18-related cervical disease.

Endpoint	qHPV vaccine			Placebo			Efficacy	
	N	n	Rate[a]	N	n	Rate[a]	%	95% CI
PPE population								
HPV16/18-associated								
CIN 2+	1265	0	0.0	1237	7	0.1	100	32.3, 100
CIN 1+	1265	0	0.0	1237	12	0.2	100	65.2, 100
HPV6/11/16/18-associated								
CIN 2+	1272	0	0.0	1243	7	0.1	100	32.2, 100
CIN 1+	1272	0	0.0	1243	14	0.2	100	70.9, 100
HNRT population								
HPV16/18-associated								
CIN 2+	1454	0	0.0	1432	12	0.1	100	64.9, 100
CIN 1+	1454	1	0.0	1432	18	0.2	94.6	65.9, 99.9
HPV6/11/16/18-associated								
CIN 2+	1461	0	0.0	1440	12	0.1	100	64.9, 100
CIN 1+	1461	2	0.0	1440	21	0.2	90.8	62.3, 99.0
FAS								
HPV16/18-associated								
CIN 2+	1481	22	0.3	1478	31	0.4	29.9	−25.1, 61.3
CIN 1+	1481	28	0.3	1478	41	0.5	32.7	−11.5, 59.9
HPV6/11/16/18-associated								
CIN 2+	1481	22	0.3	1478	31	0.4	29.9	−25.1, 61.3
CIN 1+	1481	31	0.4	1478	44	0.5	30.5	−12.5, 57.6

N, number of participants in the given population with ≥1 follow-up visit for the given endpoint after Month 7; n, number of cases.
AIS, adenocarcinoma in situ; CI, confidence interval; CIN, cervical intraepithelial neoplasia; FAS, full analysis set; HNRT, naïve to the relevant HPV type; PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus.
CIN 2+ includes CIN 2, CIN 3, AIS, and cervical cancer; CIN 1+ includes CIN 1, CIN 2, CIN 3, AIS, and cervical cancer.
[a] The rate is the number of participants with the endpoint per 100 person-years at risk.

3.3. Efficacy against PI

At the end of Month 30, efficacy in the PPE population against HPV6/11/16/18-related cervical, non-cervical and overall 6-month PI was 91.6% (95% CI: 66.0, 99.0), 87.9% (95% CI: 60.3, 97.7), and 75.9% (95% CI: 43.5, 91.1), respectively, among women aged 20–45 years (Table 3). Efficacy against cervical (100%), non-cervical (91.2%), and overall (93.1%) 12-month PI at the end

of Month 30 was slightly higher than against the corresponding 6-month endpoints (data not shown). At the end of Month 78, efficacy against HPV6/11/16/18-related cervical, non-cervical, and overall 12-month PI was 97.5% (95% CI: 85.1, 99.9), 91.7% (95% CI: 77.2, 97.8), and 91.0% (95% CI: 77.7, 97.2), respectively, among women aged 20–45 years in the PPE population (Table 3). Efficacy in the HNRT and FAS populations can be found in Table 3.

At the end of Month 30, efficacy in the PPE population against HPV6/11/16/18-related, 6-month PI+ was 76.0% (95% CI: 43.7, 91.1; 7 vs 28 cases) and 82.3% (95% CI: 38.3, 96.7; 3 vs 16 cases) among women aged 20–45 and 20–26 years, respectively. The 2 co-primary efficacy objectives of the base study were met.

3.4. Impact on Pap test abnormalities

The qHPV vaccine significantly reduced HPV6/11/16/18-related Pap test abnormalities in the PPE population at Month 78 with an efficacy of 94.0% (95% CI: 81.5, 98.8; 3 vs 48 cases) (Table 4). There were no cases of HSIL or atypical squamous cells where HSIL could not be ruled out (ASC-H) in the qHPV vaccine group, compared with 3 HSIL and 3 ASC-H cases in the placebo group (Table 4).

3.5. Correlation between PI and cervical disease

The analysis of correlations between HPV16-, HPV18-, and HPV16/18-related 12-month PI and CIN 2+ in the HNRT population and placebo group showed high (≥14.8) positive likelihood ratios (Table 5).

4. Discussion

The qHPV vaccine demonstrated robust and sustained efficacy against HPV6/11/16/18-related PI and cervical disease for up to 6.5 years after vaccination among women who were not infected with the relevant HPV types before receiving the full vaccination regimen (PPE population). The vaccine demonstrated 100% efficacy against CIN 1+ or CIN 2+ associated with any vaccine type in the PPE population. No cases of high-grade cervical disease (CIN 2+) related to any vaccine type were observed among women who were uninfected with the relevant type before receiving the first vaccination (HNRT population). The vaccine also demonstrated robust efficacy (94%) in reducing cases of HPV6/11/16/18-related abnormal cervical cytology in the PPE population.

Table 3
Efficacy of qHPV vaccine against HPV6/11/16/18-related PI.

Endpoint, HPV6/11/16/18-associated	qHPV vaccine			Placebo			Efficacy	
	N	n	Rate[a]	N	n	Rate[a]	%	95% CI
PPE population								
6-M PI (up to Month 30)	1275	7	0.3	1245	28	1.2	75.9	43.5, 91.1
6-M cervical PI	1275	2	0.1	1246	23	1.0	91.6	66.0, 99.9
6-M non-cervical PI	1276	3	0.1	1245	24	1.0	87.9	60.3, 97.7
12-M PI (up to Month 78)	1276	5	0.1	1245	53	0.8	91.0	77.7, 97.2
12-M cervical PI	1275	1	0.0	1246	38	0.6	97.5	85.1, 99.0
12-M non-cervical PI	1277	4	0.1	1245	46	0.7	91.7	77.2, 97.8
HNRT population								
6-M PI (up to Month 30)	1462	17	0.5	1434	54	1.6	69.8	47.2, 83.6
6-M cervical PI	1462	9	0.3	1435	43	1.2	79.9	58.2, 91.4
6-M non-cervical PI	1463	12	0.3	1434	47	1.4	75.5	53.1, 88.2
12-M PI (up to Month 78)	1462	16	0.2	1439	67	0.8	77.2	60.2, 87.6
12-M cervical PI	1462	10	0.1	1440	50	0.6	80.8	61.7, 91.3
12-M non-cervical PI	1463	14	0.2	1439	59	0.7	77.3	58.8, 88.3
FAS								
6-M PI (up to Month 30)	1482	81	2.3	1472	106	3.1	25.0	−1.1, 44.6
6-M cervical PI	1482	58	1.6	1472	83	2.4	31.5	3.1, 51.9
6-M non-cervical PI	1482	62	1.7	1472	87	2.5	30.1	2.0, 50.3
12-M PI (up to Month 78)	1482	55	0.6	1477	106	1.3	49.6	29.5, 64.3
12-M cervical PI	1482	37	0.4	1477	71	0.8	49.2	23.3, 66.8
12-M non-cervical PI	1482	49	0.6	1477	93	1.1	48.6	26.7, 64.4

N, number of participants in the given population with ≥1 follow-up visit for the given endpoint after Month 7; n, number of cases.
6-M PI, 6-month persistent infection; 12-M PI, 12-month persistent infection; CI, confidence interval; FAS, full analysis set; HNRT, naïve to the relevant HPV type; PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus.
[a] The rate is the number of participants with the endpoint per 100 person-years at risk.

Table 4
Impact of qHPV vaccine on the incidence of Pap test abnormalities associated with HPV6, 11, 16, or 18 in the PPE population.

Endpoint	qHPV vaccine (N = 1271)		Placebo (N = 1243)		Efficacy	
	n	Rate[a]	n	Rate[a]	%	95% CI
Pap test abnormalities	3	0.0	48	0.7	94.0	81.5, 98.8
ASC-US and high risk-HPV positive	2	0.0	23	0.3	91.6	66.0, 99.0
LSIL	1	0.0	29	0.4	96.7	80.2, 99.9
ASC-H	0	0.0	3	0.0	100	−133.8, 100
HSIL	0	0.0	3	0.0	100	−130.3, 100

N, number of participants in the given population with ≥1 follow-up visit for the given endpoint after Month 7; n, number of cases.
ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells-undetermined significance; CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou; PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus.
[a] The rate is the number of participants with the endpoint per 100 person-years at risk.

Table 5
Correlation between HPV16/18-related, 12-month, PI and HPV16/18-related CIN 2+ (HNRT population; placebo group).

12-M PI		CIN 2+ case[a]		Likelihood ratio			
				Positive		Negative	
		Yes (n)	No (n)	LR+	95% CI	LR−	95% CI
HPV16/18-associated (N = 1431)	Yes (n)	6	48	14.8	(5.3, 24.9)	0.52	(0.24, 0.86)
	No (n)	6	1371				
HPV16-associated (N = 1287)	Yes (n)	5	35	16.6	(5.1, 30.2)	0.56	(0.27, 0.88)
	No (n)	6	1241				
HPV18-associated (N = 1379)	Yes (n)	1	16	86.1	(NA, 137.7)	0.00	(NA, NA)
	No (n)	0	1362				

N, number of participants in the given population with ≥1 follow-up visit for the given endpoint after Month 7; n, number of participants in indicated category based on presence of HPV16/18-associated 12-M PI and CIN 2+ . CIN 2+ includes CIN 2, CIN 3, AIS, and cervical cancer.
12-M PI, 12-month persistent infection; AIS, adenocarcinoma in situ; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HNRT, naïve to the relevant HPV type; LR+, likelihood ratio positive; LR−, likelihood ratio negative.
[a] CIN 2 + case following 12-M PI.

This is the first time that the qHPV vaccine has been shown to demonstrate efficacy in Chinese women. These results are generally consistent with global data [13–15,18,19]. In the global trials, the vaccine similarly demonstrated 100% efficacy against HPV6/11/16/18-related CIN 2+ in the FUTURE I study [13], 98% efficacy against HPV16/18-related CIN 2+ in the FUTURE II study [14], and 98% efficacy against HPV6/11/16/18-related CIN 2+ in a pooled analysis [19]. The qHPV vaccine also demonstrated 100% efficacy against HPV6/11/16/18-related CIN 1+ in the FUTURE I study [13] and 96% against HPV6/11/16/18-related CIN 1 in a pooled analysis [18]. As in the global studies, efficacy was lower when women infected with HPV at baseline were included in the analysis, as the qHPV vaccine is prophylactic and does not impact infections or lesions that are already present.

No cases of genital warts were observed. Compared with the incidence of genital warts observed in the global qHPV vaccine trials (193 HPV6/11/16/18-related cases in 7902 placebo recipients in the PPE population during 3-year follow-up [20]), the incidence of HPV6/11/16/18-related genital warts observed here was low (0 cases among 1249 placebo recipients in the PPE population during 6.5-year follow-up). Therefore, the sample size was underpowered to evaluate efficacy against genital warts. However, the qHPV vaccine was highly efficacious (efficacy >89%) against HPV6/11-related PI. In China, HPV6/11 have been detected in up to 83% of genital warts cases [21], and global data indicate these types account for >90% of cases of genital warts [7]. Therefore, the high efficacy against HPV6/11-related PI supports the potential of the vaccine to prevent genital warts associated with these types.

The efficacy against overall (cervical and external genitalia) 6-month PI was lower than that observed in the FUTURE III study [15]. Because overall PI includes cases with one infection at cervix and another infection at external genital regions, incidental HPV contamination at external regions (for example, due to sexual activity) may occur before the visit, therefore contributing to a "mixed" case of 6-month overall PI, which appears to lower the efficacy. In fact, there were 4 such cases (qHPV: placebo = 3:1) out of 35 cases. By comparison, there were only 2 such cases (qHPV: placebo = 1:1) out of 96 cases in the FUTURE III study. When considering cervical or external genital regions separately, the qHPV vaccine showed consistently high efficacy against PI, indicating less impact of incidental HPV contamination on the region-specific efficacy.

HPV vaccination programs are expected to be particularly impactful and cost-effective in regions where secondary cervical cancer prevention programs (screening) have not been widely implemented [22–26].

In China, estimates based on GLOBOCAN 2012 data indicate that approximately 69% of cervical cancer cases are attributable to HPV16/18 [1,3]. Considering 100% efficacy against HPV16/18-related CIN 2+ and the estimated 61,691 annual cervical cancer cases and 29,526 deaths [3], the vaccine has potential to prevent 42,567 cases and 20,373 deaths in China annually. However, reports suggest cervical cancer incidence may be underestimated in China [12]. Chen et al estimated there were 98,900 cervical cancer cases and 30,500 deaths in China in 2015 [27]. Based on these estimates and the 84.5% prevalence of HPV16/18 in cervical cancer reported in a Chinese hospital-based study [28], the qHPV vaccine may have potential to prevent up to 83,571 cervical cancer cases and 25,773 deaths in China annually. The significant impact on Pap test abnormalities provides further public health benefits. By reducing abnormal cytological results, qHPV vaccination may reduce the need for colposcopy examination, biopsy, and definitive therapy, reducing health expenditures.

Despite only 12 HPV16/18-related CIN 2+ cases in the HNRT population, a high and statistically significant positive likelihood ratio was computed when analyzing the correlation between HPV16/18-related 12-month PI and HPV16/18-related CIN 2+, indicating that 12-month PI is a potential surrogate endpoint for CIN 2+ in HPV vaccine evaluation. This result is consistent with previous correlation analyses between PI and CIN 2+, and is harmonious with WHO recommendations [29,30].

One study limitation is that efficacy against 6-month PI could not be assessed up to Month 78. Because the extension stage aimed to accrue cases of CIN 2+, genital specimens were obtained annually. In addition, cross-protection against non-vaccine HPV types could not be evaluated because the same HPV type had to be detected twice (to confirm positives) in a given specimen to diagnose HPV6/11/16/18-related lesions or PI, while non-vaccine HPV types were assayed only once. While partial cross-protection has been observed in some clinical studies, the extent, duration, and public health implication are unknown [5,8,31].

5. Conclusion

The qHPV vaccine demonstrated sustained efficacy against anogenital infection and disease, including high-grade cervical disease, over up to 6.5 years of follow-up among Chinese women 20–45 years of age.

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Shaoming Wang has received grants from MSD R&D (China) during the conduct of this study.

Xueyan Liao had been employed by Sanofi Pasteur China, and is a full-time employee of MSD R&D (China).

Qiong Shou is a full-time employee of MSD R&D (China).

Yuanzheng Qiu had been employed by Sanofi Pasteur China, and is a full-time employee of MSD R&D (China).

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Alfred J. Saah is a full-time employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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Author contributions

All authors attest they meet the ICMJE criteria for authorship; specific contributions are included below. All authors reviewed the version of the manuscript to be submitted and agreed with its content and submission.

Lihui Wei: Conception, design or planning of the study, acquisition of the data, analysis of the data, and interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Xing Xie: Acquisition of the data; critically reviewing or revising the manuscript for important intellectual content.

Jihong Liu: Acquisition of the data, analysis of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Yun Zhao: Acquisition of the data, analysis of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Wen Chen: Acquisition of the data; critically reviewing or revising the manuscript for important intellectual content.

Chao Zhao: Acquisition of the data, analysis of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Shaoming Wang: Acquisition of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Xueyan Liao: Acquisition of the data, analysis of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Qiong Shou: Analysis of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Yuanzheng Qiu: Analysis of the data, interpretation of the results; drafting the manuscript.

Youlin Qiao: Conception, design, or planning of the study; acquisition of the data, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Alfred J. Saah: Conception, design, or planning of the study, interpretation of the results; critically reviewing or revising the manuscript for important intellectual content.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.08.009.

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