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Safety of a quadrivalent human papillomavirus vaccine in a Phase 3, randomized, double-blind, placebo-controlled clinical trial among Chinese women during 90 months of follow-up

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ABSTRACT

Background: A quadrivalent human papillomavirus (qHPV) vaccine (HPV6/11/16/18) has demonstrated efficacy and acceptable safety in international studies. However, these studies did not include participants from mainland China, which has a substantial burden of HPV-related disease. This is the first safety report with a follow-up period of up to 90 months from a randomized, double-blind, placebo-controlled trial of qHPV vaccine in Chinese women 20–45 years of age.

Methods: Participants were randomized 1:1 to receive three doses of qHPV vaccine or placebo (Day 1, Month 2, and Month 6). Efficacy outcomes are reported elsewhere. Injection-site and systemic adverse events (AEs) were collected using vaccination report cards (VRCs) for 15 days following each vaccination. Serious AEs (SAEs), pregnancy outcomes, new medical conditions, and fetal/infant SAEs were collected during the entire study.

Results: Of 3006 participants randomized, AEs were reported by 926 (61.8%) qHPV vaccine recipients and 856 (57.1%) placebo recipients over the entire study. Four participants (two in each group) discontinued the study vaccination due to AEs that were considered vaccination-related. Within 15 days following any vaccination, injection-site AEs prompted for on the VRC were more frequent among qHPV vaccine recipients (37.6% vs 27.8%), and systemic AEs prompted for on the VRC were similar in frequency between qHPV vaccine and placebo groups (46.8% vs 45.1%). Thirty-eight and 43 participants reported SAEs in qHPV vaccine and placebo groups, respectively. No SAE was considered qHPV vaccine-related. Pregnancy outcomes, fetal/infant SAEs, and new medical conditions were generally similar in frequency between the qHPV vaccine and placebo groups, and within normal ranges.

Conclusion: The qHPV vaccine was well tolerated and demonstrated a favorable safety profile in Chinese women 20–45 years of age, consistent with findings from global trials and safety surveillance studies.

Trial registration: clinicaltrials.gov; NCT00834106.

1. Introduction

Human papillomavirus (HPV)-related disease presents a substantial public health concern in China. More than 60,000 new cervical cancer cases (29,000 deaths) and 13,000 cases of other cancers (including anal, penile, vulvar, and vaginal cancer) are estimated to be attributable to HPV in China annually, based on 2012 data [1,2].

Vaccination against high-risk HPV types provides an opportunity to substantially diminish the burden of HPV-related disease.

Abbreviations: AE, adverse event; CI, confidence interval; HPV, human papillomavirus; qHPV, quadrivalent human papillomavirus; SAE, serious adverse event; VRC, vaccination report card.

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A quadrivalent HPV (qHPV; types 6/11/16/18) vaccine has potential to prevent up to ~70% of cervical cancers attributable to HPV16/18 globally [3]; similarly, in China, HPV16/18 are associated with 69% of cervical cancers and 44% of high-grade cervical lesions [4]. The vaccine also has potential to prevent the >90% of cases of genital warts related to HPV 6/11 [5].

The efficacy and safety of the qHPV vaccine have been demonstrated in global, placebo-controlled, randomized clinical trials [6]. Across the clinical development program, rates of systemic adverse events (AEs), serious AEs (SAEs), and new medical conditions were generally similar between the qHPV vaccine and placebo groups [7]. Moreover, real-world data collected over the 10 years since the introduction of the HPV vaccination also support the effectiveness and safety of vaccination [8,9]. Global post-licensure safety data collected as part of rigorous active and passive safety surveillance programs have confirmed that the qHPV vaccine has a favorable safety profile [9]. Safety data are also regularly reviewed by various national and international health authorities and regulatory agencies, including the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS). To date, the GACVS has not identified any safety concerns based on the available data that would alter WHO recommendations for HPV vaccination [10,11].

The global Phase 2/3 qHPV vaccine trials did not include participants from mainland China, a country with a substantial burden of HPV-related disease. Given the possibility that differences in host populations could potentially impact vaccination outcomes, and to meet the Chinese regulatory requirements to support HPV vaccine licensure, additional studies in China were warranted. Vaccine immunogenicity and tolerability were previously demonstrated in Chinese males 9–15 years of age and females 9–45 year of age with a follow-up period of 7 months [12]. Robust vaccine efficacy has also been demonstrated against persistent infections and disease related to vaccine HPV types, including against the primary efficacy endpoints of high-grade cervical dysplasia and a composite endpoint of persistent infection, cervical intraepithelial neoplasia, adenocarcinoma in situ, and external genital lesions [13]. This is the first safety report with a follow-up period of up to 90 months from a Phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating qHPV vaccine efficacy and safety in Chinese women 20–45 years of age. The lower age bound is per the legal marriage age in China (20 years). While new HPV infections occur most frequently among sexually active women <25 years of age, mid-adult women (35–39 years of age) also experience a high disease burden globally, and a second peak of infection has been reported among women in their 30s in China [14,15].

2. Methods

2.1. Study design and participants

Study V501-041 (NCT00834106) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, safety and efficacy study conducted in China. The study was divided into two phases: a 30-month base study and an extension study. Women were enrolled at six sites, beginning January 3, 2009. The end-of-study results from the extension are based on cumulative data through September 30, 2016, corresponding with 90 months of safety follow-up. Details of the study design have been reported elsewhere [13]; features relevant to the analyses of safety are described below.

To be eligible for this study, women were 20–45 years of age with 1–4 lifetime sexual partners (or planned to become sexually active within the first 3 months of the study); had no history of genital warts or cervical disease, active cervical disease, or prior vaccination with HPV vaccine; and were not pregnant. Participants were randomized in blocks at each study site, stratified by age at enrollment (≤26 years [planned n = 1800] or >26 years [planned n = 1200]). Those who received at least one vaccination in the base study were eligible to continue into the extension. Participants and study site, laboratory, pathology panel, and sponsor personnel were blinded to treatment assignments during the entire study.

In addition to the primary efficacy endpoints reported elsewhere, safety was a primary endpoint of the base and extension study phases, and pregnancy outcomes were assessed as a secondary endpoint of the extension phase.

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

2.2. Vaccination and follow-up

Each dose of the qHPV vaccine (Merck & Co., Inc., Kenilworth, NJ, USA) contains 20/40/40/20 μg HPV6/11/16/18 L1 virus-like particles, respectively, and 225 μg amorphous aluminum hydroxyphosphate sulfate adjuvant. Vaccine doses or matching placebo (containing 225 μg adjuvant) were administered by intramuscular injection at Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks). Pregnancy testing (sensitive to 25 IU β-human chorionic gonadotropin [hCG]) was performed prior to each vaccination; women who were pregnant at the Day 1 visit were excluded from the study, and those who became pregnant after receiving one or more doses were not vaccinated further until resolution of the pregnancy and normalization of β-hCG levels.

Participants were followed for efficacy and safety for up to 78 months and only for safety at a close-out visit (phone call) scheduled at approximately 90 months. The primary efficacy hypothesis for the extension study was met while the 78-month follow-up was ongoing, in response to a request from the Chinese regulatory agency; therefore, the efficacy follow-up was terminated at the Month 78 visit. Safety information collected at the close-out visit included SAEs, pregnancies and pregnancy outcomes, and new medical condition.

2.3. Safety measurements

All participants were followed for safety throughout the study. Participants were observed for at least 30 min following vaccination for any immediate reactions (particularly for allergic reactions). All participants received vaccination report cards (VRCs) after each vaccination, where they were asked to record their axillary temperature daily for 5 days beginning 4 h after each injection. Participants recorded injection-site and systemic AEs for 15 days after each vaccination (including the day of vaccination). The VRC prompted participants to record injection-site erythema, swelling, pain, induration and pruritus, and systemic AEs including diarrhea, nausea, vomiting, fatigue, pyrexia, hypersensitivity, myalgia, headache, and cough. The causal relationship of an AE to vaccination (definitely related, probably related, possibly related, probably not related, or definitely not related) was assessed by the investigator who was a qualified physician, based on factors including exposure (i.e., evidence that the participant was exposed to test vaccine), time course (i.e., whether the AE followed in a reasonable temporal sequence from vaccine administration), likely cause (i.e., whether the AE could be reasonably explained by another etiology, drug, or other participant or environmental factor), and consistency with previous knowledge of the study vaccine profile. AE severity was assessed by using the grading scales issued by the China Food and Drug Administration.

SAEs were defined in the protocol as AEs that resulted in death, persistent or significant disability or incapacity, prolonged hospitalization; or were life-threatening, congenital anomalies or birth defects, cancers, associated with overdoses, or other important medical events. All SAEs were recorded for 15 days after each vaccination. Beyond the 15-day period after each dose, SAEs deemed possibly, probably, or definitely related to vaccination were recorded. However, all SAEs regardless of relationship to vaccination were collected after the "Vaccine Clinical Trial Serious Adverse Event Reporting Regulation" was issued by the China Food Drug Administration on January 17, 2014. SAEs were actively solicited at each study visit by the investigators, and spontaneously reported by the participants during the intervals between two visits.

Participants were evaluated for any new medical conditions, defined as those conditions not already recorded as medical history at Day 1 or AEs. At each scheduled study visit during the entire study, the participants were questioned by the investigators about the occurrence of new medical conditions.

All pregnancies during the study were recorded and followed for outcomes. SAEs occurring in infants born to participants were reported through end of study.

2.4. Statistical analyses

Safety was assessed in all participants who received at least one vaccination and had available safety data.

3. Results

3.1. Participants

A total of 3006 participants were randomized, and all received at least one dose. Of them, 2759 and 2602 completed the base study and the extension study, respectively (Fig. 1). Safety was assessed in 1499 participants in the qHPV vaccine group and 1498 in the placebo group, who were vaccinated and had available safety follow-up data.

Participant baseline characteristics were generally well balanced between vaccination groups and have been described in detail elsewhere [13]. The mean age was 28.7 years in both groups. The mean (median) duration of safety follow-up was 7.0 (7.5) years after the first vaccination.

3.2. AEs in study participants

AEs were reported by 926 qHPV vaccine recipients (61.8%) and 856 placebo recipients (57.1%) over the study duration, including 846 (56.4%) and 773 (51.6%) participants with vaccination-related AEs (Table 1). Five participants (qHPV:placebo = 2:3) discontinued the study vaccination due to AEs, including four (qHPV:placebo = 2:2) due to vaccination-related AEs (Table 1).

Within 15 days following any vaccination, injection-site AEs prompted for on the VRC occurred more frequently among qHPV vaccine recipients (n = 564; 37.6%) compared with placebo

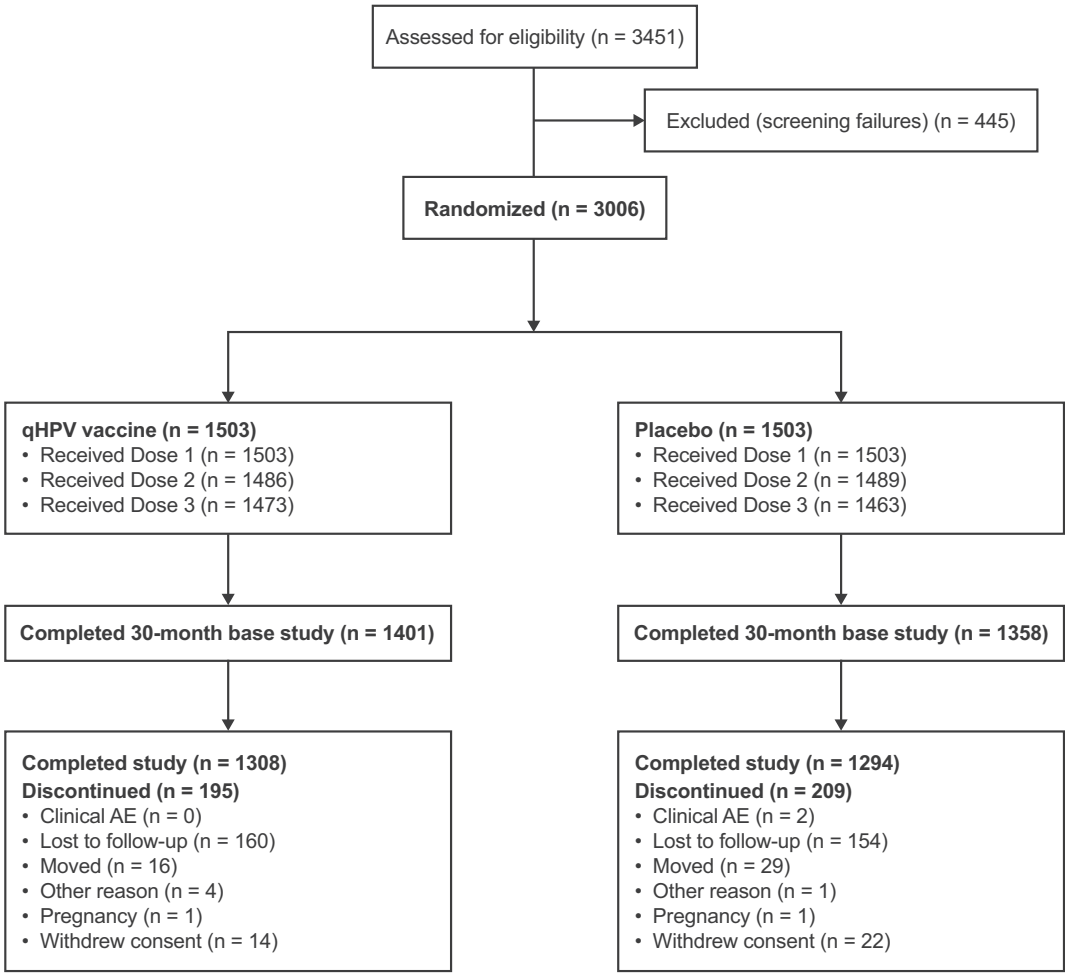

Fig. 1. Participant disposition. AE, adverse event; qHPV, quadrivalent human papillomavirus vaccine.

Table 1
AE summary over the entire study period of 90 months.

n (%)	qHPV vaccine (N = 1499)	Placebo (N = 1498)
Any AE	926 (61.8)	856 (57.1)
Injection-site AE	564 (37.6)	417 (27.8)
Systemic AE	770 (51.4)	750 (50.1)
Vaccination-related[a] AE	846 (56.4)	773 (51.6)
Injection-site AE	564 (37.6)	416 (27.8)
Systemic AE	639 (42.6)	628 (41.9)
Serious AE	38 (2.5)	43 (2.9)
Vaccination-related[a]	0	1 (0.1)
Death	2 (0.1)	0
Discontinuation[b] due to AE	2 (0.1)	3 (0.2)
Vaccination-related[a]	2 (0.1)	2 (0.1)

AE, adverse event; qHPV, quadrivalent human papillomavirus.
[a] Considered by the Investigator to be related to the vaccine.
[b] Study vaccination withdrawn.

recipients (n = 416; 27.8%) (Table 2). The most common injection-site AEs were pain, erythema, and swelling, all of which were more frequent among qHPV vaccine recipients. Within 15 days following any vaccination, systemic AEs prompted for on the VRC were reported by 46.8% (n = 702) of qHPV vaccine recipients and 45.1% (n = 676) of placebo recipients (Table 3). The most common systemic AEs were pyrexia, fatigue, headache, and myalgia (Table 3). Only myalgia occurred more frequently among qHPV vaccine recipients (Table 3), and all other systemic AEs occurred at similar rates among the two groups (Table 3). The majority of both the injection-site and systemic AEs were classified as Grade 1 or 2 (Tables 2 and 3), and were self-limited. Considering all AEs (including those not prompted for on the VRC) occurring within 15 days following any vaccination, the most common AEs judged by the investigator to be vaccination-related were injection-site pain (qHPV vaccine: 32.9%; placebo: 23.0%), pyrexia (qHPV vaccine: 23.3%; placebo: 21.9%), fatigue (qHPV vaccine: 12.5%; placebo: 10.1%), and myalgia (qHPV vaccine: 13.1%; placebo: 9.0%).

3.3. SAEs

A total of 96 SAEs were reported by 81 participants (qHPV:placebo = 38:43). The most frequently reported SAEs were uterine leiomyoma (8), uterine polypectomy (7), and ectopic pregnancy (6). One SAE (pyrexia occurring 3 days post-dose 3 in a placebo participant) was considered by the investigator to be vaccination-related; this SAE resolved 29 days after symptom onset. Two participants died (both qHPV vaccine recipients): one death (traffic accident) occurred 628 days after vaccine dose 3 and one (Stage 3 ovarian cancer) occurred 2044 days after vaccine dose 3. Neither death was considered related to vaccination.

3.4. New medical conditions

A total of 1619 participants (54.0%) experienced new medical conditions over the course of the study, at similar frequency in the qHPV vaccine (n = 814, 54.3%) and placebo (n = 805, 53.7%) groups (Table 4). Among system organ classes for the new medical

Table 2
VRC-prompted injection-site AEs by maximum intensity (Days 1–15 following any vaccination visit).

	qHPV vaccine (N = 1499)		Placebo (N = 1498)		Difference in % vs Placebo	
					Estimate	*P*-value*
	n	(%)	n	(%)	(95% CI)*	
Any injection-site AE	564	(37.6)	416	(27.8)	9.8 (6.5, 13.1)	<0.001
Grade 1	484	(32.3)	379	(25.3)		
Grade 2	69	(4.6)	24	(1.6)		
Grade 3	10	(0.7)	13	(0.9)		
Grade 4	1	(0.1)	0	(0.0)		
Injection-site erythema	176	(11.7)	133	(8.9)	2.9 (0.7, 5.0)	0.010
Grade 1	158	(10.5)	119	(7.9)		
Grade 2	18	(1.2)	12	(0.8)		
Grade 3	0	(0.0)	1	(0.1)		
Unknown	0	(0.0)	1	(0.1)		
Injection-site induration	115	(7.7)	64	(4.3)	3.4 (1.7, 5.1)	<0.001
Grade 1	94	(6.3)	57	(3.8)		
Grade 2	18	(1.2)	7	(0.5)		
Grade 3	3	(0.2)	0	(0.0)		
Injection-site pain	494	(33.0)	346	(23.1)	9.8 (6.6, 13.0)	<0.001
Grade 1	465	(31.0)	339	(22.6)		
Grade 2	27	(1.8)	7	(0.5)		
Grade 4	1	(0.1)	0	(0.0)		
Unknown	1	(0.1)	0	(0.0)		
Injection-site pruritus	113	(7.5)	77	(5.1)	2.4 (0.7, 4.2)	0.007
Grade 1	100	(6.7)	62	(4.1)		
Grade 2	7	(0.5)	4	(0.3)		
Grade 3	5	(0.3)	11	(0.7)		
Unknown	1	(0.1)	0	(0.0)		
Injection-site swelling	160	(10.7)	78	(5.2)	5.5 (3.5, 7.4)	<0.001
Grade 1	131	(8.7)	72	(4.8)		
Grade 2	26	(1.7)	5	(0.3)		
Grade 3	3	(0.2)	1	(0.1)		

Every participant is counted a single time for each applicable specific injection-site AE, and is classified according to the highest non-missing intensity grading.
AEs are graded per the AE grading scale issued by the China Food and Drug Administration.
AE, adverse event; qHPV, quadrivalent human papillomavirus; VRC, vaccination report card.
* Based on Miettinen and Nurminen method, stratified by age stratum; if no participants are in one of the vaccination groups involved in a comparison for a particular stratum, then that stratum is excluded from the vaccination comparison.

Table 3
VRC-prompted systemic AEs by maximum grade (Days 1–15 following any vaccination visit).

	qHPV vaccine (N = 1499)		Placebo (N = 1498)		Difference in % vs Placebo	
					Estimate	*P*-value*
	n	(%)	n	(%)	(95% CI)*	
Any systemic AE	702	(46.8)	676	(45.1)	1.6 (−1.9, 5.2)	0.362
Grade 1	571	(38.1)	563	(37.6)		
Grade 2	110	(7.3)	94	(6.3)		
Grade 3	18	(1.2)	17	(1.1)		
Grade 4	2	(0.1)	1	(0.1)		
Unknown	1	(0.1)	1	(0.1)		
Diarrhea	89	(5.9)	94	(6.3)	−0.3 (−2.1, 1.4)	0.689
Grade 1	83	(5.5)	86	(5.7)		
Grade 2	5	(0.3)	7	(0.5)		
Grade 3	1	(0.1)	1	(0.1)		
Nausea	100	(6.7)	95	(6.3)	0.3 (−1.5, 2.1)	0.723
Grade 1	95	(6.3)	84	(5.6)		
Grade 2	4	(0.3)	10	(0.7)		
Grade 3	1	(0.1)	0	(0.0)		
Grade 4	0	(0.0)	1	(0.1)		
Vomiting	24	(1.6)	14	(0.9)	0.7 (−0.1, 1.5)	0.102
Grade 1	23	(1.5)	11	(0.7)		
Grade 2	0	(0.0)	3	(0.2)		
Grade 3	1	(0.1)	0	(0.0)		
Fatigue	227	(15.1)	193	(12.9)	2.2 (−0.2, 4.7)	0.077
Grade 1	202	(13.5)	162	(10.8)		
Grade 2	20	(1.3)	24	(1.6)		
Grade 3	4	(0.3)	5	(0.3)		
Grade 4	1	(0.1)	1	(0.1)		
Unknown	0	(0.0)	1	(0.1)		
Pyrexia	388	(25.9)	353	(23.6)	2.3 (−0.8, 5.3)	0.146
Grade 1	346	(23.1)	329	(22.0)		
Grade 2	34	(2.3)	21	(1.4)		
Grade 3	6	(0.4)	3	(0.2)		
Grade 4	1	(0.1)	0	(0.0)		
Unknown	1	(0.1)	0	(0.0)		
Hypersensitivity	49	(3.3)	39	(2.6)	0.7 (−0.6, 1.9)	0.283
Grade 1	26	(1.7)	27	(1.8)		
Grade 2	21	(1.4)	9	(0.6)		
Grade 3	2	(0.1)	3	(0.2)		
Myalgia	224	(14.9)	153	(10.2)	4.7 (2.3, 7.1)	<0.001
Grade 1	194	(12.9)	126	(8.4)		
Grade 2	28	(1.9)	26	(1.7)		
Grade 3	2	(0.1)	1	(0.1)		
Headache	218	(14.5)	193	(12.9)	1.6 (−0.8, 4.1)	0.193
Grade 1	203	(13.5)	176	(11.7)		
Grade 2	14	(0.9)	17	(1.1)		
Grade 4	1	(0.1)	0	(0.0)		
Cough	84	(5.6)	90	(6.0)	−0.4 (−2.1, 1.3)	0.629
Grade 1	56	(3.7)	61	(4.1)		
Grade 2	22	(1.5)	22	(1.5)		
Grade 3	6	(0.4)	7	(0.5)		

Every participant is counted a single time for each applicable specific AE, and is classified according to the highest non-missing intensity grading.
AEs are graded per the AE grading scales issued by the China Food and Drug Administration.
AE, adverse event; CI, confidence interval; qHPV, quadrivalent human papillomavirus; VRC, vaccination report card.
* Based on Miettinen and Nurminen method, stratified by age stratum; if no participants are in one of the vaccination groups involved in a comparison for a particular stratum, then that stratum is excluded from the vaccination comparison.

conditions, surgical and medical procedures (e.g. intra-uterine contraceptive device insertion and removal) were most common, followed by infections and infestations.

3.5. Pregnancy outcomes

Pregnancy outcomes from randomization to end of study are summarized in Table 5. A total of 537 (35.7%) qHPV vaccine recipients and 527 (35.1%) placebo recipients became pregnant throughout the study, resulting in 719 and 704 fetuses/infants. Among the fetuses/infants with known outcomes (qHPV: placebo = 488:444), the rates of fetal/infant abnormalities were similar between the qHPV vaccine and placebo groups (n = 18 or 3.7% vs n = 12 or 2.7%, respectively), and the rates of fetal/infant congenital anomalies were also similar between the groups (n = 11 or 2.3% vs n = 6 or 1.4%). Outcomes were generally similar between the placebo and vaccine groups and were within ranges previously reported [16]. There were 445 (61.9%) live births and 274 (38.1%) events of fetal loss in the qHPV vaccine group, and 414 (58.8%) live births and 290 (41.2%) events of fetal loss in the placebo group. Most events of fetal loss were due to elective abortions. Spontaneous abortions occurred in 4.2% of pregnancies

Table 4
New medical conditions occurring in ≥ 1% in one or more vaccination groups (follow-up period after Month 7).

	qHPV vaccine (N = 1499)		Placebo (N = 1498)	
	n	(%)	n	(%)
Any new medical condition	814	(54.3)	805	(53.7)
Infections and infestations	332	(22.1)	340	(22.7)
Cervicitis	57	(3.8)	51	(3.4)
Chlamydial infection	13	(0.9)	15	(1.0)
Ureaplasma infection	52	(3.5)	63	(4.2)
Vaginitis, bacterial	79	(5.3)	73	(4.9)
Vulvovaginal candidiasis	18	(1.2)	6	(0.4)
Vulvovaginal mycotic infection	52	(3.5)	45	(3.0)
Vulvovaginitis, trichomonal	99	(6.6)	126	(8.4)
Injury, poisoning, and procedural complications	18	(1.2)	11	(0.7)
Neoplasms, benign, malignant, and unspecified (incl cysts and polyps)	56	(3.7)	54	(3.6)
Uterine leiomyoma	26	(1.7)	27	(1.8)
Pregnancy, puerperium, and perinatal conditions	23	(1.5)	17	(1.1)
Reproductive system and breast disorders	181	(12.1)	200	(13.4)
Cervical polyp	22	(1.5)	20	(1.3)
Cervix enlargement	7	(0.5)	20	(1.3)
Uterine cervical erosion	90	(6.0)	104	(6.9)
Surgical and medical procedures	472	(31.5)	485	(32.4)
Caesarean section	142	(9.5)	112	(7.5)
Female sterilization	121	(8.1)	126	(8.4)
Intra-uterine contraceptive device insertion	173	(11.5)	196	(13.1)
Intra-uterine contraceptive device removal	193	(12.9)	195	(13.0)

Every participant is counted a single time for each applicable specific condition. A participant with multiple conditions within a system organ class is counted a single time for that system organ class. The same participant may appear in different system organ classes.
qHPV, quadrivalent human papillomavirus.

Table 5
Summary of pregnancy outcomes from randomization to end of study.

	qHPV vaccine (N = 1503)		Placebo (N = 1503)	
	n	(%)	n	(%)
Participants with pregnancies	537	(35.7)	527	(35.1)
Number of fetuses/infants	719		704	
Outcome known	488	(67.9)	444	(63.1)
Normal	470	(96.3)	432	(97.3)
Abnormal	18	(3.7)	12	(2.7)
Congenital anomaly	11	(2.3)	6	(1.4)
Other abnormality	7	(1.4)	6	(1.4)
Outcome unknown	231	(32.1)	260	(36.9)
Live birth[a]	445		414	
Method of delivery				
Caesarean section	223	(50.1)	185	(44.7)
Vaginal	222	(49.9)	229	(55.3)
Infant outcome				
Normal	438	(98.4)	409	(98.8)
Abnormal	6	(1.3)	3	(0.7)
Congenital anomaly	6	(1.3)	2	(0.5)
Other abnormality	0	(0.0)	1	(0.2)
Unknown	1	(0.2)	2	(0.5)
Fetal loss[a]	274		290	
Type of loss				
Spontaneous abortion	30	(10.9)	26	(9.0)
Late fetal death	3	(1.1)	1	(0.3)
Elective abortion	240	(87.6)	260	(89.7)
Fetal/maternal condition	16	(5.8)	13	(4.5)
Personal decision	231	(84.3)	254	(87.6)
Ectopic pregnancy	1	(0.4)	3	(1.0)
Fetal outcome				
Normal	32	(11.7)	23	(7.9)
Abnormal	12	(4.4)	9	(3.1)
Congenital anomaly	5	(1.8)	4	(1.4)
Other abnormality	7	(2.6)	5	(1.7)
Unknown	230	(83.9)	258	(89.0)

A participant may have more than one pregnancy during the study. Each pregnancy is counted once. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually.
For a pregnancy with multiple fetuses, each infant is counted individually and each abortion was counted for fetal loss.
N, number of vaccinated participants in each vaccination group; n, number of participants with the indicated characteristic; qHPV, quadrivalent human papillomavirus.
[a] Percentages under "Method of delivery" and "Infant outcome" are calculated based on "Live births". Percentages under "Type of loss" and "Fetal outcome" are calculated based on "Fetal loss".

(n = 30) among qHPV vaccine recipients and 3.7% (n = 26) among placebo recipients.

3.6. Fetal/infant SAEs

A total of 22 fetal/infant SAEs were reported in 19 (qHPV:-placebo = 12:7) fetuses/infants born to vaccinated women who were potentially exposed to qHPV vaccine or placebo, with 17 reported congenital anomalies, one reported newborn pneumonia, and one fetal death. Among fetuses or infants who developed SAEs, one was born 11 months after the participant completed the last vaccination, and all the others were born or aborted at least one year after the participants completed the last vaccination. None of the fetal/infant SAEs were considered related to vaccination. The most common fetal/infant SAE was congenital heart disease, which was reported in three fetuses/infants born to qHPV vaccine recipients and one fetus/infant born to a placebo recipient. Trisomy 21 was reported in two fetuses/infants (both born to women in the placebo arm).

4. Discussion

Administration of the qHPV vaccine was generally well tolerated in Chinese women 20–45 years of age. With the exception of injection-site AEs, which occurred more frequently in qHPV vaccine recipients, the AE profiles over a follow-up period of 90 months were similar between the vaccine and placebo groups. The majority of injection-site and systemic AEs were mild to moderate (or Grade 1 to 2) in severity and self-limited, and very few (n = 5) participants discontinued the study vaccination due to AEs. Only one SAE, affecting a placebo recipient, was considered vaccination-related.

The qHPV vaccine has previously demonstrated robust immunogenicity in Chinese females 9–45 years of age with a follow-up period of 7 months [12]. Together with the sustained efficacy of the qHPV vaccine against HPV6/11/16/18-related persistent infection and cervical disease observed in Chinese women aged 20–45 years published previously [13], the favorable safety profile observed over up to 90 months of follow-up supports the implementation of widespread vaccination in China, where there is the largest susceptible population and a huge HPV-associated disease burden. These safety data will be valuable in informing healthcare professionals and decision-makers involved in HPV vaccination programs.

Injection-site AEs were reported at relatively lower rates in this study (37% with qHPV vaccine; 27% with placebo) compared with the global trial population of girls/women aged 9–26 years and boys aged 9–16 years (83% with qHPV vaccine [N = 6160]; 77% with placebo [N = 3470] [7]), and mid-adult women aged 24–45 years (77% with qHPV vaccine [N = 1450]; 64% with placebo [N = 1886] [17]), which was largely due to the much higher rate of injection-site pain observed in the global trials. Systemic AEs generally occurred at similar frequencies between the qHPV vaccine and placebo groups in this study, as reported previously for the global clinical trials [7,17]. Evidence from post-marketing safety surveillance and the perspective of the Global Advisory Committee on Vaccine Safety (GACVS) further support the favorable safety profile of the qHPV vaccine [9,18,19]. The current study in Chinese women 20–45 years of age, which included up to 90 months of follow up, adds to the body of evidence supporting the safety profile of the qHPV vaccine, and also further demonstrates the generally favorable safety profile of the qHPV vaccine across regions and ethnicities.

In this study, 537 qHPV vaccine recipients and 527 placebo recipients became pregnant, resulting in 719 and 704 pregnancies, respectively. The majority of them resulted in live births. Most events of fetal loss were due to elective abortions. The frequencies of spontaneous abortions and congenital anomalies were similar between the qHPV vaccine and placebo groups, and were within normal ranges reported for pregnant women (up to one-third of pregnancies) [20–23]. Similarly, previous analyses of pregnancy outcomes in women vaccinated with qHPV vaccine in the global clinical program found similar rates of adverse pregnancy outcomes across the placebo and qHPV vaccine groups without evidence of a negative impact of vaccination on pregnancy outcomes [16]. Post-marketing registry data also suggest that qHPV vaccine exposure is not associated with an increased risk of adverse pregnancy outcomes, including spontaneous abortion or major birth defects [24–28].

During the entire study, no SAE was considered to be qHPV vaccine-related. The SAE profile was similar between qHPV vaccine and placebo groups, and also similar with that observed in the global trials. Analyses of the new medical conditions did not raise any safety concerns with qHPV vaccine.

Despite the well-documented evidence of vaccine safety from clinical trials and post-marketing surveillance studies, public misconceptions and concerns regarding vaccine safety can pose barriers to implementation of HPV vaccination programs [10,29]. Clusters of anxiety-related reactions to immunization have occurred in some regions with detrimental effects on HPV vaccination programs, leaving young women vulnerable to preventable HPV-related disease [10,29–31]. Preparation, communication, and enhancing of vaccine infrastructure can ensure implementation of high coverage and sustainable vaccination programs [32].

5. Conclusion

The qHPV vaccine was well tolerated and demonstrated a favorable safety profile among Chinese women 20–45 years of age, consistent with findings from the global clinical trials. Data support the implementation of widespread vaccination in China, and will be useful in informing healthcare professionals and decision-makers involved in the implementation of vaccine programs for HPV-related disease prevention.

Disclosures

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

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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).

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

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.

Wen Chen: Acquisition of the data; 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

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.

Jingran Li: Acquisition of the data, analysis of the data, interpretation of the results; 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

Minghuan Zheng: Analysis of the data, interpretation of the results; drafting the manuscript.

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

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.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.12.030.

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