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Long-term effectiveness of at least one dose of human papillomavirus vaccine in adolescents: A test-negative case–control study

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ABSTRACT

Objectives: Human papillomavirus (HPV) vaccination has been recommended by the World Health Organization as part of the cervical cancer elimination strategy. Many countries have introduced single-dose or two-dose vaccination schedules. However, data on the effectiveness of at least one dose of the HPV vaccine among school-aged girls remain limited.

Methods: The study was a test-negative case–control conducted to estimate the effectiveness of HPV vaccines (VE) against high-risk types of HPV among adolescents in a real-world setting. Demographics and risk factors data were collected. Cases were adolescent who tested positive for high-risk HPV DNA. Time-matched controls were those who tested negative.

Results: Overall, 760 participants with a mean (SD) age of 18.2 (2.9) years underwent for HPV DNA testing. Among 114 vaccinated participants, 34 had received one dose and 80 had received two doses; the mean (SD) time since vaccination was 65.89 (23.67) months. A total of 100 participants tested positive for high-risk HPV types. The four most common high-risk types were HPV 16, 59, 52, and 58. The overall adjusted VE against high-risk HPV types among young women with a duration of >5 years was 91.0% (95% confidence interval: 33.4-98.8). The VEs against HPV high-risk infection among the age groups 9-18, 9-15, and 9-12 years who had received at least one dose were similar for >5 years.

Conclusion: At least one dose of the HPV vaccine was shown to be highly effective in preventing high-risk HPV types for >5 years across vaccination age up to 18 years.

Introduction

Cervical cancer is ranked the fourth most common cancer among women globally. Persistent human papillomavirus (HPV) infection is associated with 90% of all cases of cervical cancer [1]. The World Health Organization (WHO) estimated that 670,000 new cases of cervical cancer were diagnosed in 2024, with high mortality (350,000 deaths reported in 2024). HPV infection is one of the most common sexually transmitted infection in young adults [2].

HPV vaccination is the most effective primary prevention strategy for HPV-related cervical diseases and cervical cancer. Since licensure in 2006, highly efficacious prophylactic HPV vaccines have been introduced into national immunization programs in over 110 countries, with the primary goal of preventing cervical cancer [3]. There are three commercially available HPV vaccines globally. The bivalent and quadrivalent vaccines protect against oncogenic HPV types 16 and 18, which cause approximately 70% of cervical cancers [4], and the nonavalent vaccine targets five additional oncogenic types. The quadrivalent and nonavalent vaccines also protect

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against HPV types 6 and 11, which are the most common cause of genital warts (>90%) [5].

The effectiveness of the vaccine is highest when receiving before the first sexual intercourse [6]. Therefore, WHO recommended primary target population of young adolescent girls, aged 9-14. Since 2009, WHO has recommended their use in pre-adolescent girls for the prevention of cervical cancer, initially using the originally trialed three-dose schedule and, from 2014, in a two-dose schedule (based on immunobridging data) for those aged <15 years at dose one [7]. In 2022, the WHO issued new recommendations aimed at optimizing the HPV vaccination schedule to improve vaccine access. These recommendations provide countries with an opportunity to expand HPV vaccination coverage among girls while reducing the logistical and financial burden associated with completing multi-dose vaccination schedules. The recommended vaccination schedule varies according to the age of the vaccine recipient: a one- or two-dose schedule for girls aged 9-14 years; a one- or two-dose schedule for girls and women aged 15-20 years; and two doses with a 6-month interval for women >21 years old. Vaccination of secondary targets such as boys and older females is recommended where feasible and affordable [8]. Approval of the two-dose schedule was based on demonstration of non-inferiority of the immunogenicity outcome when compared with young adult women in whom three-dose efficacy has been proven [9–11].

In a randomized trial in Kenya (KENSHE study), after 18 months of follow-up, single doses of both the bivalent and nonavalent vaccines demonstrated 97.5% vaccine efficacy against high-risk strains of HPV and after 3 years following vaccination, bivalent vaccine efficacy remained at 97.5% (95% confidence interval [CI] 90.0-99.4%), whereas nonavalent vaccine efficacy was 98.8% (CI 91.3-99.8%) [12,13].

However, HPV vaccine coverage remains low; in 2019, the global coverage for HPV vaccination was 15% among adolescent girls [14]. In developing country, the main barriers include vaccine cost and the logistics of reaching girls with standard multi-dose vaccine schedule; single-dose vaccination could halve vaccination costs, potentially increase coverage, and simplify the logistics compared with multi-dose administration [15,16].

Several study designs have been used to quantify the real-world effectiveness of vaccines. A 7-year cross-sectional study in Scotland showed that bivalent HPV vaccination substantially reduced the prevalence of HPV types 16 and 18 from 30.0% (95% CI 26.9-33.1) in the 1988 cohort to 4.5% (3.5-5.7) in the 1995 cohort, giving a vaccine effectiveness (VE) of 89.1% (85.1-92.3) for those vaccinated at age 12-13 years [17]. Moreover, the real-world effectiveness of HPV vaccination against cervical cancer among women with three doses of HPV vaccine in Thailand demonstrated no cases of HPV 16/18-associated LSIL+ (Low-Grade Squamous Intraepithelial Lesion or worse) in the vaccinated group (36.5% and 63.5% received bivalent and quadrivalent HPV vaccines, respectively), whereas there were four cases in the unvaccinated group. HPV VE was 88.0% (95% CI 2.0-98.5) for the reduction of HPV 16/18-associated ASC-US+, and 84.6% (95% CI 43.5-95.8) in the reduction of HPV 16/18 positivity [18].

From a systematic review study, the frequency of infection was significantly lower in one-dose recipients compared with unvaccinated controls (P <0.01 for all infection endpoints in each study) [19]. Furthermore, comparison of trial outcomes confirmed that women who had received fewer than three doses were protected against HPV16/18-related cervical precancer [20,21]. Moreover, the study of HPV VE in preventing persistent oncogenic HPV infection over 18 months in Kenyan women aged 15-20 years showed that single doses of bivalent and nonavalent HPV vaccines were each highly effective; nonavalent vaccine efficacy was 97.5% (95% CI: 81.7-99.7%; $P \leq 0.0001$), and bivalent vaccine efficacy was 97.5% (95% CI: 81.6-99.7%; $P \leq 0.0001$), similar to multi-dose regimens [22]. The vaccine effects persisted up to year 7. After bivalent HPV vaccination, the prevalence of HPV16 and HPV18 was also not statistically significantly different by number of doses. Only 1.0% (95% CI: 0.6-1.5%), 1.3% (95% CI: 0.1-6.1%), 1.0% (95% CI , 0.2-3.4%), and 0.0% (95% CI: 0.0-2.2%) of the three-dose, two-dose (0/6 month), two-dose (0/1 month), and one-dose groups, respectively, had prevalent HPV16 or HPV18 at year 7 [23].

In Thailand, the HPV vaccine has been available in the private sector since 2007. A two-dose regimen was launched in 2017 under the Thai national immunization program for girls in the fifth-grade (11-12 years old). However, during certain periods, some individuals received only a single dose due to vaccine shortage, particularly just prior or during the SAR-CoV-2 pandemic. This study is aimed to estimate the real-world effectiveness of at least one dose of the HPV vaccine in reducing HPV high-risk types among adolescents aged 10-18 years after receiving the vaccine for at least 3 years.

Methods

Study design

The test-negative case–control study was conducted during March to October 2024 to estimate the long-term HPV VE of one or two doses HPV vaccines in real-world settings. Women aged 12-25 years who were interested in the study and were willing to provide informed consent and/or assents (depending on age at enrollment) for HPV DNA testing from urine or self-collected swab samples were enrolled. Those with a history of total hysterectomy and loop electrosurgical excision procedure, who had received three doses of the HPV vaccine, or who had any condition that might confound the interpretation of VE, as determined by the investigator, were excluded. Recruitment activities were done in Bangkok, Chachoengsao, and Chonburi provinces.

Definition of case and control

Cases were sexually active women aged 12-25 years who met the inclusion criteria and tested positive for high-risk HPV DNA types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using self-collected morning urine and/or cervical swabs. Time-matched controls included those who met inclusion criteria but tested negative for HPV DNA. Both cases and controls were selected from the same source population, and exposure status (immunization history) was ascertained retrospectively.

Demographic and sexual behavior data were collected after obtaining informed consents and/or assents, depending on enrollment age.

Vaccination history of the participants was confirmed by documentation of receiving at least one dose/single dose or two doses of the HPV vaccine (bivalent, quadrivalent, or nonavalent) from the Department of Health, Bangkok Metropolitan Administration (BMA) registry, Provincial Medical Office registry, school registries, or, less commonly, parent records (2014-2023).

HPV DNA testing

HPV testing for high-risk HPV DNA types was performed using urine or cervical self-swab (optional) samples. First-void urine or cervical swab samples were self-collected after brief training on the sample collection method using a commercially available collection device (Colli-Pee®; Novosanis, Wijnegem, Belgium). Collected urine samples were stored at room temperature and sent to the central laboratory for HPV testing. All urine samples were processed within 96 hours of collection.

For cervical swab, participants self-collected a vaginal sample using cobas polymerase chain reaction female swab sample packets

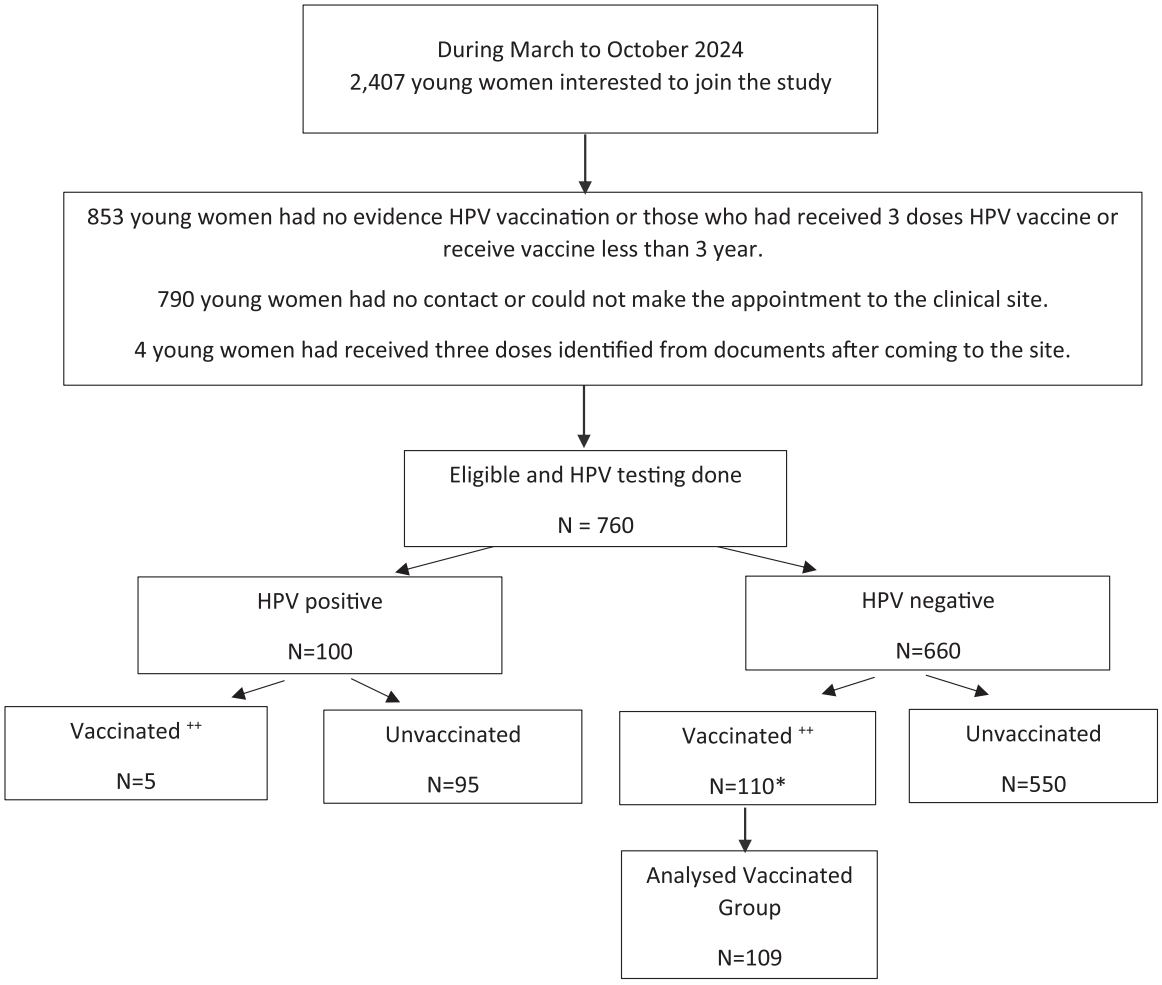

Figure 1. Flow diagram of study participants. Between March and October 2024, 2407 young women expressed interest in the study. After exclusions and loss to follow-up, eligible participants underwent HPV testing and were classified by HPV status and vaccination status. Vaccinated participants had a confirmed history of one or two doses of HPV vaccine (bivalent, quadrivalent, or nonavalent).
++Vaccinated participants refer to adolescents/young women who had a confirmed history of either one or two doses of HPV vaccine (bivalent, quadrivalent, or nonavalent vaccines).
*One subject who received vaccination at age 25 was excluded from analysis because she was an outlier.
HPV, human papillomavirus; VE, vaccine effectiveness.

(Roche Molecular Systems). DNA extraction was performed at the Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, using a NucliSENS® easyMAG® total nucleic acid extractor (bioMérieux, Marcyl'Etoile, France). All samples were then processed by Anyplex II HPV testing (Anyplex-HR; Seegene, Seoul, South Korea). The multiplex real-time polymerase chain reaction design, using tagging oligonucleotide cleavage and extension technology, allows for simultaneous detection and genotyping of 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and an internal control (human beta-globin) in a single reaction [21].

Data analysis and statistics

VE, defined as the proportionate reduction in the risk of disease among vaccinated participants attributable to the vaccine, will be calculated using matched odds ratio from a logistic regression model with vaccination as the exposure and case/control status as the outcome. Multivariate modeling analysis were used for adjusting the potential confounder. For all analyses, a type I error of 5% (two sided) was used to test for statistical significance.

The study protocol was approved by the Faculty of Tropical Medicine Ethical Committee and the BMA Human Research Ethics Committee (BMAHREC). The study is registered at ClinicalTrials.gov with the identifier NCT06220747.

Results

From March to October 2024, the vaccination history of 2407 participants was reviewed. Of these, 853 adolescents had no evidence to confirm HPV vaccine history or had received three doses of the HPV vaccine. Overall, 790 had no contact, could not make appointment, had received three doses of the HPV vaccine, or had received the vaccine >3 years ago. Only four participants who had received three doses were identified from documents after coming to the site (Figure 1). A total of 760 adolescents with confirmed history, with or without HPV vaccination, were appointed for HPV testing. All parents/participants signed consent and/or assent as appropriate for age. Of the 760 participants, 100 participants tested positive for high-risk HPV DNA, including five participants who had a confirmed history of HPV vaccination. Among the 660 participants with negative HPV test results, 110 of them had received at least one dose of HPV vaccine. One subject in this group had received vaccination at the age of 25 years (outlier) and was excluded from the analysis, whereas 550 participants were unvaccinated (Figure 1).

Table 1
Summary of general demographic characteristics of the study groups.

Status	All		HPV positive (cases)		HPV negative (control)	
	Vaccinated (N = 114) (n, %) (95% CI)	Unvaccinated (N = 645) (n, %) (95% CI)	Vaccinated (N = 5) (n, %) (95% CI)	Unvaccinated (N = 95) (n, %) (95% CI)	Vaccinated (N = 109) (n, %) (95% CI)	Unvaccinated (N = 550) (n, %) (95% CI)
Age, (years)	114	645	5	95	109	550
Mean (SD)	16.55 (1.53)	18.47 (3.00)	15.80 (0.84)	19.57 (2.76)	16.59 (1.55)	18.28 (3.01)
Median (q1-q3)	16 (16.00-17.00)	18 (16.00-21.00)	16 (15.00-6.00)	20 (17.00-22.00)	16 (16.00-17.00)	18 (16.00-21.00)
Min-Max	14-24	12-25	15-17	13-25	14-24	12-25
Race, n (%)						
Thai	114 (15.02)	645 (84.98)	5 (5.00)	95 (95.00)	109 (16.54)	550 (83.46)
HPV vaccination status, n (%)						
No	0 (0.00)	645 (84.98)	0 (0.00)	95 (95.00)	0 (0.00)	550 (83.46)
Yes	114 (15.02)	0 (0.00)	5 (5.00)	0 (0.00)	109 (16.54)	0 (0.00)
2 valent[a]	34 (29.82)	0 (0.00)	1 (20.00)	0 (0.00)	33 (30.28)	0 (0.00)
4 valent[b]	75 (65.79)	0 (0.00)	4 (80.00)	0 (0.00)	71 (65.14)	0 (0.00)
9 valent[c]	5 (4.39)	0 (0.00)	0 (0.00)	0 (0.00)	5 (4.59)	0 (0.00)
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of HPV vaccine doses administered, n (%)						
One dose	34 (29.82)	0 (0.00)	4 (80.00)	0 (0.00)	30 (27.52)	0 (0.00)
Two doses	80 (70.18)	0 (0.00)	1 (20.00)	0 (0.00)	79 (72.48)	0 (0.00)
Age at vaccination, (years)						
N	114		5		109	
Mean (SD)	11.70 (1.50)		12.60 (1.52)		11.66 (1.50)	
Median (q1-q3)	11.00 (11.00-12.00)		12 (12.00-13.00)		11.00 (11.00-12.00)	
Min-Max	10-18		11-15		12-18	
Duration between vaccination and enrollment/HPV testing						
N	114		5		109	
Mean (SD)	65.89 (23.67)		47.00 (25.71)		66.76 (23.34)	
Median (q1-q3)	69 (54.00-82.00)		54 (22.00-54.00)		69 (64.00-82.00)	
Min-Max	8-122		22-83		8-122	
Among those received one dose						
Duration between vaccination and enrollment/HPV testing						
N	34		4		30	
Mean (SD)	52.56 (24.61)		38.00 (18.48)		54.50 (24.91)	
Median (q1-q3)	54 (22.00-77.00)		38 (22.00-54.00)		54 (49.00-77.00)	
Min-Max	8-83		22-54		8-83	
Among those received two doses						
Duration between vaccination and enrollment/HPV testing						
N	80		1		79	
Mean (SD)	71.56 (20.97)		83.00 (83.00-83.00)		71.42 (21.06)	
Median (q1-q3)	70 (65.00-83.00)		83 (83.00-83.00)		70 (65.00-83.00)	
Min-Max	13-122		83-83		13-122	

CI, confidence interval; HPV, human papillomavirus.
[a] Bivalent, received Cervarix (2015-2017), received Cecolin (2023)
[b] Quadrivalent, received Gardasil 4 (2014 and 2018-2022)
[c] Nonavalent, received Gardasil 9 (2014).

Vaccination status

The age range of those who had received HPV vaccine was 10-18 years (N = 114), with the mean (SD) age of 11.70 (1.50) years. Thirty-four had received one dose, and 80 had received two doses. Of those 114 vaccinated participants, 34 (30%) received the bivalent (26 participants received Cervarix® and eight participants received Cecolin®), 75 (66%) received the quadrivalent (Gardasil® 4), and five (4%) received the nonavalent HPV vaccine (Gardasil® 9). The mean (SD) duration between vaccine and HPV testing of the study group was 65.89 (23.67) months (Table 1). Among those who received one dose of the HPV vaccine (N = 34), the mean (SD) duration between vaccination and HPV testing was 52.56 (24.61) months. Among those who received two doses, the mean (SD) duration was 71.56 (20.97) months.

Characteristics of women with high-risk HPV positivity

Among the 100 cases positive for high-risk HPV types, 95 women had no history of HPV vaccination. Five women had a history of HPV vaccination (one of them had received one dose and four of them had received two doses of HPV vaccines). It was unknown whether HPV infection occurred prior to vaccination, as participants had not undergone HPV testing before.

The prevalence of vaccine-matched HPV genotypes (16 and 18) were 20% and 12%, respectively. The most common high-risk types identified were HPV 59 (21%), 16 (20%), 52 (20%), 58 (20%), and 66 (17%) (Supplementary Figure 1).

Factors associated with HPV DNA test positivity among the study population were smoking, use of hormonal contraceptives, and having a sexual history. Among participants with a sexual history (N = 366), the factor associated with HPV DNA test positivity was having multiple sexual partners (Table 2).

HPV VE, age effects, and duration after vaccination

The overall VE against high-risk HPV infection appeared higher among those vaccinated at younger ages (9-12 years). However, VE was similar across age groups 9-12, 9-15, and 9-18 years after >5 years, as shown in Figure 2.

Table 2
Factors associated with HPV positivity and cOR among the study group (9-18 years old adolescents/young women).

	HPV positive N (%)	HPV negative N (%)	*P*-value	cOR (95% confidence interval)
History of smoking				
Never	85 (12.13)	616 (87.87)		ref
Ex-smoker	5 (18.52)	22 (81.48)	0.3267	1.65 (0.61-4.46)
Smoker	10 (32.26)	21 (67.74)	0.0020	3.45 (1.57-7.58)
Hormonal contraceptive use				
No	43 (7.83)	506 (92.17)		ref
Yes	57 (27.14)	153 (72.86)	<0.0001	4.38 (2.84-6.78)
Pregnancy history				
No	93 (12.77)	635 (87.23)		ref
Yes	7 (22.58)	24 (77.42)	0.1205	1.99 (0.83-4.75)
Sexual history				
Never	10 (2.54)	383 (97.46)		ref
Yes	90 (24.59)	276 (75.41)	<0.0001	12.48 (6.38-24.43)
Number of partners				
1	27 (15.98)	142 (84.02)		ref
≥2	40 (29.41)	96 (70.59)	0.0054	2.19 (1.26-3.81)
Unwilling to answer	23 (37.70)	38 (62.30)	0.0006	3.18 (1.64-6.17)

cOR, crude odd ratio; HPV, human papillomavirus; ref, reference.

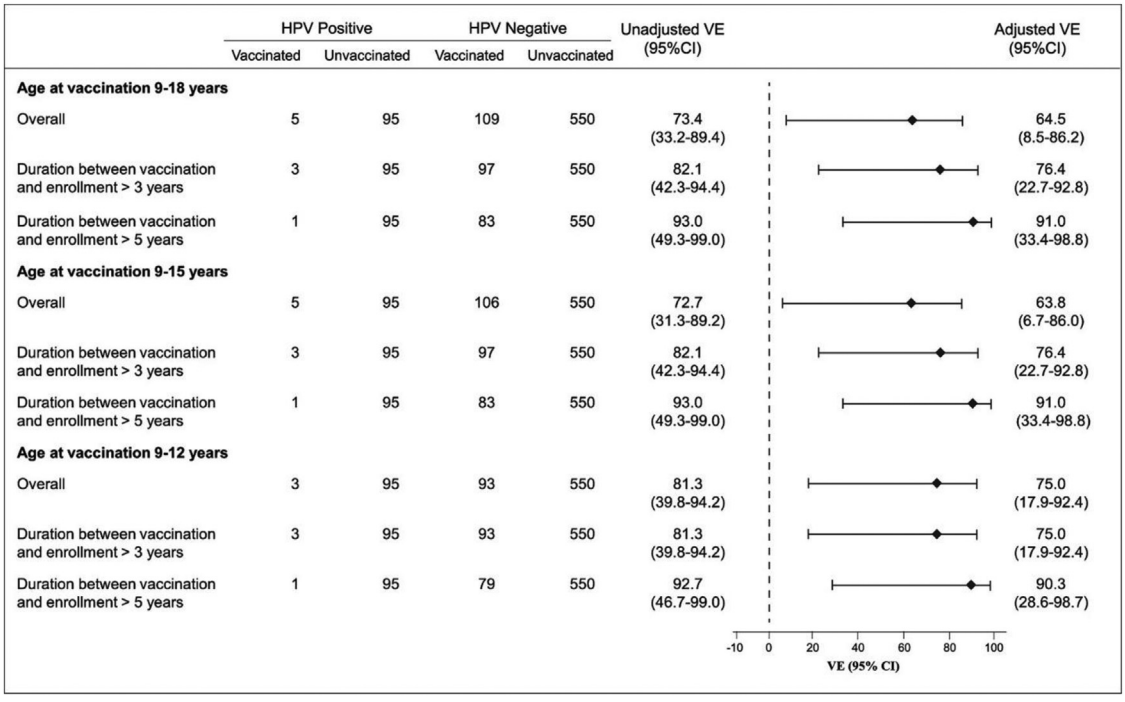

Figure 2. VE of the HPV vaccine among adolescents/young women by age range and duration since vaccination.
VE against HPV infection was estimated by comparing vaccinated and unvaccinated participants, overall and stratified by age at vaccination (9-18, 9-15, and 9-12 years) and time since vaccination (>3 and >5 years). Unadjusted and adjusted VE estimates with 95% CI are presented. HPV testing was performed at enrollment.
CI, confidence interval; HPV, human papillomavirus; VE, vaccine effectiveness.

Overall VE among those aged 9-18 years

The overall VE against HPV infection was 64.47% (95% CI: 8.45-86.21). Among participants with >3 years between vaccination and HPV DNA testing, the overall VE was 76.44% (95% CI: 22.65-92.82), and among those with >5 years between vaccination and HPV DNA testing, VE was 90.97% (95% CI: 33.42-98.77), based on adjusted analysis accounting for the number of sexual partners (Figure 2).

Overall VE among those aged 9-15 years

The VE, regardless of duration, for those aged 9-15 years was 63.82 (95% CI: 6.71-85.97). VE against overall HPV infection among participants with a duration of >3 years between vaccination and HPV DNA testing was 76.44 (95% CI: 22.65-92.82), and VE against overall HPV infection among participants with a duration of >5 years between vaccination and HPV DNA testing was 90.97 (95% CI: 33.42-98.77) (Figure 2).

Overall VE among the primary vaccine target group aged 9-12 years

The VE for those aged 9-12 years was 75.02 (95% CI: 17.87-92.40). VE against HPV infection with >3 years between vaccination and HPV DNA testing was 75.02 (95% CI: 17.87-92.40). VE against overall HPV infection with >5 years between vaccination and HPV DNA testing was 90.33 (95% CI :28.60-98.69) (Figure 2).

Table 3
HPV vaccine effectiveness against HPV types 16/18 among the study group (9-18 years), by time since vaccination.

Population	VE against HPV types	HPV vaccination	HPV positive (case)	HPV negative (control)	Crude VE (95% CI)	Adjusted VE (95% CI)
Overall population						
Overall	All HPV types	No	95	550	73.44	64.47
		Yes	5	109	(33.20-89.44)	(8.45-86.21)
	HPV type	No	28	617	80.5	72.99
	16/18	Yes	1	113	(−44.77-97.37)	(−103.54-96.42)
Duration since last vaccination >3 years	All HPV types	No	95	550	82.09	76.44
		Yes	3	97	(42.34-94.44)	(22.65-92.82)
	HPV type	No	28	617	77.74	68.96
	16/18	Yes	1	99	(−65.44-97.01)	(−134.25-95.89)
Duration since vaccination >5 years	All HPV types	No	95	550	93.02	90.97
		Yes	1	83	(49.29-99.04)	(33.42-98.77)
	HPV type	No	28	617	100	100
	16/18	Yes	0	84	(100.00-100.00)	(100.00-100.00)

CI, confidence interval; HPV, human papillomavirus.

VE against matched vaccine strains in the 9-18 year age group

Table 3 showed the overall VE and VE against vaccine-matched HPV types 16/18. However, the results of VE against non-vaccine-matched high-risk HPV types are elaborated in the text below. The overall VE against HPV type 16 and/or 18 infection was 72.99 (95% CI: −103.54-96.42) and overall VE against non-HPV type 16 and 18 infection was 56.34 (95% CI: −13.01-83.14) (Table 3). VE against HPV type 16 and/or type 18 infection among participants with >3 years between vaccination and HPV DNA testing was 68.96 (95% CI: −134.25-95.89), whereas VE against non-HPV type 16 and 18 infection was 71.14 (95% CI: 4.91-91.24). With >5 years between vaccination and HPV DNA testing, VE against HPV type 16 and/or type 18 infection was 100.0% (95% CI: 100.0–100.0), whereas VE against non-HPV type 16 and 18 infection was 88.91 (95% CI: 18.08-98.50). Similar VE results for HPV 16/18 and non-HPV 16/18 types were obtained in the 9-15 and 9-12 year age groups.

Discussion

Receiving at least one dose of the HPV vaccine has been shown to be highly effective in a real-world setting. The overall VE against HPV infection was 64.47% (95% CI: 8.45-86.21). Among participants with >3 years between vaccination and HPV DNA testing, the overall VE was 76.44% (95% CI: 22.65-92.82), and among those with >5 years between vaccination and HPV DNA testing, VE was 90.97% (95% CI: 33.42-98.77), based on adjusted analysis accounting for the number of sexual partners. The mean age at vaccination was 11.70 (SD: 1.50) years, while most participants had their first sexual intercourse at >15 years of age. Most HPV vaccinations were given before sexual debut. However, this study was aimed to study long-term VE, especially after 5 years, in a real-world setting.

VE, regardless of duration, for ages 9-15 and 9-12 years was 63.82 (95% CI: 6.71-85.97) and 75.02 (95% CI: 17.87-92.40), respectively. It appeared that younger vaccination age was associated with higher overall VE. However, the higher VE against high-risk HPV infections over a 5-year period was similar across age groups up to 18 years (90.97% [95% CI: 33.42-98.77], 90.97 [95% CI: 33.42-98.77], and 90.33 [95% CI :28.60-98.69] for ages 9-18, 9-15, 9-12 years, respectively).

VE against HPV 16/18 infections, which are the vaccine-matched HPV types, was higher than against non-HPV 16/18 types. Overall VE for HPV 16/18 was 72.99 (95% CI: –103.54-96.42), and overall VE for HPV 16/18 among participants with a duration of >5 years between vaccination and HPV DNA testing was 100.0% (95% CI: 100.0-100.0) compared with VE of 56.34 (95% CI: –13.01-83.14) for non-HPV 16/18 infections. VE appeared to be higher with longer time since vaccination. We hypothesized that in the >3-year results, some girls infected prior to vaccination were still shedding the virus and had not yet cleared the infection, whereas by 5 years post-vaccination, most had cleared the infection. Thus, the prevalence of infection was lower at >5 years than at >3 years. In addition, with single-time point sampling, the presence of HPV DNA could be because of infection or recent deposition if the girl is sexually active. VE based on a single sample will always be lower than efficacy based on the more rigorous endpoint of >6 months' persistent infection.

Similar results were reported from the Netherlands assessing two-dose bivalent HPV VE up to 4 years following routine immunization; VE against incident infections with high-risk types HPV-16/18/31/33/45/52/58 was 64.9% (95% CI: 20.2-81.0%), VE against vaccine types HPV-16/18 was 84.0% (95% CI: 27.0-96.5%), and VE against non-HPV 16/18 types (HPV-31/33/45) was 86.5% (95% CI: 39.5-97.08%) [24]. A 7-year cross-sectional study from Scotland also showed the VE against HPV 16/18 infection was 89.1% (95% CI: 85.1-92.3%) among girls offered vaccination at age 12-13, and VE against HPV-31/33/45 was 85.1% (95% CI: 77.3-90.9%) [17]. The overall VE 72.99% for HPV-16/18 is in line with HPV-naive cohorts in the Costa Rica Vaccine and PATRICIA trials, in which the efficacy against incident HPV-16/18 infections for two doses of the bivalent vaccine was 76.0% (95% CI: 62.0-85.3) [4].

The first population–based effectiveness report from low- and middle-income countries (Rwanda and Bhutan, both with school-based Gardasil programs during 2013-2014 [baseline survey] and 2017 [repeat survey] in both countries) showed type–specific effectiveness of 78% (95% CI 51-90) in Rwanda and 88% (95% CI 6-99) in Bhutan against infection with HPV 6/11/16/18 in vaccinated age groups, along with significant reductions in other alpha-9 types (HPV-31, -33, -35, -52, -58), indicating cross–protection [25], with approximately up to 4 years' duration. However, our real-world study demonstrated higher VE for longer duration of >5 years with at least one dose of either bivalent or quadrivalent HPV vaccine.

The HPV vaccine is highly effective in the long term in preventing specific HPV types covered by the vaccine. A community intervention of a one- to two-dose regimen of the bivalent HPV vaccine among schoolgirls in Thailand showed that crude VE for the single-dose regimen after 4 year post-vaccination was 90.6% (95% CI: 86.6-94.6%), and for the two-dose regimen was estimated at 95.4% (95% CI: 93.2-97.6%) [26]. Likewise, a cross-sectional, case–control study evaluated the VE for prevention HPV types 16 and 18 over 7 years among schoolgirls after two-dose administration showed VE of 100% (95% CI: ND) [27].

Although higher VE has been found with younger age at vaccination [17], this study showed that even when extending the

age to 18 years (9-18 years), the vaccine was still effective,with an overall VE of 64.47% and VE for HPV 16 and/or 18 of 72.99%.

However, the lower overall VE against HPV type 16 and/or 18 in this group can be partially explained by HPV type distribution. The most prevalent HPV strains in this study were 59, 16, 52, 58, and 66. A previous study in Thailand showed HPV types 66, 58, 59, 52, and 18 were the most common types of HPV infection [27]. Consistent with a previous study review, in South-east Asia, the most prevalent genotypes were HPV 52 (12.9%), 16 (8.5%), 58 (5.2%), 18 (5.0%), and 66 (4.9%) [28]. Worldwide, the most common HPV types were 16, 18, 31, 33, 35, 45, 52, and 58 [4]. Therefore, the new generation of HPV vaccines, such as the nonavalent HPV vaccine, might offer more benefit.

Cross-protective effects were observed against other high-risk HPV types. Results from a community intervention study demonstrated VE against HPV-31, 33, or 45 at 4-year follow-up after vaccination of 27.3% for the single-dose regimen and 48.2% for the two-dose regimen [26]. An 11-year follow-up analysis of the Costa Rica Vaccine trial established statistically significant cross-protection against a composite outcome of HPV-31, 33, and 45, with VE of 54.4% (95% CI: 21.0-73.7%) for single-dose bivalent HPV vaccination [29]. A 10-year follow-up study in India demonstrated significant VE of 43.5% (95% CI: 25.4-56.5%) against HPV-31, 33, and 45 after single-dose quadrivalent HPV vaccination [30]. Among women who received three doses of HPV vaccine, the bivalent vaccine demonstrated statistically significant cross-protective efficacy, although with wide confidence intervals, against 6- and 12-month persistent infections and CIN2+ (Cervical Intraepithelial Neoplasia Grade2 and higher) consistently for HPV 31 and 45, with the highest effect observed for HPV 31 (range 64.6% [95% CI: 27.6-83.9] to 79.1% [97.7% CI: 27.6-95.9] for 6-month persistent infection; maximal follow-up 4.7 years). No cross-protection was shown in extended follow-up. The quadrivalent vaccine efficacy reached statistical significance for HPV 31 (46.2% [15.3-66.4]; follow-up: 3.6 years). Similarly, observational studies consistently found significant effectiveness only against HPV 31 and 45 with both vaccines [31].

The reduction in other high-risk HPV types could be partly due to continuous natural exposure to other high-risk types over time, as the most common high-risk types identified were HPV 59 (21%), 16 (20%), 52 (20%), 58 (20%), and 66 (17%). The higher prevalent of HPV infections among young women in our study compared with previous study in Thailand could be partially explained by demographic data, as most participants came from Bangkok and central region industrial provinces, had history of higher number of sex partners, a history of pregnancy, and high smoking behavior.

The study has some limitations, as single specimen was used for HPV DNA testing. Unfortunately, there was not enough sample size of single-dose vaccination to calculate single-dose VE in this study. Due to the inherent limitations of the test-negative case–control study design, complete balance of exposure between vaccinated and unvaccinated groups could not be achieved. Furthermore, the difference between VE against HPV types 16 and/or 18 infection (68.96% [95% CI: −134.25-229.95]) and VE against non-HPV 16/18 infection (71.14% [95% CI: 4.91-91.24]) was not statistically significant, as indicated by the wide confidence intervals.

However, a strength of the current study is the real-world investigation of at least one dose. Vaccinated and unvaccinated participants were comparable regarding sociodemographic and sexual characteristics. VEs against HPV high-risk infection among those aged 9-18, 9-15, and 9-12 years were similar, especially at >5 years after vaccination. These results could support extending HPV vaccination up to 18 years of age in other developing countries, even though the distribution of high-risk HPV types might be different from HPV types 16 and 18. With the WHO Cervical cancer elimination goal, many countries have shifted HPV vaccination programs from a two-dose regimen to a one- or single-dose regimen. The combined data of high VE of at least one dose of HPV vaccine will help to strengthen the evidence during the transition period.

Conclusion

HPV vaccination with at least one dose was highly effective in preventing HPV infection, particularly for HPV types 16 and 18, which are the main targets of the vaccine in long-term follow-up. The combined data of high VE of at least one dose of HPV vaccine will help to strengthen the evidence during the transition period.

Declaration of competing interest

The authors have no competing interests to declare.

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Author contributions

Conceptualization and methodology: **PP and SK.** Data curation: **PP, SLN, and SK.** Formal analysis: **SLN.** Funding acquisition: **PP.** Resources and investigation: **CR, NI, KS, and SS.** Validation and visualization: **PP, SS, SM, JD, KS, NH, CR, NI, SLN, and SK.** Supervision: **PP.** Writing – original draft preparation: **SK and PP.** Writing – review and editing: **PP, SS, SM, JD, KS, NH, CR, NI, SLN, and SK.**

Clinical trial registration

Registered at ClinicalTrials.gov: NCT06220747

Role of funding source

The funders of the study had no role in data collection, data analysis, writing of the statistical report, interpreting data, or critical review of this report. All authors had full access to all data in the study and accepted responsibility for the decision to submit the manuscript for publication.

Data availability

The data that support the findings of this study are available upon request from the corresponding author at punnee.pit@mahidol.ac.th.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2026.108489.

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