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REVIEW

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Impact of human papillomavirus vaccines in the reduction of infection, precursor lesions, and cervical cancer: A systematic literature review

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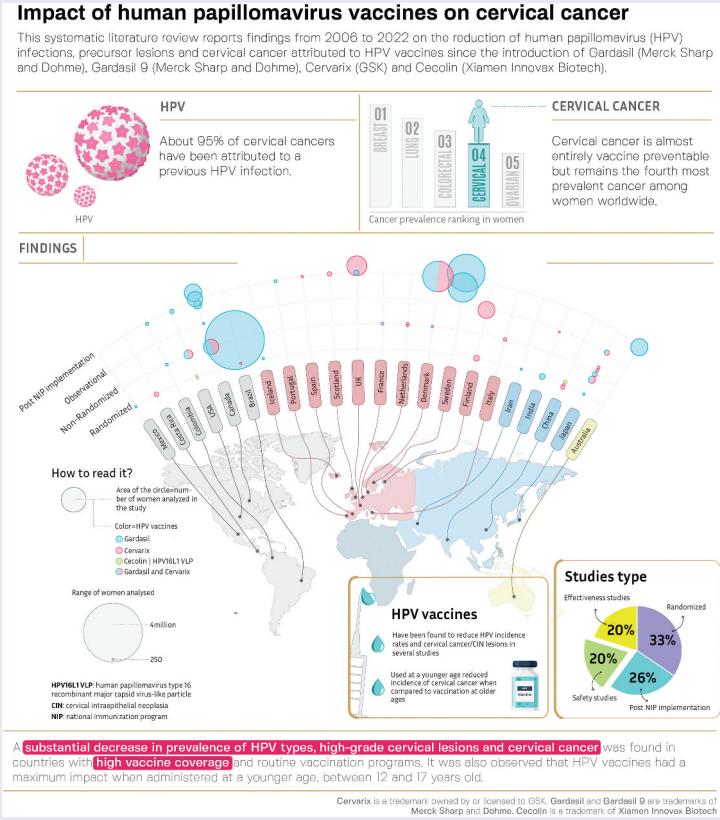
ABSTRACT

Cervical cancer is a preventable disease for which vaccines are available to provide long-term protection against human papillomavirus (HPV) infection. This systematic literature review (SLR) was performed to summarize the efficacy, effectiveness, impact, duration of protection, and safety profile of four licensed HPV vaccines against infection, precursor lesions, and cervical cancer. Data was extracted from published reports. The search resulted in 1,136 studies, of which 54 were selected for this review. A substantial decrease in the prevalence of oncogenic HPV types, high-grade cervical lesions, and cervical cancer was found in countries with high vaccine coverage and routine vaccination programs. Post-licensure studies of HPV vaccines have reported high efficacy, effectiveness, and health impact across settings and age groups. Studies emphasize vaccination in younger age groups. These findings may inform future discussions about HPV vaccination strategies.



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Research in context

Evidence before this study

The incidence of cervical cancer has been significantly reduced in countries that recommend cervical cancer screening and vaccination through national immunization programs (NIPs). It is necessary to consider the available evidence on the long-term efficacy, effectiveness, and health impact of HPV vaccines to advance future HPV vaccination strategies. Therefore, we performed a systematic literature review (SLR) in three electronic databases (Medline [via PubMed], Embase, and Cochrane) using a comprehensive set of search terms. The methodological quality and risk of bias of the shortlisted studies were assessed. The search was performed on 02/01/2022. Eligible studies included randomized controlled trials and observational studies that analyzed females ≥9 years of age and were published between 01/01/2006 (the year of marketing of the first HPV vaccine) and 1/31/2022.

Added value of this study

This review provides updated evidence on the efficacy, effectiveness, and health impact of HPV vaccines by presenting substantially longer follow-up periods than previous reviews and data from countries worldwide. The efficacy and effectiveness of each vaccine against infection, precursor lesions, and cervical cancer were reviewed based on data from controlled clinical trials and real-world settings, respectively. In addition, long-term studies provided data on the public health impact of HPV vaccines against cervical cancer, extending their scope to include herd immunity. This SLR also summarizes safety data, including short- and long-term adverse events. The prevalence of oncogenic HPV types, high-grade cervical lesions, and cervical cancers was found to have decreased in countries with high vaccine coverage and routine vaccination programs. Individuals vaccinated at a younger age had a greater reduction in HPV infection, precursor lesions, and cervical cancer than those vaccinated at older ages. HPV vaccination has also provided long-term protection lasting at least 11 years in real-world settings.

Implications of all the available evidence

Because many HPV infections are vaccine-preventable, public health authorities should focus on promoting HPV vaccine uptake in NIPs and targeting children and pre-adolescents for vaccination. Future research based on the findings of this review may focus on HPV vaccination in younger age groups (9–12 years of age).

Introduction

Cervical cancer is the fourth most common cancer among women globally. In 2022, cervical cancer caused an estimated 350,000 deaths worldwide.[1] Approximately 91% of the 604,000 diagnosed cases in 2020 were reported in low- and middle-income countries.[2] The large geographical disparities in cervical cancer incidence and mortality may be attributed to the availability of appropriate healthcare resources, preventive health policies, and risk factors.[3] This imbalance may be widening, with declining incidence in most high-income countries[3] and rising incidence in sub-Saharan Africa and several Eastern European countries.[3,4] In East Asian countries, incidence rates remained stable.[3]

Approximately 95% of cervical cancers have been attributed to human papillomavirus (HPV) infection.[1] Among the different HPV genotypes, HPV types 16/18 are considered the highest risk and account for at least 70% of invasive cervical cancers.[1] In addition to routine screening, HPV vaccination is also a widely used, cost-effective strategy to decrease the incidence of cervical cancer.[5] Moreover, there is high-certainty evidence that HPV vaccines protect against cervical pre-cancer in adolescent girls and young women.[6]

Currently, four HPV vaccines are prequalified by the World Health Organization (WHO): one 9-valent vaccine (Gardasil 9 [Merck Sharp and Dohme; United States], first approved on 10/12/2014 by the FDA), one quadrivalent vaccine (Gardasil [Merck Sharp and Dohme; United States], first approved on 08/06/2006 by the FDA) and two bivalent vaccines (Cervarix [GSK, Belgium], first approved on 10/09/2007 by the EMA and Cecolin [Xiamen Innovax Biotech; China], first approved on 31/12/2019 by the China's National Medical Products Administration).[7–11] All four vaccines contain noninfectious virus-like particles (VLPs) that stimulate an immune response against HPV.[12] The quadrivalent vaccine contains VLPs against HPV types 6/11/16/18 while the 9-valent vaccine contains VLPs against HPV types 6/11/16/18/31/33/45/52/58.[13,14] Bivalent vaccines contain VLPs against HPV types 16/18 and are indicated for the prevention of anogenital lesions and cancers of the cervix and anus.[12] Gardasil vaccines use an aluminum-based adjuvant, while Cervarix uses a proprietary adjuvant, AS04.[14] This adjuvant system contains 3-O-desacyl-4′-monophosphoryl lipid A (50 μg) adsorbed on an aluminum salt (500 μg) and is critical for enhancing humoral and cellular responses. HPV vaccines are typically administered in two or three doses and are recommended for individuals between 9 and 26 or 45 years of age, depending on the vaccine.[12] Recently, the WHO also recommended an off-label alternative single-dose regimen for target populations aged 9–20 years, based on comparable efficacy and duration of protection as the two-dose schedule.[12] The Government of Quebec provides a similar recommendation.[15] The United Kingdom's Joint Committee on Vaccination and Immunization (JCVI) also recommends a single-dose schedule for girls and boys up to 25 years of age.[16] Since 2024, the Spanish vaccination schedule has recommended a single dose up to the age of 18.[17] Global randomized clinical trials (RCTs) have also demonstrated the safety and efficacy (≥93%) of HPV vaccines against persistent infections and precancerous cervical lesions.[18–20] Since the introduction of HPV vaccines in national immunization programs (NIPs), substantial reductions in the incidence of vaccine-type HPV (73–85%), high-grade lesions (41–57%), and cervical cancer rates (34–87%) have been observed in countries with high (>50%) HPV vaccination coverage.[5,21,22]

In May 2018, the WHO issued a call to eliminate cervical cancer.[23] The WHO recognized that cervical cancer mortality

is preventable with appropriate systems in place to vaccinate, screen, and treat women diagnosed with the disease. Lack of management of precursor lesions preceding cervical cancer was responsible for preventable deaths in women. This has been readily observed in low-income countries despite having the healthcare expertise to prevent, screen, and treat women with the disease.[23] As a result, global partners created the Cervical Cancer Elimination Modelling Consortium (CCEMC) to determine the benefits and risks of multiple vaccination, screening, and treatment strategies.[24] To determine the most efficient and cost-effective strategy, the CCEMC developed a model using a 100-year time frame. This model predicted that a vaccination program targeting only girls vaccinated at 9 years of age could reduce cervical cancer by 99% (range: 89–100%) in low- and middle-income countries (LMICs), assuming a coverage rate of 90% and a threshold of ≤ 10 cases per 100,000 women-years.[25] Furthermore, the European Centre for Disease Prevention and Control (ECDC) suggested that increasing vaccination coverage among girls and boys could be cost-effective in preventing cervical disease in women.[26]

With this goal in mind, an analysis of all available information on HPV vaccination and cervical cancer prevention was required to inform further discussions on HPV vaccination strategies. Here, we summarize the results of a systematic literature review (SLR) conducted to estimate the reduction in HPV infections, pre-cancer lesions, and cervical cancer following the introduction of HPV vaccines for females. This review reports the published efficacy, effectiveness, health impact, duration of protection, and safety profile of available bivalent (Cervarix and Cecolin), quadrivalent, and 9-valent (Gardasil and Gardasil 9, respectively) HPV vaccines. To enhance the accessibility of this manuscript, a concise visual representation of the research can be found in the graphical abstract.

Methods

Search strategy

A SLR was conducted according to the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) guidelines.[27] In line with the PRISMA guidelines, a search strategy was developed based on the modified Population, Intervention, Comparison, and Outcomes (PICO) methodology and the use of Boolean operators to answer the following research question: What is the clinical effect of HPV vaccines on the reduction of infection, precursor lesions, and cervical cancer? The investigated outcomes included efficacy (based on data from controlled clinical trials), effectiveness (based on data from real-world settings), public health impact (such as herd immunity and reduction of cervical cancer), duration of protection, and safety profile (including short- and long-term adverse events) of HPV vaccines. The search was conducted on 02/01/2022 in three electronic databases (Medline [via PubMed], Embase, and Cochrane) using a comprehensive set of search terms (Supplementary Tables S1–S6). This review has not been registered with any database due to the use of previously published data in the public domain.

Study selection and data extraction

The population of interest included females ≥9 years of age, and the intervention studied was HPV vaccines, which were compared to the unvaccinated cohort, placebo, or other HPV vaccines. Vaccines studied included Cervarix, Cecolin, Gardasil, and Gardasil 9. Eligible studies included RCTs and observational studies, which assessed the outcomes described in the search strategy. In this review, the vaccine effect was defined as estimates of the reduction in HPV infection, precursor lesions, or cervical cancer at the population level over time in vaccine-eligible individuals (regardless of vaccination status). Studies were published between 1/01/2006 (the year of marketing the first HPV vaccine) and 1/31/2022 (Supplementary Table S7). In cases where multiple articles by the same author or authors analyzing the same cohort of patients and outcome variables were identified, the most recent and comprehensive data were included.

The eligibility of the retrieved articles was assessed through a two-phase screening process and a full-text review by two reviewers (N.M and M.Y). Any discrepancy between the reviewers was mutually resolved or decided by a third reviewer (I.O). Finally, data were extracted from the final list of eligible publications based on a priori established criteria.

Quality assessment

The methodological quality and risk of bias in the shortlisted studies were determined using the Cochrane checklist for randomized trials.[28] For non-randomized studies, the risk of bias was assessed based on the ROBINS-I checklist.[29]

Role of the funding source

GSK funded this SLR and was involved in all stages of study conduct, including analysis of the data. GSK also took charge of all costs associated with the development and publication of this manuscript.

Results

The studies included in this review describe the efficacy, effectiveness, public health impact, duration of protection, and safety profile of the four licensed HPV vaccines (Cervarix, Cecolin, Gardasil, and Gardasil 9) from 2006 to 2022. The search protocol shortlisted 1,136 publications (641 in PubMed, 169 in Cochrane, 322 in Embase, and 4 through hand search). From these, 238 duplicate studies were identified and excluded. During the screening process, 526 studies were excluded as the title or abstract was irrelevant to the review. The full texts of the remaining 372 publications were analyzed, and 54 studies were selected for this review (Figure 1). Data from these studies were elaborated in a Microsoft Excel data matrix. Results were presented according to the study type classified based on the methodology used: randomized control trials, observational studies and post-implementation in NIP or Regional Immunization Programs (RIPs). Key findings

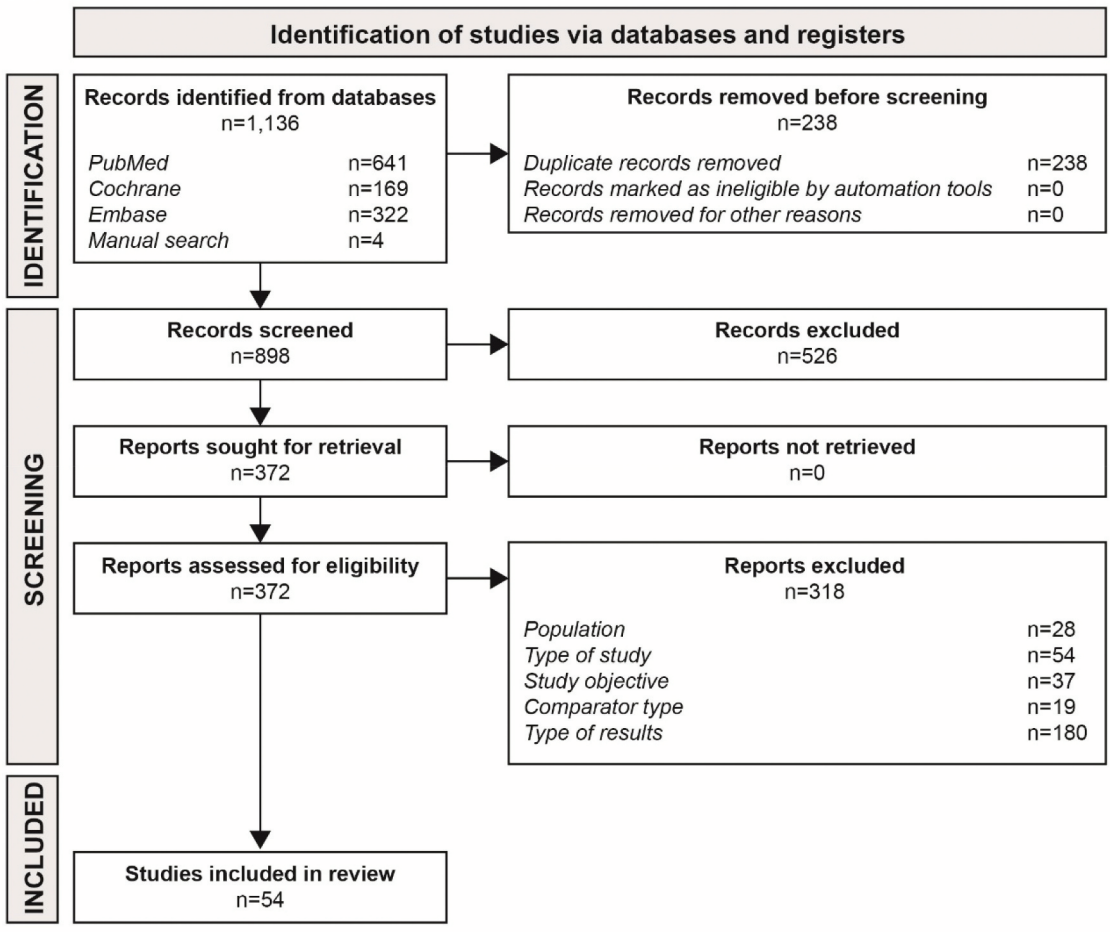

Figure 1. PRISMA flow diagram.

were summarized, clinical implications were discussed, and limitations were reported.

In total, 54 studies were identified, sorted by year of publication, and characterized by country, study type, population, and comparator (Table 1).[30–83] Among these, 20 studies (37%) were RCTs.[30,34,35,38,46–48,55,57,63,63,69,70,74–76,78,79,81,83] The remaining 34 studies (63%) were observational studies on vaccine effectiveness (10 studies),[31,33,39–41,44,57,62,64,68] health impact (14 studies on implementing HPV vaccines in NIP/RIP programs),[32,37,50,51,53,54,59–61,66,67,71,80,82] or vaccine safety profile (10 studies).[36,42,43,45,49,52,56,58,72,73,77] In total, 19 studies (35%) included Cervarix,[35,36,38,40,42,44,47,48,52,54,56,63,66,68,70,73,79,80,83] 22 studies (41%) included Gardasil,[30,32–34,37,39,46,50,51,53,55,59–61,65,69,71,74,75,77,78,82] one study (2%) included Gardasil 9,[57] eight studies (15%) analyzed both Cervarix, and Gardasil,[31,41,43,45,58,62,64,72] two studies (4%) analyzed Cervarix, Gardasil, and Gardasil 9,[49,67] one study (2%) analyzed Cecolin,[81] and one study (2%) analyzed HPV16 recombinant major capsid (L1) VLP vaccines (Table 1).[76]

Focusing on the comparators used, 19 studies (35%),[32,33,36,41,45,51–54,59,60,62,66–68,70,71,80,82] compared the vaccinated cohort to the unvaccinated cohort while two studies (4%) compared vaccination using different numbers of doses.[30,50] The comparator was placebo in 15 studies (28%),[31,34,35,38,39,46,48,55,57,63,69,75,76,78,81] and an active comparator in one study (2%).[61] There was no comparator in 16 studies (30%).[37,40,42–44,47,64,72–74,77,83] In one study (2%),[79] two different scenarios were assessed where the comparator was placebo in one scenario and the unvaccinated cohort in the other (Table 1).

Geographically, the 54 studies had a global representation, including studies conducted in Japan ($n = 6$),[41,45,46,62,64,68] Canada ($n = 5$),[33,37,53,72,82] the United States ($n = 3$),[49,59,76] China ($n = 3$),[47,63,81] the United Kingdom ($n = 2$),[54,61] Sweden ($n = 2$),[60,71] Finland ($n = 2$),[36,70] India ($n = 2$),[30,42] Colombia ($n = 2$),[51,74] Denmark ($n = 2$),[43,67] Netherlands ($n = 2$),[44,52] and Brazil ($n = 2$).[48,77] Australia,[50] Costa Rica,[79] France,[58] Iceland,[34] Iran,[65] Italy,[56] Mexico,[69] Portugal,[32] Scotland,[66] and Spain[80] were represented by one study each. Only one study reported multiple European countries,[75] while ten studies reported multiple countries from various regions.[31,35,38–40,55,57,73,78,8] Participants ranged in age from 9 to 69 years of age, with 30 studies (56%) analyzing participants between 14 and 26 years of age.[31,32,34,38–41,44–48,51,52,55,57,59,61,63,64,68–71,75,76,78–80,83] In 22 studies (41%),[30,33,35–37,42,43,50,53,54,56,58,60,62,65–67,62,72,74,77,81,82] the participants were outside the 14–26 years of age group. The age group was not available for two studies (4%).[49,73] Baseline characteristics of the studies included in this SLR are summarized in Table 1.

A total of 20 RCTs were analyzed, which reported the results on vaccine efficacy from 2006 to 2022.[30,34,35,38,46–48,55,63,65,69,70,75,76,78,79,81,83] Among these, ten studies reported

Table 1. Baseline study characteristics.

Randomized studies					
Hu[63]	China	A post-hoc of randomized, controlled trial	871 women (18–25 years)	Cervarix	Placebo
Basu[30]	India	A longitudinal, prospective, cohort study.	17,729 women (10–18 years)	Gardasil	Different doses (0,1,2,3)
Porras[79]	Costa Rica	Costa Rica HPV Vaccine Trial (CVT): randomized, double-blinded Long-term follow-up (LTFU) phase: non-randomized, observational, unblinded	CVT: 7,466 women LTFU: 2,836 women (18–25 years)	Cervarix	Control for CVT and unvaccinated for LTFU
Karimi-Zarchi[65]	Iran	A randomized controlled trial	328 women (21–45 years)	Gardasil	–
Qiao[81]	China	A multicenter, randomized, double-blind, controlled clinical trial	7,372 women (18–45 years)	Cecolin	Placebo
Giuliano[57]	Several countries	A double-blind, 4vHPV vaccine-controlled, dose-ranging study comparing with historic placebo by direct comparison	14,000 women (16–26 years)	Gardasil 9	Placebo
Zhu[47]	China	A follow-up of a Phase II/III, multicenter, double- blind, randomized, controlled study	6,081 women (18–25 years)	Cervarix	–
Lehtinen[70]	Finland	A cluster-randomized follow-up study (PATRICIA)	2,465 vaccinated and 15,627 unvaccinated women (16–19 years)	Cervarix	Unvaccinated
Skinner[35]	Several countries	A phase 3, multinational, double-blind, randomized controlled trial (VIVIANE)	5,752 women (26–46 + years)	Cervarix	Placebo
Luna[74]	Colombia	A randomized, placebo-controlled, double-blind trial	1,910 women (24–45 years)	Gardasil	–
Yoshikawa[46]	Japan	A randomized double-blind placebo-controlled phase II trial	1,030 women (18–26 years)	Gardasil	Placebo
Roteli-Martins[48]	Brazil	A randomized clinical trial, placebo-controlled study	436 women (15–25 years)	Cervarix	Placebo
Szarewski[38]	Several countries	A follow-up of a Phase III, double-blind, randomized, controlled, multicenter study (PATRICIA)	TVC Vaccine: 9,319 women Control: 9,325 women (15–25 years)	Cervarix	Placebo
Romanowski[83]	Several countries	A double-blind, randomized, placebo-controlled study	1,113 women(15–25 years)	Cervarix	–
Olsson[78]	Several countries	A Phase II/Phase III, randomized, multi-center, double blind, placebo-controlled study	2,617 women (16–26 years)	Gardasil	Placebo
Lazcano-Ponce[69]	Mexico	A post-hoc analysis of Phase III Trial (FUTURE I/II)	679 women (18–23 years)	Gardasil	Placebo
Majewski[75]	Several countries	A follow-up of a Phase III, double-blind, randomized, controlled, multicenter study	9,265 women (16–24 years)	Gardasil	Placebo
Sigurdsson[34]	Iceland	A Phase III, double-blind, randomized, controlled, multicenter study	710 women (18–23 years)	Gardasil	Placebo
FUTURE II Study Group[55]	Several countries	Two randomized, placebo-controlled trials	17,622 women (15–26 years)	Gardasil	Placebo
Mao[76]	US	A randomized, double-blind, placebo-controlled trial	2,391 women (16–23 years)	HPV16 L1 VLP vaccine	Placebo
Observational studies					
Hiramatsu[62]	Japan	A multicenter, prospective cohort study (OCEAN)	2,814 women (12–18 years)	Cervarix and Gardasil	Unvaccinated
Tozawa-Ono[41]	Japan	A retrospective multi-municipality study	11,903 women (20–25 years)	Cervarix and Gardasil	Unvaccinated
Verma[42]	India	A pilot interventional study	302 cases (9–26 years)	Cervarix	–
Ikeda[64]	Japan	A nationwide case-control study	14,779 women (20–24 years)	Cervarix and Gardasil	–
Mauro[77]	Brazil	A retrospective, descriptive study	3,390,376 hPV vaccine doses (9–13 years)	Gardasil	–
Ryser[31]	Several countries	A post-hoc analysis of Phase III trials	PATRICIA study (AS04-HPV) Total vaccinated cohort (TVC) 17,292 women (15–25 years) FUTURE I/II studies (4vHPV) Intention-to-treat cohort (ITT) 17,160 women (15–26 years)	Cervarix and Gardasil	Placebo
Yaju[45]	Japan	A Nagoya City's surveillance data study	30,793 women (15–21 years)	Cervarix and Gardasil	Unvaccinated
Bonaldo[49]	US	A vaccine safety surveillance data study	55,356 Case Safety Reports	Cervarix, Gardasil and Gardasil 9	–
Kudo[68]	Japan	An interim analysis of an ongoing cross-sectional study	2,197 women (20–22 years)	Cervarix	Unvaccinated
Ward[43]	Denmark	A retrospective observational study	976 women (12–25 years)	Cervarix and Gardasil	–

(*Continued*)

Table 1. (Continued).

Randomized studies					
Sarr[33]	Canada	A prospective cohort study (HERITAGE)	1,051 pregnant women (27–32 years)	Gardasil	Unvaccinated
Skufca[36]	Finland	An observational retrospective nationwide register-based cohort study	240,605 women (11–15 years)	Cervarix	Unvaccinated
Donken[52]	Netherlands	A prospective cohort study	1,635 women (14–16 years)	Cervarix	Unvaccinated
Woestenberg[44]	Netherlands	An observational post marketing study (PASSYON)	1,087 women (16–24 years)	Cervarix	–
López-Fauqued[73]	Several countries	A pregnancy exposure registry study	306 pregnancy exposure reports	Cervarix	–
Grimaldi-Bensouda[58]	France	A systematic prospective case-referent study	Cases:510 Referents: 1,953 (11–25 years)	Cervarix and Gardasil	–
Tota[40]	Several countries	A pooled analysis of two randomized trials (Costa Rica and PATRICIA)	21,596 women (CVT: 18–25 years PATRICIA: 15–25 years)	Cervarix	–
Liu[72]	Canada	A population-based study	195,270 women (9–24 years)	Cervarix and Gardasil	–
Gasparini[56]	Italy	A post-licensure study	4,643 women (12–26 years)	Cervarix	–
Tay[39]	Several countries	Three phase III clinical trials	814 women (16–26 years)	Gardasil	Placebo
Post NIP implementation					
Combita[51]	Colombia	A comparative cross-sectional study	3,273 women (18–25 years)	Gardasil	Unvaccinated
Falcaro[54]	UK	A register-based observational study	27,946 women diagnosed of cervical cancer and 318,058 of CIN3 (20–30 years)	Cervarix	Unvaccinated
Kjaer[67]	Denmark	A nationwide cohort study	867 689 women (17–30 years)	Cervarix, Gardasil and Gardasil 9	Unvaccinated
Donken[53]	Canada	An ecological study	Number of Pap smears 16–19 years: 21,880 and 1,456 20–23 years: 39,340 and 9,015 24–28 years: 54,867 and 35,736	Gardasil	Unvaccinated
Lei[71]	Sweden	A population-based cohort study	796,014 women (17–22 years)	Gardasil	Unvaccinated
Saldanha[32]	Portugal	A retrospective, cross-sectional study	2,183 women (14–24 years)	Gardasil	Unvaccinated
Racey[82]	Canada	A school-based HPV immunization program study	192,659 women (9–18 years)	Gardasil	Unvaccinated
Brotherton[50]	Australia	A national cohort study	250,648 women (12–15 years)	Gardasil	Different doses (0,1,2,3)
Purriños-Hermida[80]	Spain	A post-vaccination study	745 women (18–26 years)	Cervarix	Unvaccinated
Kavanagh[66]	Scotland	A cross-sectional study	8,708 cytology samples (12–13 years)	Cervarix	Unvaccinated
Herweijer[60]	Sweden	A register-based cohort study	1,333,691 women (13–29 years)	Gardasil	Unvaccinated
Smith[37]	Canada	A population-based retrospective cohort study	260,493 women (12–14 years)	Gardasil	–
Hariri[59]	US	An observational cohort study	7,346 women (20–24 years)	Gardasil	Unvaccinated
Hibbitts[61]	UK	A pseudo-anonymous prospective cohort study	13,306 females (20–22 years)	Gardasil	Cervarix

4vHPV: quadrivalent human papillomavirus vaccine; AS04, aluminum salt- and TLR4 agonist-based adjuvant system; CIN3, cervical intraepithelial neoplasia grade 3; HPV: Human papillomavirus; L1, L1 major capsid protein; UK: United Kingdom; US: United States; VLP, virus-like particle.
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vaccine efficacy against HPV types 16/18 infections,[30,35,38,47,48,63,70,79,81,83] nine studies reported vaccine efficacy against HPV types 6/11/16/18 infections,[34,46,55,57,65,69,74,75,78] and one study reported vaccine efficacy against HPV type 16 infections (Table 2).[76] Additionally, ten out of the 20 RCTs reported duration of protection with a follow-up period ranging from 2 to 11 years.[47,48,65,69,70,74,75,78,79,83] Overall, based on the results of these

Table 2. VE against HPV type-related infections, persistent infection, CIN grade 1, 2, and 3 lesions and cervical cancer as reported in RCTs.

Author, Year	Results								
Hu[63]	**2vHPV - VE against HPV 16/18/31/33/45 infections in women with HR-HPV infections at baseline**								
	Women DNA-positive to any of 14 HR-HPV species (HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68) at Month 0						**Vaccinated**	**Control**	**VE %, (95% CI)**
	Incident infection with:					HPV 16/18	13	45	74.7% (52.2 to 87.5)
						HPV 31/33/45	31	61	55.5% (30.3 to 72.1)
	12-month persistent infection with					HPV 16/18	0	8	100% (47.2 to 100)
						HPV 31/33/45	9	11	25.0% (-99.1 to 72.5)
	CIN2+					HPV	0	5	
Porras[79]	**2vHPV - VE against HPV 16/18 associated CIN2+ and CIN3+ in the analytic cohort at year 11**								
	At year 11				**CIN2+**			**CIN3+**	
				Vaccinated	**Unvaccinated**		**Vaccinated**	**Unvaccinated**	
	Number of women included			1,913	2,237		1,913	2,237	
	Women with CIN			0	34		0	18	
	Cumulative rate per 100 women (95% CI)			0.08 (0.01 to 0.29)	3.06 (2.42 to 3.82)		0.08 (0.01 to 0.29)	1.56 (1.11 to 2.13)	
	Cumulative VE (95% CI)			97.4 (88.0 to 99.6)	94.9 (73.7 to 99.4)		–	–	
Karimi-Zarchi[65]	**4vHPV - Efficacy of the HPV vaccine in women with CIN after 2 years of follow-up**								
				Post-injection condition of the lesion after 2 years of follow-up					
				Normal (%)	**CIN1**		**CIN2/3**	**Efficacy**	**P value**
	CIN1	**Control (N = 35)**		16 (45.7%)	19 (54.3)		–	54.9	0.02
		Two or more doses of vaccination (N = 45)		34 (75.6%)	11 (24.4)		–	–	–
	CIN2	**Control (N = 35)**		14 (40%)	–		21 (60)	63.3	0.01
		Two or more doses of vaccination (N = 50)		39 (78%)	–		11 (22)	–	–
	CIN3	**Control (N = 34)**		14 (41.2%)	–		20 (58.2)	52.5	0.03
		Two or more doses of vaccination (N = 43)		31 (72.1%)	–		12 (27.9)	–	–
Qiao[81]	**VE against genital lesions, PI, or incident infection associated with HPV 16/18**								
	Endpoint	**Vaccine group**				**Control group**			
		Total participants	Person-years at risk	No. of cases	Rate	Total participants	Person-years at risk	No. of cases	Rate	VE, % (95% CI)
	High grade lesion of the cervix, vagina, and vulva related to HPV 16/18 (mITT)	3,386	9,304.1	0	0	3,386	9,291.1	10	0.1	100.0% (55.4 to 100.0)
	Persistent infection >6-month duration related to HPV 16 or 18 (mITT)	3,313	9,219.9	1	0.01	3,330	9,113.4	48	0.5	97.9% (88.0 to 99.9)
	Incident infection related to HPV 16 or 18 (mITT)	3,388	9,263	45	0.5	3,391	9,161.6	153	1.7	70.9% (59.2 to 79.6)
Zhu[47]	**2vHPV – VE against CIN and PI associated with HPV 16 and/or HPV 18 in women who were HPV DNA-negative and seronegative at baseline for the corresponding HPV type (ATP-E and TVC-E) up to 72 months of follow-up**								
				ATP-E			**TVC-E**		
			Vaccine	**Control**	**% VE**	**Vaccine**	**Control**	**% VE (95% CI)**	
	HPV 16/18 endpoint		**N/n**	**N/n**	**(95% CI)**	**N/n**	**N/n**		
	CIN2+		2,524/1	2,535/8	87.3% (5.3 to 99.7)	2,567/1	2,587/9	88.7% (18.4 to 99.7)	
	CIN1+		2,524/1	2,535/15	93.2% (56.1 to 99.8)	2,567/2	2,587/17	88.0% (49.6 to 98.7)	
	CIN1+/6M PI		2,524/2	2,535/60	96.7% (87.4 to 99.6)	2,567/5	2,587/78	93.6% (84.4 to 98.0)	
	6M PI		2,480/2	2,488/54	96.3% (85.9 to 99.6)	2,551/4	2,571/71	94.4% (84.9 to 98.5)	
	12M PI		2,425/1	2,455/32	96.9% (81.1 to 99.9)	2,516/3	2,536/41	92.6% (76.9 to 98.5)	

(*Continued*)

Table 2. (Continued).

Author, Year	Results
Lehtinen[70]	**2vHPV – VE (95% CI) against CIN3+ associated with vaccine and/or non-vaccine HPV types in women vaccinated in 2004/2005 with the HPV 16/18 vaccine between ages 16 and 17 years and in an age-aligned control cohort of originally 18–19 years of age women passively followed via Finnish Cancer Registry for up to 10 years post vaccination**

CIN3+	Vaccinated (N = 2,465)	Control (N = 15,627)	VE (95% CI)
HPV 16/18	3	43	27 (-140 to 74)
HPV 31/33/45	–	13	100 (-120 to 100)
All detected HPV types	3	46	56 (-38 to 84)
Total	4	79	66 (8.4 to 88)

Skinner[35] **2vHPV – VE and number of cases prevented for the combined primary endpoint, 6M PI, CIN1+, CIN2+, and ASC-US+ associated with HPV 16/18**

	Vaccinated			Control			Efficacy (97.7% CI)	Number cases prevented per 100,000 woman-years (97.7% CI)
	N	Cases	Rate	N	Cases	Rate		
Combined primary endpoint (6M PI or CIN1+)	1,898	7	0.11	1,854	36	0.58	81.1% (52.1 to 94.0)	474 (252 to 751)
6M PI	1,859	6	0.09	1,822	34	0.55	82.9% (53.8 to 95.1)	459 (245 to 730)
CIN1+	1,898	1	0.02	1,854	7	0.11	86.1% (-35.4 to 99.9)	98 (-8 to 248)
CIN2+	1,898	0	0	1,854	4	0.06	100% (-100.7 to 100.0)	65 (-17 to 192)
ASC-US+	1,898	2	0.03	1,854	31	0.51	93.7% (71.5 to 99.5)	475 (291 to 731)
HPV 16	2,126	6	0.08	2,094	34	0.48	82.8% (53.6 to 95.1)	–
HPV 18	2,160	2	0.03	2,127	11	0.15	82.2% (2.5 to 98.7)	–
Composite HPV 31/33/35/52/58	2,179	63	0.87	2,154	80	1.12	22.9% (-14.4 to 48.4)	–

Yoshikawa[46] **4vHPV – Efficacy of quadrivalent vaccine against PI or disease associated with HPV 6/11/16/18 in the per-protocol population**

Types of PI and genital disease	Vaccine				Placebo				Efficacy estimate (%) 95% CI
	N	No. cases	Person-years at risk	Incidence rate (/100 person-years at risk)	N	No. cases	Person-years at risk	Incidence rate (/100 person-years at risk)	
HPV 6-, 11-, 16- or 18-related	419	3	776.4	0.4	422	24	769.1	3.1	87.6% (59.2 to 97.6)
HPV 6- or 11-related	400	2	743	0.3	376	7	698.5	1	73.1% (-41.1 to 97.3)
HPV 6 related	400	2	743	0.3	376	7	698.5	1	73.1% (-41.1 to 97.3)
HPV 11 related	400	0	746	0	376	0	704	0	NA
HPV 16- or 18-related	415	1	771.9	0.1	417	18	763.8	2.4	94.5% (65.2 to 99.9)
HPV 16 related	371	0	689.5	0	378	11	698	1.6	100% (59.7 to 100.0)
HPV 18 related	403	1	750.5	0.1	396	7	734.9	1	86% (-8.9 to 99.7)

Roteli-Martins[48] **2vHPV – VE against HPV 16/18 associated endpoints up to 8.4 years after first vaccination**

	HPV 16/18 vaccine		Placebo		VE, % (95% CI)	HPV 16/18 vaccine		Placebo		VE, % (95% CI)
	N	n	N	n		N	n	N	n	
Incident infection	176	0	122	5	100% (25.6 to 100.0)	193	3	175	46	95.1% (84.6 to 99.0)
PI (6M)	178	0	144	0	–	193	0	175	17	100% (79.8 to 100)
PI (12M)	178	0	152	0	–	193	0	175	9	100% (56.1 to 100)
≥ ASC-US	198	0	165	1	100.0% (-3,131.1 to 100.0)	224	1	219	28	96.9% (81.0 to 99.9)

(*Continued*)

Table 2. (Continued).

Author, Year	Results									
	≥ LSIL	198	0	174	1	100.0% (-3,309.9 to 100.0)	224	1	219	17	94.6% (65.7 to 99.9)
	CIN1+	199	0	182	0	–	219	0	212	7	100% (35.0 to 100)
	CIN2+	199	0	184	0	–	219	0	212	3	100% (-128.0 to 100)
Szarewski[38]	**2vHPV – VE against virological and histopathological endpoints associated with HPV 16/18 (by PCR) in women who were HPV 16/18 DNA negative, regardless of serological status (TVC)**										
			Vaccine				Control			VE % (96.1% CI)	
			n/N		AR		n/N	AR			
	Incident infection		437/8,806		1.78		1,535/8,800	6.62			73.1% (69.9 to 76.0)
	6-M PI		88/8,491		0.36		746/8,490	3.14			88.7% (85.7 to 91.1)
	12-M PI		63/8,345		0.26		387/8,335	1.61			84.1% (78.9 to 88.2)
	CIN1+		17/8,610		0.07		156/8,619	0.63			89.1% (81.6 to 94.0)
	CIN2+		8/8,610		0.03		105/8,619	0.42			92.4% (84.0 to 97.0)
Romanowski[83]	**2vHPV – Cumulative number of endpoint events associated with HPV 16/18 up to 6.4 years of follow-up**										
	Endpoint		**Cervarix**				**Placebo**				VE (%; 95% CI)
			Total number of women		Women reporting ≥1 event		Total number of women	Women reporting ≥1 event			
	Incident infection with HPV 16/18		401		4		372	70			95.3% (87.4 to 98.7)
	≥ASC-US		505		2		497	54			96.7% (87.3 to 99.6)
	CIN1+		481		0		470	15			100% (73.4 to 100)
	CIN2+		481		0		470	9			100% (51.3 to 100)
	VE against cytological and histopathological endpoints independent of HPV DNA in lesions up to 6.4 years of follow-up										
	Endpoint		**Cervarix**				**Placebo**				**VE (%; 95% CI)**
			Total number of women		**Women reporting ≥1 event**		**Total number of women**	**Women reporting ≥1 event**			
	≥ASC-US		505		118		497	162			35.4% (17.6 to 49.5)
	≥LSIL		505		62		497	93			39.4% (15.6 to 56.8)
	CIN1+		505		20		497	38			50.3% (12.5 to 72.6)
	CIN2+		505		5		497	17			71.9% (20.6 to 91.9)
Olsson[78]	**4vHPV - Efficacy against HPV 6/11/16/18-related CIN1 or worse (seropositive, DNA negative subjects) followed for an average of 40 months**										
			Vaccine				**Placebo**				
			n		**Cases**		**n**	**Cases**			**Efficacy (%) 95% CI**
	HPV 6/11/16/18		1,243		0		1,283	7			100% (28.7 to 100)
	CIN1		1,243		0		1,283	6			100% (<0 to 100)
	CIN2 or worse		1,243		0		1,283	4			100% (<0 to 100)
	CIN3 or worse		1,243		0		1,283	4			100% (<0 to 100)
Lazcano-Ponce[69]	**4vHPV - Efficacy against HPV 6/11/16/18-related CIN for the Mexican and non-Mexican subpopulations of FUTURE I and II up to 3.35 years of follow-up**										
	Prevention of HPV 6/11/16/18 related CIN					**Mexican**					**Non-Mexican (N=16,919)**
			Vaccine (N=339)				**Placebo (N=339)**			**VE % (95% CI)**	
			N	**Cases**	**Rate**	**N**	**Cases**	**Rate**			
	CIN1		270	2	0.3	271	4	0.6		100.0% (<0.0 to 95.5)	97.0% (92.9 to 99.0)
	CIN2		270	0	0	271	3	0.4		100.0% (<0.0 to 100.0)	100.0% (94.5 to 100.0)
	CIN3		270	0	0	271	1	0.1		100.0% (<0.0 to 100.0)	97.0% (92.9 to 99.0)
	AIS		270	0	0	271	2	0.3		100.0% (<0.0 to 100.0)	100.0% (<0.0 to 100.0)
	HPV 6		252	0	0	239	1	0.2		100.0% (<0.0 to 100.0)	100.0% (91.6 to 100.0)
	HPV 16		229	2	0.3	239	6	0.9		100.0% (<0.0 to 96.6)	95.5% (89.9 to 98.4)
Majewski[75]	**4vHPV - VE against HPV 6/11/16/18 related cervical stratified by severity in the per-protocol European population up to 36 months of follow-up**										
			Vaccine (N=4,555)				**Vaccine (N=4,551)**				**Efficacy (%) 95% CI**
			N	**Cases**	**Rate**	**N**	**Cases**	**Rate**			
	CIN1 or worse		4,043	3	0	4,043	71	0.7			95.8% (87.2 to 99.2)
	CIN2 or worse		4,043	0	0	4,043	38	0.4			100.0% (89.8 to 100.0)
	CIN3		4,043	0	0	4,043	26	0.3			100.0% (84.8 to 100.0)
	AIS		4,043	0	0	4,043	2	0			100.0% (< 0.0 to 100.0)

(*Continued*)

Table 2. (Continued).

Author, Year	Results						
Sigurdsson[34]	**4vHPV - Women enrolled in the Future II study in Iceland at age 18–23. Distribution of cytological and histological results and procedures counted per woman starting M12 with no abnormal smear before that month (mITT)**						
		Age 20–23 at enrolment			**Age 18–19 at enrolment**		
		Number of women		**P-value**	**Number of women**		**P-value**
		Gardasil	Placebo		Gardasil	Placebo	
	First abnormal Pap at month ≥12	34	40	0.71	25	45	0.007
	HSIL+	2	4	0.47	1	3	0.33
	LSIL	21	26	0.64	12	33	0.001
	ASCUS	11	10	0.67	12	9	0.44
	<3 Abnormal Pap	29	29	0.72	22	32	0.16
	>2 Abnormal Pap	5	11	0.17	3	13	0.01
	1 Colposcopy cervix	13	18	0.49	11	21	0.72
	>1 Colposcopy cervix	4	7	0.44	2	9	0.035
	CIN 2+3	7	7	0.87	3	7	0.22
	≤CIN1	10	18	0.18	10	23	0.02
FUTURE II Study Group[55]	**4vHPV - Analysis of prophylactic efficacy against CIN related to HPV 6/11/16/18 in a subset of subjects who were PCR positive or seropositive for at least 1 HPV vaccine type at day 1**						
		Vaccine recipients			**Placebo recipients**		**Observed efficacy (CI), %**
		N	Cases	Rate	N	Cases	Rate	
	HPV 6/11/16/18	2,188	4	0.1	2,182	45	0.8	91.1% (75.7 to 97.7)
	CIN1	2,188	4	0.1	2,182	34	0.6	88.3% (67.1 to 97.0)
	CIN2	2,188	0	0	2,182	12	0.2	100.0% (64.0 to 100.0)
	CIN3/AIS	2,188	0	0	2,182	10	0.2	100.0% (55.3 to 100.0)
Mao[76]	**HPV 16 L1 VLP - Analysis of efficacy for persistent HPV 16 infection and HPV 16-related CIN**						
		Vaccine (N = 1,193)			**Placebo (N = 1,198)**		**Observed**
		N	**Cases**	**Rate**	**N**	**Cases**	**Rate**	**Efficacy (%) 95% CI**
	Persistent HPV 16 infection with HPV 16-related CIN	755	0	0	750	24	1.1	100% (85 to 100)
	Persistent HPV16 infection without HPV 16-related CIN	755	0	0	750	68	3	100% (95 to 100)
	CIN1	755	0	0	750	14	0.6	100% (71 to 100)
	CIN2	755	0	0	750	7	0.3	100% (33 to 100)
	CIN3	755	0	0	750	6	0.3	100% (18 to 100)
Basu[30]	**4vHPV - VE for the prevention of persistent HPV infections**						
	Adjusted VE (95% CI)	**Single dose cohort**		**Two-dose cohort**		**Three-dose cohort**	
	PI HPV 16 and 18	95.4% (85.0 to 99.9)		93.1% (77.3 to 99.8)		93.3% (77.5 to 99.7)	
	Any PI HPV	35.4% (3.7 to 56.0)		36.7% (1.6 to 57.9)		39.3% (6.8 to 60.2)	
	CIN and invasive cancer detection						
			Unvaccinated			Vaccinated	
	CIN2/3		5			0	
	Invasive cancer		1			0	

(*Continued*)

Table 2. (Continued).

Author, Year	Results					
Giuliano[57]	**9vHPV - Effect of 9vHPV vaccine on the reduction in incidence of cervical disease (subjects PCR-negative to 14 HPV types at baseline)**					
		9vHPV vaccine (N = 4,365)		**Historic placebo (N = 5,887)**		**Reduction in incidence % (95% CI)**
	Endpoint	**Observed cases**	**Incidence per 10,000 person-years cases (95% CI)**	**Observed cases**	**Incidence per 10,000 person-years cases (95% CI)**	
	Subjects contributing to the analysis	4,229		5,756		
	Cervical disease, any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	4	2.5 (0.7 to 6.4)	315	159.7 (142.5 to 178.3)	98.4% (96.0 to 99.5)
	High-grade cervical disease, any of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58	2	1.3 (0.2 to 4.5)	141	71.0 (59.7 to 83.7)	98.2% (93.6 to 99.7)
	Effect of 9vHPV vaccine on the reduction in incidence of cervical disease stratified by baseline HPV status (mITT population)					
		Day 1 PCR-positive to ≥1 of the indicated HPV types		**Percent risk reductions (95% CI) [incidence rate (95% CI)[a] 9vHPV (N = 6,997): historic placebo (N = 8,748)]**		
		HPV 6, 11, 16, or 18	**HPV 31, 33, 45, 52, or 58**	**Related to HPV 6, 11, 16, or 18**	**Related to HPV 31, 33, 45, 52, or 58**	
	Cervical disease, any grade	No	No	99.0 (96.4 to 99.8) [1.1 (0.1 to 3.9): 106.4 (93.3 to 120.9)]	96.9 (93.4 to 98.7) [3.2 (1.2 to 7.0): 104.3 (91.3 to 118.6)]	
			Yes	97.4 (85.6 to 99.9) [3.9 (0.1 to 22.0): 154.4 (110.8 to 209.5)]	18.9 (-4.8 to 37.7) [420.9 (342.8 to 511.4): 519.1 (434.3 to 615.6)]	
		Yes	No	-2.2 (-32.7 to 20.7) [511.9 (423.0 to 614.0): 501.0 (416.7 to 597.3)]	95.1 (81.9 to 99.1) [8.3 (1.0 to 30.0): 168.3 (121.8 to 226.7)]	
			Yes	24.5 (-0.6 to 43.4) [663.4 (534.8 to 813.6): 879.1 (721.1 to 1,061.3)]	13.3 (-15.0 to 35.4) [682.3 (551.4 to 835.0): 787.0 (638.9 to 959.1)]	
	High-grade cervical disease	No	No	100 (96.1 to 100) [0.0 (0.0 to 2.0): 49.4 (40.6 to 59.6)]	95.3 (88.4 to 98.4) [2.1 (0.6 to 5.5): 45.8 (37.4 to 55.6)]	
			Yes	95.8 (76.9 to 99.8) [3.9 (0.1 to 22.0): 93.7 (60.6 to 138.3)]	6.8 (-32.6 to 34.6) [254.2 (195.3 to 325.2): 272.7 (213.4 to 343.4)]	
		Yes	No	-2.3 (-40.9 to 25.8) [333.6 (264.1 to 415.8): 326.2 (259.8 to 404.3)]	91.1 (67.5 to 98.5) [8.3 (1.0 to 30.0): 93.4 (59.9 to 139.0)]	
			Yes	12.7 (-24.3 to 38.7) [455.2 (352.0 to 579.1): 521.4 (404.9 to 661.0)]	-14.4 (-67.3 to 21.4) [462.9 (358.7 to 587.9): 404.5 (303.0 to 529.1)]	
Luna[74]	**4vHPV - Effectiveness of 4vHPV vaccination in women 24–45 years of age against HPV 6/11/16/18-related CIN or condyloma (cumulative incidence in the EVG, day 1 to year 6)**					
	Endpoint			**Early Vaccination Group (N = 1,910)**		
		N	**Cases**	**Person year at risk**	**Rate**	**95% CI**
	HPV 6/11/16/18-related CIN or condyloma	1,617	1	6,705.6	0	(0.0 to 0.1)
	CIN1	1,599	0	6,352.4	0	(0.0 to 0.1)
	CIN2+	1,599	1	6,349.8	0	(0.0 to 0.1)
	HPV 31/33/35/39/45/51/52/56/58/59-related CIN or condyloma	1,910	93	8,403.7	1.1	(0.9 to 1.4)
	CIN1	1,909	72	8,210.3	0.9	(0.7 to 1.1)
	CIN2+	1,909	40	8,296.4	0.5	(0.3 to 0.7)

A Estimated number of cases per 10,000 person-years of follow-up.

Abbreviations: 6 M: 6-month; 12 M: 12-month; 2vHPV: bivalent human papillomavirus vaccine; 4vHPV: quadrivalent human papillomavirus vaccine; 9vHPV: nonavalent human papillomavirus vaccine; AIS, adenocarcinoma in situ; AR, attack rate (100 person-year rate); ASC-US, atypical squamous cells of undetermined significance or greater; ATP-E, according-to-protocol cohort for efficacy; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN1 + , cervical intraepithelial neoplasia grade 1 or greater; CIN2 + , cervical intraepithelial neoplasia grade 2 or greater; DNA, deoxyribonucleic acid; HR, high risk; HPV, human papillomavirus; HSIL + , high-grade squamous intraepithelial lesion or greater; II, incident infection; HPV16 L1 VLP: human papillomavirus type 16 major capsid protein virus-like particles based vaccine; LSIL, low-grade squamous intraepithelial lesion or greater; mITT: modified intention to treat; NA, not applicable; n/N, number of subjects reporting at least one event in each group/number of subjects included in each group; N, number of participants included in each group; n, number of cases; No., number; PCR, polymerase chain reaction; PI, persistent infection; RCT, randomized clinical trial; TVC, total vaccinated cohort; TVC-E, total vaccinated cohort for efficacy; VE, vaccine efficacy.

RCTs, HPV vaccines demonstrated high efficacy over long follow-up periods against HPV vaccine-type-related persistent infection, cervical intraepithelial neoplasia (CIN) grade 1, 2, and 3 level lesions and adenocarcinoma in situ (AIS) (Table 2).[84]

A total of 24 studies reported data from observational studies on vaccine effectiveness and health impact from 2006 to 2022. Among these, nine studies (42%) reported vaccine effectiveness,[31,33,39–41,44,62,64,68] and 14 studies (58%) reported the impact of HPV vaccination post-implementation in NIPs/RIPs.[32,37,50,51,53,54,59–61,66,67,71,80,82] A summary of the results of each study is presented in Table 3. Among the 24 observational studies, 13 (54%) assessed vaccine impact on CIN,[31,39,41,50,53,54,59–62,64,71,82] while seven (29%) assessed overall vaccine effectiveness.[33,37,40,44,66,68,80] Six studies (25%) analyzed vaccine efficacy data from clinical trials (i.e., pooled analysis, clinical trial analysis, and a post-hoc analysis).[31,32,39,40,51,67] Of note, the total percentage of analyzed outcomes is superior to 100% since some studies reported multiple outcomes.

An analysis of the included studies reporting results after HPV vaccine implementation in the NIPs of different countries was performed. A total of 14 studies reported data post-vaccine implementation in NIPs,[32,37,50,51,53,54,59–61,66,67,71,80,82] among which eight studies described vaccine effectiveness or health impact based on an age-specific comparison between vaccinated and non-vaccinated females.[51,53,54,60,66,67,71,82] The remaining six studies described results based on HPV type-specific vaccine effectiveness or impact measures.[32,37,50,59,61,80] Overall, a lower risk of cervical cancer was observed among vaccinated females compared to non-vaccinated women (Table 3). Lei et al. and Kjaer et al. reported a substantial reduction in the incidence of cervical cancer in vaccinated females, especially in females vaccinated at younger ages.[67,71] Two studies also showed higher than natural titers against HPV 31/33/45, suggesting cross-protection against these genotypes.[66,80] Three studies revealed a significant decline in CIN rates after the introduction of HPV vaccines over a period of 4 to 14 years.[53,54,59] Among these, Falcaro et al. showed a 97% (95% confidence interval [CI] 96–98) reduction in grade 3 CIN (CIN3) lesions and a 87% reduction (95% CI 72–94) in cervical cancer among females vaccinated at 12–13 years of age.[54]

Among the studies published since 2006, 11 assessed the safety profile of HPV vaccines.[36,42,43,45,49,52,56,58,72,73,77] Among these, five studies (45%) analyzed the adjuvanted bivalent vaccine (Cervarix),[36,42,52,56,73] and one study (9%) examined the quadrivalent vaccine (Gardasil).[77] Both bivalent and quadrivalent vaccines were assessed in four studies (36%).[43,45,58,72] One study (9%) compared the quadrivalent, 9-valent, and adjuvanted bivalent vaccines.[49]

Four studies comparing Cervarix versus Gardasil described fatigue, dizziness, and headache as the most frequent nonspecific adverse events for both vaccines.[43,45,58,72] Among these, two studies also reported autoimmune diseases and venous thromboembolism following HPV vaccination.[58,72] Yaju et al.[45] reported memory impairment, dyscalculia, and involuntary movements following HPV vaccination. All four studies did not specify the particular vaccine being attributed to these side effects. The causality between HPV vaccination and these side effects could not be proven, with no biologically plausible mechanism of action identified. One study comparing Cervarix, Gardasil, and Gardasil 9 reported dizziness and syncope as the two most frequent adverse events in the vaccinated groups.[49] All these studies concluded that HPV vaccines maintain a positive benefit-risk ratio (Supplementary Table S8).

The methodological quality and risk of bias of the selected studies were analyzed. Among the 20 RCTs, 8 (40%) had a low risk of bias,[35,46,47,57,65,75,79,83] 9 (45%) had an unclear risk of bias,[30,34,55,69,70,74,76,78,81] and three studies (15%) had a high risk of bias (Supplementary Table S9).[38,48,63] Among the 34 observational studies, 28 (82%) had a critical risk of bias,[31–33,36,39,41–45,49–54,56,59–62,64,67,68,71,72,77,82] 3 (9%) had a low risk of bias,[40,58,73] and three (9%) had a moderate risk of bias,[37,66,80] (Supplementary Table S10). Given these varying degrees of bias, it is important to note that the observed magnitude of the observed effects is substantial, making it implausible that all of the observed effects could be attributed to bias alone.

Discussion

The incidence of cervical cancer has been reduced in many high-income countries through HPV screening and vaccination. However, the disease burden remains considerable due to uneven implementation, especially in LMICs. This disparity persists due to insufficient screening and treatment, vaccine availability, low vaccine coverage, and high vaccine costs. The coronavirus disease 2019 (COVID-19) further reduced HPV vaccine coverage in many countries. In 2019, the global coverage of HPV vaccination was 20%, and further decreased to 16% in 2021.[85]

In this SLR, 14 studies on the health impact of HPV vaccine implementation in NIPs were reviewed (Tables 2 and 3). Of these, eight reported vaccine effectiveness by comparing vaccinated and non-vaccinated females, while six focused on HPV type-specific measures. Overall, vaccinated women had a reduced risk of cervical cancer. Notably, Lei et al. and Kjaer et al. reported significant declines in the incidence of cervical cancer, particularly among women vaccinated at younger ages. Two studies on Cervarix demonstrated cross-protection against HPV genotypes 31/33/45, and three reported significant declines in CIN rates over 4 to 14 years. In addition, Falcaro et al. reported that the HPV immunization program in England markedly reduced cervical cancer and CIN3 incidence in eligible cohorts (women <30 years), especially for those vaccinated at age 12–13.[54] Multiple other studies consistently showed higher vaccine effectiveness (64–89.1%) for preventing HPV in females aged 12–17 years vs. >17 years (25–28.9%).[60,66,67,71] Another observation was that HPV vaccination not only offers cross-protection against multiple HPV types, but also contributes to herd immunity, reducing transmission and ultimately lowering the prevalence of HPV infection in the population.[66,80] However, despite vaccine availability, immunization programs can be hampered by

Table 3. Vaccine effectiveness toward HPV vaccine-type related infections, persistent infection, CIN grade 1, 2, and 3 lesions and cervical cancer as reported in the observational studies identified in this systematic literature review.

Author, year	Results					
Observational studies						
Hiramatsu[62]	**2vHPV and 4vHPV - Ratio of high-risk HPV, HPV 16/18 infection and incidence of CIN1, CIN2**					
			Unvaccinated		**Vaccinated**	**OR (95%CI)**
	High risk HPV		19.7%		12.9%	0.61 (0.38 to 0.98)
	HPV 16 and 18		4.9%		0%	0.06 (0.003 to 0.92)
	CIN1		1.3%		2.4%	1.90 (0.60 to 6.03)
	CIN2		0.5%		0%	0.57 (0.03 to 10.622)
Tozawa-Ono[41]	**2vHPV and 4vHPV - Clinical outcomes difference between vaccinated and unvaccinated**					
			Cases		**Cumulative rates**	
	Cervical intraepithelial neoplasia		**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**
	CIN1		29	136	1.4% (42/3,102)	2.1% (178/8,611)
	CIN2		10	28	0.42% (13/3,102)	0.49% (42/8,611)
	CIN3		3	14	0.096% (3/3,102)	0.163% (14/8,611)
	Cervical cancer screening results		**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**
	Negative for intraepithelial lesion or malignancy (NILM)		3,009	8,292	–	
	Atypical squamous cells of undetermined significance (ASC-US)		46	182	3.3% (103/3,112)	5.6% (496/8,788)
	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)		1	19	1.8% (57/3,112)	3.5% (314/8,788)
	Low-grade squamous intraepithelial lesion (LSIL)		48	223	1.7% (56/3,112)	3.3% (295/8,788)
	High-grade squamous intraepithelial lesion (HSIL)		8	72	0.26% (8/3,112)	0.81% (72/8,788)
Ryser[31]	**2vHPV and 4vHPV - VE (%) with 95% CI in Future I/II and Patricia trials**					
	Study			**Future I/II trials**		**Patricia trial**
				Total Vaccinated Cohort (Gardasil)	**Total Vaccinated Cohort-Naive**	**Total Vaccinated Cohort (Cervarix)**	**Total Vaccinated Cohort-Naive**
	CIN1	**HPV 16/18 including coinfections**		68.7% (61.3 to 74.9)	97.8% (93.3 to 99.5)	72.4% (62.7 to 79.8)	94.7% (87.2 to 98.3)
		Cross-protective efficacy including co-infections		11.5% (2.1 to 20)	15.5% (-0.6 to 29.1)	23.4% (13.3 to 32.4)	39.8% (26.3 to 51)
	CIN2	**HPV 16/18 including coinfections**		54.6% (40.6 to 65.6)	100% (91.9 to 100)	65.6% (54.5 to 74.3)	98.9% (93.9 to 100)
		Cross-protective efficacy including co-infections		10.7% (-6.6 to 25.3)	26.8% (-4.1 to 48.9)	23.1% (8.2 to 35.6)	47.5% (27.3 to 62.3)
	CIN3	**HPV 16/18 including coinfections**		45.1% (29.6 to 57.4)	100% (90.5 to 100)	44.2% (20 to 61.5)	100% (81.8 to 100)
		Cross-protective efficacy including co-infections		1.2% (-21.9 to 20)	13.1% (-39 to 45.9)	46.7% (24.1 to 63)	88.5% (62.4 to 97.8)
Kudo[68]	**2vHPV - Adjusted vaccine effectiveness against HPV infection in 1,454 study participants who were vaccinated before sexual debut**					
	Variable		**HPV positive No. (%)**	**Adjusted OR (95% CI)**	**Adjusted vaccine effectiveness (95% CI)**	**P value**
	HPV 16/18					
	Unvaccinated		10 (2.2%)	1 (reference)		
	Vaccinated		1 (0.1%)	0.06 (0.01 to 0.55)	93.9 (44.8 to 99.3)	0.01
	HPV 31/45/52					
	Unvaccinated		21 (4.6%)	1 (reference)		
	Vaccinated		13 (1.3%)	0.32 (0.14 to 0.75)	67.7 (24.9 to 86.1)	0.01
Tota[40]	**2vHPV - Overall efficacy of the HPV 16/18 vaccine against oncogenic and oncogenic/non-oncogenic HPV infections excluding types that the vaccine has shown evidence of efficacy against HPV 6/11/16/18/31/33/45/51/74**					
	HPV infection		**Vaccinated**		**Control**	**Rate difference (95% CI)**	**Efficacy (95% CI), %**
			No. of cases	Rate per 1,000 infection-years (95% CI)	No. of cases	Rate per 1,000 infection-years (95% CI)	
	Oncogenic HPV infection (types 35, 39, 52, 56, 58, 59, and 68/73)		5,247	13.2 (12.7 to 13.7)	5,842	14.8 (14.3 to 15.3)	1.6 (0.9 to 2.3)	10.8% (6.1 to 15.4)
	Oncogenic or non-oncogenic HPV infection (types 34, 35, 39, 40, 42, 43, 44, 52, 53, 54, 56, 58, 59, 66, 68/73, and 70)		9,866	2.8 (2.4 to 3.1)	10,548	3.0 (2.6 to 3.4)	0.2 (-0.3 to 0.7)	7.7% (-10.5 to 22.9)

(*Continued*)

Table 3. (Continued).

Author, year	Results				
Tay[39]	**4vHPV - Vaccine efficacy in preventing HPV 6/11/16/18-related lesions by lesion grade in 16- to 26-year-old Asian-Pacific women participating in phase 3 trials of HPV 6/11/16/18 VLP vaccine**				
		Vaccine groups (n=348)		**Placebo groups (n=353)**	**Efficacy (95% CI), %**
		No. of cases	No. of evaluable participants	No. of cases	No. of evaluable participants	
	CIN1	0	302	10	312	100% (54.2 to 100)
	CIN2	0	302	4	312	100% (-56.0 to 100)
	CIN3	0	302	1	312	100% (-3,926 to 100)
	AIS	0	302	0	312	–
Woestenberg[44]	**2vHPV - Vaccine effectiveness against pooled estimates, stratified by sexual activity when vaccination was offered and time since vaccination was offered**				
				VE (95%CI)	
		n (%)	**HPV 16/18**	**HR 9-valent types**	**All hrHPV (HPV 16/18/31/33/35/39/45/51/52/56/58/59)**
	Women not sexually active when vaccination was offered				
	Unvaccinated	303 (37.7%)			
	Vaccinated (≥1 dose)	501 (62.3%)	92.2 (83.2 to 96.4)	60.1 (47.1 to 70.0)	29.6 (13.4 to 42.7)
	Women (possibly) sexually active when vaccination was offered				
	Unvaccinated	119 (47.6%)			
	Vaccinated (≥1 dose)	131 (52.4%)	81.1 (52.1 to 92.5)	60.2 (36.2 to 75.2)	39.9 (16.3 to 56.8)
	Women offered vaccination <5 years ago				
	Unvaccinated	178 (43.1%)			
	Vaccinated (≥1 dose)	235 (56.9%)	83.2 (57.9 to 93.3)	50.7 (23.9 to 68.1)	33.0 (10.4 to 49.8)
	Women offered vaccination 5/6 years ago				
	Unvaccinated	244 (38.1%)			
	Vaccinated (≥1 dose)	397 (61.9%)	92.4 (83.6 to 96.5)	65.5 (53.9 to 74.1)	34.6 (19.0 to 47.2)
Ikeda S[64]	**2vHPV and 4vHPV - HPV vaccination status and effectiveness**				
				Cumulative number of cases (with histological result)	
		Controls	**Cases**	**CIN1+**	**CIN2+**	**CIN3+**
	Vaccination (+)	2,605	404	161	25	3
	Vaccination (-)	9,691	2,079	853	192	49
	OR		0.42	0.42	0.25	0.19
	Vaccine effectiveness		58.5%	57.9%	74.8%	80.9%
	(95% CI)		(0.34 to 0.50)	(0.31 to 0.58)	(0.12 to 0.54)	(0.03 to 1.15)
Sarr[33]	**4vHPV - Adjusted vaccine effectiveness and 95% CI for different HPV types in pregnant women**				
	HPV types	**Unvaccinated (956 women)**	**Vaccinated (79 women)**	**Adjusted vaccine effectiveness (%)**	
		n (%)	**n (%)**	**(95% CI)**	
	HPV 16/18	69 (7.2%)	1 (1.3%)	86.1% (15.0 to 99.7)	
	HPV 6/11/16/18	82 (8.6%)	3 (3.8%)	61.9% (-23.5 to 92.6)	
	HPV 31	24 (2.5%)	1 (1.3%)	74.1% (-81.5 to 99.4)	
	HPV 31/33/45	52 (5.4%)	3 (3.8%)	57.0% (-47.7 to 92.0)	
	HR-HPV	242 (25.3%)	25 (31.6%)	-1.8% (-76.5 to 42.8)	
Post-implementation in NIP/RIP					
Combita[51]	**4vHPV - Clinical outcomes in vaccinated and unvaccinated women aged 18–25 years**				
				Vaccinated	**Unvaccinated**
	Against HPV 16/18 type infections			61.5%; 95% CI, (54.3 to 67.6)	–
	Against all HPV types			62.5 %; 95% CI, (56.1 to 68.2)	–
	Before sexual debut			91.5%; 95% CI, (86.8 to 94.5)	–
	After sexual debut			36.2%; 95% CI, (23.6 to 46.7)	–
	Normal cytology			93.7%	90.5%
	Infections associated with HPV 16 in women with normal cytology			4.51%	10.5%
Saldanha[32]	**4vHPV - Rate of HPV 16, 16/18, other HR-HPV, or any HR-HPV, according to birth date**				
	HPV	**Born < 1992 (n = 331)**	**Born 1992–1994 (n = 901)**	**Born > 1994 (n = 951)**	
	HPV 16	6.3% (21)	3.3% (30)	0.7% (7)	
			RR 0.52 (0.305 to 0.904), p = 0.02	RR 0.12 (0.050 to 0.270), p < 0.0001	
	HPV 18	1.5% (5)	0.4% (4)	0.2% (2)	
			RR 0.29 (0.079 to 1.09), p = 0.07	RR 0.14 (0.027 to 0.714), p = 0.02	
	HPV 16 and/or 18	7.9% (26)	3.6% (32)	0.9% (9)	
			RR 0.45 (0.274 to 0.747), p = 0.0018	RR 0.12 (0.057 to 0.254), p < 0.0001	
	HR-HPV others	31.7% (105)	32.5% (293)	33.2% (316)	
			RR 1.02 (0.853 to 1.232), p = 0.791	RR 1.05 (0.873 to 1.256), p = 0.617	
	Any HR-HPV (HPV 16 and/or 18 and or others)	34.4% (114)	34.0% (306)	33.6% (320)	
			RR 0.99 (0.828 to 1.174), p = 0.875	RR 0.98 (0.822 to 1.162), p = 0.792	

(*Continued*)

Table 3. (Continued).

Author, year	Results							
Racey[82]	**4vHPV - Adjusted vaccine effectiveness and 95% CI for the vaccine status groups: At least one dose of HPV vaccine at 9–14 and complete series on-schedule at 9–14 years of age vs unvaccinated**							
	Vaccine status (n)				**HSIL**	**CIN2**	**CIN3**	**CIN2+**
	At least one dose (9–14 years of age) vs unvaccinated (20,738)				46.4% (35.0% to 55.9%)	38.7% (0.00% to 58.3%)	72.7% (57.0% to 83.2%)	56.60% (42.0% to 67.7%)
	Complete series and on-schedule (9–14 years of age) doses vs unvaccinated (18,975)				47.1% (35.6% to 56.7%)	40.6% (0.00% to 60.1%)	73.6% (57.5% to 84.1%)	57.9% (43.2% to 69.0%)
	At least one dose (15+ years of age) vs unvaccinated (3,436)				1.2% (0.00% to 25.3%)	18.4% (0.00% to 56.5%)	32.0% (0.00% to 65.3%)	25.3% (0.00% to 52.4%)
	Complete series and on-schedule (15+ years of age) doses vs unvaccinated (1,997)				20.3% (0.00% to 46.0%)	20.8% (0.00% to 65.2%)	52.1% (0.00% to 83.3%)	36.8% (0.00% to 66.1%)
	Unvaccinated (14,130)				–	–	–	–
Brotherton[50]	**4vHPV - Rate of histologically confirmed CIN2/AIS+ (due to any HPV type) and hazard ratios by number of quadrivalent human papillomavirus vaccine doses received, national cohort of screening women born in 1992 or later, 2007–2014**							
	Abnormalities				**No. women**	**No. abnormalities**	**Rate per 1,000 women**	**Hazard ratio**
	CIN2+/AIS	Unvaccinated			48,845	645	13.2	1.0
		1 dose			8,618	89	10.3	0.65 (0.52 to 0.81)
		2 doses			18,190	174	9.6	0.61 (0.52 to 0.72)
		3 doses			174,995	1,496	8.5	0.59 (0.54 to 0.65)
Herweijer[60]	**4vHPV - IRRs comparing fully vaccinated individuals with unvaccinated individuals by age at vaccination initiation in the total population for CIN2+ and CIN3+**							
			CIN2+			CIN3+		
		Person-years	**IR (95% CI)**	**IRR (95% CI)**	***p* values**	**Person-years**	**IR (95% CI)**	**IRR (95% CI)**	***p* values**
	Unvaccinated	6,647,642	336 (331 to 340)	Reference		6,688,615	187 (184 to 190)	Reference	
			Age at vaccination initiation						
	<16 years	441,315	7 (5 to 11)	0.25 (0.18 to 0.35)	<0.001	441,355	2 (1 to 4)	0.16 (0.08 to 0.32)	<0.001
	17–19 years	138,960	100 (85 to 118)	0.54 (0.46 to 0.64)	<0.001	139,156	37 (28 to 49)	0.43 (0.33 to 0.57)	<0.001
	20–29 years	24,179	513 (430 to 612)	0.78 (0.65 to 0.93)	0.006	24,644	268 (210 to 341)	0.75 (0.59 to 0.95)	0.019
Smith[37]	**4vHPV - Impact of 4vHPV Vaccination on the risk of cervical dysplasia**							
			RDs, per 1,000 girls (95% CI)			**Risk ratio (95% CI)**		**NNT (95% CI)**
	Dysplasia							
	Broad program impact		22.32 (-4.02 to -0.61)			0.79 (0.66 to 0.94)		431 (248 to 1,639)
	Broad vaccine impact		25.70 (-9.91 to -1.50)			0.56 (0.37 to 0.85)		175 (101 to 667)
Hibbitts[61]	**4vHPV - Absolute risk reduction analyses against CIN2+ (excluding HPV16/18) based on high-risk HPV type frequency data from the baseline cohort and ORs expressing cross-protection for bivalent and quadrivalent vaccines from the TVC-naïve cohorts in the PATRICIA and FUTURE I/II trials**							
			Number of HR-HPV types included in analysis			Projected absolute risk reduction		95% CI
	Cervarix		10			47.1%		27.5% to 57.8%
	Gardasil		10			33.2%		13.6% to 45.5%
	Gardasil versus Cervarix		10			13.8%		-9.4% to 36.5%
Falcaro[54]	**2vHPV - Relative reduction at vaccine offer compared with the reference unvaccinated**							
	Age (years)					**Cervical cancer (95% CI)**		**CIN (95% CI)**
	16–18					34% (25 to 41)		39% (36 to 41)
	14–16					62% (52 to 71)		75% (72 to 77)
	12–13					87% (72 to 94)		97% (96 to 98)
Kjaer[67]	**2vHPV, 4vHPV and 9vHPV - IRRs of cervical cancer comparing vaccinated with unvaccinated women according to age at vaccination and with 1-year buffer period**							
	Vaccination status		**Person-years**		**Events**	**Age-adjusted IRR (95% CI)**		**Adjusted IRR (95% CI)**
	Unvaccinated		2,884,778		325	1		1
	Vaccinated, age <16 y		1,643,967		6	0.13 (0.04 to 0.40)		0.13 (0.04 to 0.41)
	Vaccinated, age 17–19 y		174,679		5	0.29 (0.08 to 1.01)		0.31 (0.09 to 1.07)
	Vaccinated, age 20-30 y		841,231		168	1.15 (0.88 to 1.50)		1.14 (0.87 to 1.49)

(*Continued*)

Table 3. (Continued).

Author, year	Results									
Donken[53]	**4vHPV - CIN2 and CIN3 rates among women 16 to 23 years of age pre and postvaccination**									
	Age (years)		**CIN2**				**CIN3**			
			Rate	**95% CI**	**RR**	**95% CI**	**Rate[a]**	**95% CI**	**RR**	**95% CI**
	16-23	**Prevaccination**	6.35	(5.89 to 6.84)	Ref	–	4.56	(4.32 to 4.81)	Ref	–
		Postvaccination	2.41	(2.03 to 2.85)	0.38	(0.32 to 0.46)	1.59	(1.31 to 1.92)	0.35	(0.29 to 0.42)
Lei[71]	**4vHPV - Detection rate, PPV of cytology and RRs for CIN2+, in relation to age at vaccination initiation**									
	Cytological results	**Age at vaccination initiation**	**Screened n**	**Screen positive n**	**CIN2+**		**Detection rate of CIN2+, % (95% CI)**	**PPV for CIN2+, % (95% CI)**		**Adjusted RR (95% CI)**
	High-grade cytology	Unvaccinated	100,400	2,110	1,475		1.5% (1.4 to 1.5)	69.9% (67.9 to 71.9)		Reference
		Vaccinated at age	26,892	368	239		0.9% (0.8 to 1.0)	64.9% (59.8 to 69.8)		0.92 (0.85 to 1.00)
		17–22 years	25,865	244	140		0.5% (0.5 to 0.6)	57.4% (50.9 to 63.7)		0.83 (0.74 to 0.93)
	Low-grade cytology	Vaccinated at age	100,400	12,293	2,325		2.3% (2.2 to 2.4)	18.9% (18.2 to 19.6)		Reference
		<17 years	26,892	2,940	377		1.4% (1.3 to 1.5)	12.8% (11.6 to 14.1)		0.72 (0.65 to 0.80)
		Unvaccinated	25,865	2,775	258		1.0% (0.9 to 1.0)	9.3% (8.2 to 10.4)		0.56 (0.49 to 0.63)
	Adjusted VE (95%CI)									
				Incidence				Persistence		
	HPV 16/18			77.5% (64.9 to 85.6%)				97.7% (83.5 to 99.7%)		
	HPV 31/33/45			55.9% (33.2 to 70.9%)				61.8% (16.7 to 82.5%)		
	HPV 16/18/31/33/45/52/58			41.0% (26.2 to 52.7%)				51.2% (33.7 to 69.8%)		
	HPV 6/11/16/18/31/33/45/52/58			33.0% (19.1 to 44.6%)				50.4% (29.7 to 65.1%)		
	HPV 16/31/33/35/52/58			39.7% (24.0 to 52.1%)				49.3% (24.4 to 66.0%)		
	HPV 18/39/45/59			23.2% (-2.3 to 42.3%)				51.4% (10.3 to 73.7%)		
Purriños-Hermida[80]	**2vHPV - Adjusted effectiveness of HR-HPV 16/18 and 31/33/45, in vaccinated vs. unvaccinated women in the postvaccination period (direct effectiveness), vaccinated women vs. women in the pre-vaccination period (total effectiveness), and vaccinated and unvaccinated women in the post-vaccination period vs. women in the prevaccination period (overall effectiveness)**									
	HR-HPV 16/18 (95% CI)									
	Prevalence		9.2% (6.5 to 12.5) in unvaccinated women				0.8% (0.2 to 2.5) in vaccinated women			
	Direct effectiveness			94% (72 to 99)						
	Total effectiveness			95% (79 to 99)						
	Overall effectiveness			61% (39 to 74)						
	HR-HPV 31/33/45 (95% CI)									
	Prevalence		8.4% (5.9 to 11.6) for unvaccinated women				1.1% (0.3 to 2.9) for vaccinated women			
	Direct effectiveness			83% (46 to 94)						
	Total effectiveness			84% (54 to 94)						
	Overall effectiveness			36% (-2 to 60)						

(*Continued*)

Table 3. (Continued).

Author, year		Results						
Kavanagh[66]	**2vHPV - Vaccine effectiveness across age groups**							
			HPV 16 and 18		**HPV 31, 33, and 45**		**Other HR-HPV types**	**Any HPV type**
		Number of doses	Adjusted vaccine effectiveness (95% CI)		Adjusted vaccine effectiveness (95% CI)		Adjusted vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)
	12–13 years	3 doses	89.1% (85.1 to 92.3)		85.1% (77.3 to 90.9)		7.8% (-7.3 to 20.9)	38.1% (28.7 to 46.3)
	14 years	3 doses	87.7% (78.9 to 93.5)		83.6% (66.2 to 93.6)		0.2% (-29.6 to 23.8)	29.6% (9.8 to 45.1)
	15 years	3 doses	82.3% (76.8 to 86.7)		69.2% (57.2 to 78.5)		-4.8% (-22.3 to 10.3)	21.7% (9.3 to 32.4)
	16 years	3 doses	75.9% (70.2 to 80.8)		56.8% (44.0 to 67.1)		-17.1% (-34.3 to -2.0)	12.5% (0.1 to 23.4)
	17 years	3 doses	58.1% (44.8 to 68.8)		57.9% (37.2 to 73.1)		-4.9% (-29.5 to 15.4)	13.8% (-5.6 to 29.6)
	≥18 years	3 doses	28.9% (4.5 to 47.8)		29.5% (-6.2 to 55.3)		16.9% (-9.0 to 37.2)	16.5% (-7.4 to 35.0)
	All ages	2 doses	39.0% (21.3 to 53.3)		40.3% (14.5 to 59.7)		-23.1% (-52.5 to 1.0)	-12.5% (-39.7 to 9.1)
	All ages	Unvaccinated	–		–		–	–
Hariri[59]	**4vHPV - Vaccine effectiveness against type-specific CIN2+ and CIN3/AIS lesions**							
			CIN2+				**CIN3/AIS**	
		n	% HPV 16/18	aPR	95% CI	n	% HPV 16/18	aPR	95% CI
	Not vaccinated	1,274	53.6%	–	–	427	69.8%	–	–
	Vaccinated ≤30 days/after trigger test	444	54.5%	1.01	0.92 to 1.10	132	67.2%	0.99	0.87 to 1.13
	Vaccinated before trigger test								
	37–48 months	85	27.1%	0.51	0.36 to 0.72	29	44.8%	0.62	0.41 to 0.93
	>48 months	54	13.0%	0.28	0.14 to 0.55	10	40.0%	0.55	0.26 to 1.16

A Age-centered per 1,000 person-years.

Abbreviations: 2vHPV: bivalent human papillomavirus vaccine; 4vHPV: quadrivalent human papillomavirus vaccine; 9vHPV: nonavalent human papillomavirus vaccine; AIS, adenocarcinoma in situ; AIS +, adenocarcinoma in situ due to any HPV type; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance or greater; aPR, adjusted prevalence ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN1 +, cervical intraepithelial neoplasia grade 1 or greater; CIN2 +, cervical intraepithelial neoplasia grade 2 or greater; CIN3 +, cervical intraepithelial neoplasia grade 3 or greater; EVG, early vaccination group; HPV, human papillomavirus; HR, high-risk; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IR, incidence rate; IRR, incidence rate ratio; LSIL, low-grade squamous intraepithelial lesion or greater; mITT: modified intention to treat; N, number of participants included in each group; n, number of cases; No., number; NNT, number-needed-to-treat; PCR, polymerase chain reaction; PPV, positive predictive value; Ref, reference; RD, risk difference; RR, risk ratio; TVC, total vaccinated cohort; VE, vaccine efficacy; VLP, virus-like particles; y, years.

challenges such as limited healthcare access, stigma related to sexually transmitted diseases, anti-vaccine campaigns, and insufficient financing. Therefore, these factors warrant careful consideration in the planning of NIPs.[86]

In this review, three selected RCTs showed the efficacy of HPV vaccination among women >26 years of age with a follow-up period ranging from 2 to 4 years.[35,65,81] These results suggested high vaccine efficacy against CIN, incident and persistent infections. Four observational studies also assessed vaccine effectiveness or health impact among women vaccinated after 26 years of age.[33,60,67,74] Studies on vaccine effectiveness reported low incidence rates of HPV 6/11/16/18 when comparing vaccinated and non-vaccinated individuals over a 2–7 year follow-up period.[33,74] Studies on health impact revealed that HPV vaccination significantly reduced the incidence of grade ≥ 2/3 CIN (CIN2/3 +) and cervical cancer among women >26 years with an 8–14 year follow-up period.[60,67] Regarding vaccine safety, 11 studies published since 2006 assessed the safety profile of HPV vaccines. Five focused on Cervarix, one on Gardasil, and four compared both vaccines. One study examined Cervarix, Gardasil, and Gardasil 9. Fatigue, dizziness, and headaches were commonly reported as nonspecific adverse events. Two studies mentioned autoimmune diseases and venous thromboembolism, though no causal link was established. Yaju et al. reported cases of memory impairment, dyscalculia, and involuntary movements.

Implementing a single-dose vaccination program could increase vaccine coverage in LMICs without compromising the long-term effectiveness or duration of protection.[12,16] This is supported by the KEN SHE study in Kenya which reported single-dose bivalent and 9-valent vaccine efficacy (98% and 99%, respectively) over three years.[87] Other studies also assessed the immunogenicity, efficacy, and effectiveness of a single dose of Cervarix, Gardasil, and Gardasil 9 vaccines in various settings. Cervarix showed 82.1% efficacy against HPV 16/18 for 11 years in the Costa Rica study (CVT).[88] In Scotland, Cervarix had 89.1% effectiveness against types 16/18 in girls vaccinated at 12–13 years of age.[66] In the Netherlands, one dose of Cervarix was immunogenic up to seven years after vaccination in girls aged 13–21 years.[89] A single dose of Cervarix or Gardasil-9 in Tanzanian girls aged 9–14 years continues to provide stable immune response 5 years after vaccination, with an IgG seropositivity > 99% for HPV16 and > 93% for HPV18.[90] Although antibody levels for both HPV16 and HPV18 after one dose were lower than after two doses, they remained stable from 1 to 5 years. In another study from Kenya, the efficacy of a single dose of Cervarix and Gardasil-9 was 97.5% against persistent HPV 16/18 infections in women aged 15–20 years with a follow-up of 18 months.[91] Similarly, an Australian study of women vaccinated with a single dose of Gardasil at 15 years of age showed 40% effectiveness against CIN2/3 and AIS over 7 years.[50] In Denmark, the incidence rate of cervical cancer reduced by 86% and 68% among girls and women vaccinated ≤ 16 and 17–19 years of age, respectively.[67] A study in Mongolia reported a decrease of 92% in HPV 16/18 infections for 6 years in girls vaccinated at 11–17 years.[92] A 10-year follow-up study in India showed 95.4% efficacy against type 16 and 18 infections.[30] A study in Fiji found that a single dose of Gardasil induced immune memory, with antibodies persisting for at least 6 years.[93] A single-dose schedule may also be beneficial in a mixed vaccination schedule with one dose of the bivalent vaccine and one dose of the 9-valent vaccine.[12,94–96] A disadvantage of using the single-dose schedule is its limited evidence, especially in immunocompromised groups.[12,30]

In pregnant women, HPV infections have also been associated with non-cancerous adverse outcomes like preeclampsia, preterm births, and premature membrane rupture.[97,98] High vaccine effectiveness among pregnant women vaccinated against HPV 16/18 infections is reported.[33] Furthermore, inadvertent exposure to the vaccine did not lead to an increased risk of teratogenicity.[73]

Although this review offers valuable insights, several limitations must be acknowledged when interpreting the findings and their broader implications. Observational studies on HPV vaccines often face confounding bias due to differences between vaccinated and unvaccinated groups. Vaccinated individuals may have distinct health histories and preventive practices or belong to birth cohorts with better healthcare access. Herd immunity might underestimate vaccine efficacy, while confounders such as vaccination at younger ages could overestimate it. Additionally, confounders such as sexual behavior, access to healthcare services, and socioeconomic status can also influence infection risk and outcomes.

These variations complicate direct comparisons of vaccine impact. Another limitation of the study is the high risk of bias reported in 20% of RCTs and 83% of observational studies due to confounding and participant selection biases. Another limitation of this study is the absence of a comparative analysis between the herd effect of a gender-neutral versus a girls-only vaccination strategy, as the selected population only included women. The variability in cutoff values used in the studies included in this SLR complicates direct comparisons.

Post-licensure studies of HPV vaccines have reported high efficacy, effectiveness, and health impact across different settings and age groups. These studies consistently emphasize that HPV vaccination during childhood and pre-adolescence can serve as an additional preventive measure against cervical cancer and its precursor lesions. In real-world settings, the long-term health impact of HPV vaccines in the context of NIPs has been shown to provide protection for at least 11 years.[71] Published literature confirms the findings of this SLR, supporting that high vaccination coverage (>50%) can increase protection through herd effects among unvaccinated individuals.[21] Studies also report that a single dose of HPV vaccination can offer protection comparable to the current two-dose vaccine schedule, although with a shorter follow-up period. This review reports that robust vaccination programs and extensive coverage reduce the incidence of oncogenic HPV types, high-grade cervical lesions, and cervical cancer. Early-age vaccination also lowers cervical cancer risk, offers cross-protection, and strengthens herd effects. The ECDC mentions that an HPV vaccination program should focus on increasing coverage among both girls and boys as it could be a cost-effective approach to reduce the prevalence of HPV infection.[26] In light of this observation, it is imperative to analyze global estimates of vaccine coverage (15% girls and 4% boys worldwide) and screening uptake (two-thirds of women remain unscreened) to combat HPV-associated diseases.[99]

The results of this SLR can guide policymakers in implementing vaccination programs to prevent cervical cancer in their countries and regions while also promoting vaccine uptake, especially in populations with limited access to vaccination or with a higher risk of HPV infections. HPV vaccines protect unvaccinated individuals through herd effects, as assessed through vaccine health impact in real-world studies. It should be noted, however, that the magnitude of herd effects is only of reasonable significance when a large proportion of the population is vaccinated.[100,101] Furthermore, future studies are needed to assess the long-term efficacy of a single-dose HPV vaccination and to address disparities in coverage among underserved populations. Equitable and effective vaccination strategies are necessary to maximize the benefits of HPV vaccination, and further research should guide their optimization and implementation.

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DMH, JANA, XB, JP, MS, and PS collectively contributed to the review of study methodology, examination of study results, data validation and review of the manuscript text. MY and NMM conceptualized and curated the data and conducted a formal analysis of study methodology and study resources. AR, AG, LMG, LVA, and HC reviewed the study methodology, results and manuscript text. YRG conceptualized and investigated the study methodology and resources in addition to supervising and validating the development of this manuscript.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The work described was carried out in accordance with the recommendations of the International Committee of Medical Journal Editors for conduct, reporting, editing, and publication of scholarly work in medical journals. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Data sharing

Search terms and eligibility criteria as well as results reported in this review have been attached separately as part of this publications supplementary material.

Ethical statement

The study does not involve human participants, and an ethical approval does not apply.

Trademark

Cervarix is a trademark owned by or licensed to GSK. Gardasil 9 and Gardasil are trademarks of Merck Sharp and Dohme. Cecolin is a trademark of Innovax.

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