HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 2, 2239085
https://doi.org/10.1080/21645515.2023.2239085

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Human papillomavirus vaccine effectiveness by age at vaccination: A systematic review

Mallory K. Ellingson[a], Hassan Sheikha[b], Kate Nyhan[c,d], Carlos R. Oliveira[b,e], and Linda M. Niccolai[a]

[a]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, USA; [b]Department of Pediatrics, Yale School of Medicine, Yale University, New Haven, USA; [c]Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, USA; [d]Department of Environmental Health Sciences, Yale School of Public Health, Yale University, New Haven, USA; [e]Department of Biomedical Informatics and Data Science, Yale School of Medicine, Yale University, New Haven, USA

ABSTRACT

Human papillomavirus (HPV) vaccines work by preventing infections prior to natural exposure. Thus, it is likely more effective at younger ages, and it is important to understand how effectiveness might be diminished when administered at older ages. We conducted a systematic review of HPV vaccine effectiveness studies published between 2007 and 2022 that included an analysis of effectiveness against vaccine-type HPV infections, anogenital warts, cervical abnormalities and cervical cancer by age at vaccine initiation or completion. Searching multiple databases, 21 studies were included and results were summarized descriptively. Seventeen studies found the highest vaccine effectiveness in the youngest age group. Vaccine effectiveness estimates for younger adolescents ages 9–14 years ranged from approximately 74% to 93% and from 12% to 90% for adolescents ages 15–18 years. These results demonstrate that the HPV vaccine is most effective against HPV-related disease outcomes when given at younger ages, emphasizing the importance of on-time vaccination.

ARTICLE HISTORY
Received 5 May 2023
Revised 30 June 2023
Accepted 14 July 2023

KEYWORDS
Vaccine; human papillomavirus; vaccine effectiveness; HPV

Introduction

Human papillomavirus (HPV) infection can lead to several types of cancers.[1] Nearly all cases of cervical cancer are associated with HPV infections, and globally there were an estimated 604,000 new cases of cervical cancer and over 300,000 related deaths in 2020.[2] Additionally, it is estimated that HPV infection is associated with approximately 124,000 cases of anal, oropharyngeal, penile, vaginal and vulvar cancers annually.[3] In the United States, approximately 37,300 people are diagnosed with HPV-related cancers annually.[1] The first-generation HPV vaccine, 4vHPV, was approved by the United States Food and Drug Administration (US FDA) in 2006 for the prevention of infection and disease associated with four strains of HPV including 6 and 11 that are associated with anogenital warts and 16 and 18 that are associated with approximately 70% of HPV-associated cervical cancers and even greater percentages of other HPV-associated cancers.[4] A nine valent HPV vaccine was approved in 2016 and protects against an additional five strains of HPV – 31, 33, 45, 52 and 58 – which collectively are associated with an additional 20% of HPV-associated cervical cancers.[5]

There are multiple ways of assessing the benefits of the HPV vaccine at the individual and population level.[6] Vaccine efficacy is a measure of how well the vaccine works at preventing disease at the individual level in a clinical trial. In clinical trials, the efficacy of the vaccine against HPV infection, genital warts and high-grade cervical lesions exceeded 90% among women without prior HPV infection.[7,8] Pre-licensure trials also demonstrated high efficacy against anogenital warts among men.[7] Post-licensure, numerous studies have evaluated the population-level impact and individual-level impact of the HPV vaccine. These studies have found substantial evidence for population benefits of the HPV vaccine, including declines in HPV infections, anogenital warts, and high-grade cervical lesions.[9] Vaccine effectiveness studies measure the direct effect that the vaccine has in preventing disease outcomes as administered in real-world conditions. Numerous studies have demonstrated the effectiveness of the HPV vaccine against several disease outcomes including infection, anogenital warts and pre-cancerous lesions and more recently cervical cancer.[10–15]

Within this body of research, there is growing evidence suggesting that the timing of HPV vaccination initiation is an important factor in vaccine effectiveness.[6] Pre-licensure clinical trials have shown that administering the vaccine prior to initiation of sexual activity and potential exposure to HPV offers the greatest protection.[7,8] Therefore, the World Health Organization (WHO) and the United States' Advisory Committee on Immunization Practices (US ACIP) recommend initiation vaccination in early adolescence (generally between ages 9–14).[16–18] Studies have also demonstrated that earlier administration of the vaccine results in greater immunogenicity and longer-lasting protection.[19,20] Numerous studies have evaluated the real-world effectiveness of the HPV vaccine by age at vaccination, yet a comprehensive review synthesizing the available

CONTACT Mallory K. Ellingson mallory.ellingson@yale.edu Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, 60 College Street, New Haven, CT 06510, USA.

evidence is lacking. In this review, we aim to evaluate the effectiveness of HPV vaccination against infection, anogenital warts, cervical abnormalities and cervical cancer by age at vaccination.

Methods

Study selection

We searched Medline and EMBASE on Ovid on January 10th, 2023 to identify articles published between 2007 and December 31st, 2022 that evaluated HPV vaccine effectiveness by age at vaccination. The search strategy contained terms to capture the exposure of interest (HPV vaccination), the outcome(s) of interest (HPV infection and related sequelae) and the measure of interest (vaccine effectiveness). A second search was run on April 14th, 2023, that incorporated subject headings and less restrictive truncation. We did not use search terms about age at initiation or completion because we anticipated that some studies with relevant data might not mention the age groups in the title, abstract, and author keywords. The full search strategies for both databases are provided in Appendix I.

Studies were eligible to be included if they conducted an analysis of HPV vaccine effectiveness by age at series initiation or completion. HPV vaccine effectiveness was defined as a comparison of the risk or likelihood of the disease outcome between vaccinated and unvaccinated individuals. We did not include studies that only assessed effectiveness by attained age, year of birth or birth cohort because these measures do not provide direct evidence of the effect of the age at which the vaccine was administered. Studies were excluded if 1) the data were collected as part of a clinical trial, 2) they were not published between 2007 and 2022, 3) they were a modeling study, 4) they were not peer-reviewed, or 5) they were not in English. Eligibility was determined independently by two authors (HS and MKE) through a review of the title and abstract followed by a full-text review. Conflicts were resolved by a third author (LMN). Screening of all manuscripts was performed using Covidence.[21] Following the completion of the screening, we conducted backwards citation chasing to identify additional studies that met the inclusion criteria.

Data extraction

Two authors (HS and MKE) independently extracted key study information and outcome measures using a standardized form. Discrepancies were resolved by a third author (LMN). Core study information extracted included title, authors, journal, year published, funding and DOI. Methodological information was also extracted, including the country where the study was conducted, years of data collection, primary study design, case definition, statistical analysis methods, vaccine evaluated, age groups for vaccine initiation or completion, and confounders controlled for in adjusted analyses. Lastly, the primary study results were extracted, including sample size (overall and by age group analyzed), overall vaccine effectiveness (at least one dose when available, otherwise series completion) and vaccine effectiveness by age group.

Bias analysis

We utilized an adapted version of the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) as described in a systematic review of the effectiveness of HPV vaccine by dose.[12] Using this adapted tool, we evaluated selection bias, information bias and confounding. For selection bias, we evaluated whether participant inclusion was influenced by participant characteristics associated with the vaccination. For information bias, we evaluated the sources of information for both vaccination and outcome measures. To evaluate confounding, we assessed whether the authors controlled for important known confounders of the relationship between vaccination and the outcomes of interest (i.e., age, sexual activity, access to healthcare, socioeconomic status), if measures were taken to control for the presence of prevalent infections (buffer periods between vaccination and outcome assessment) and whether appropriate methods were used to control for confounding. In each domain, studies could receive a rating of low, moderate, or high risk of bias. Overall assessment of bias was based on the domain with the highest rating – for example, if a study has at least one domain rated as "high risk of bias" then the overall risk of bias is considered high. No studies were excluded from the analysis based on quality. The results of the bias analysis were summarized descriptively.

Data synthesis

Study results were synthesized narratively. We first examined the studies by outcome (vaccine-type HPV infection, anogenital warts, cervical abnormalities and cervical cancer). Then, to explore further the impact of age of vaccination on vaccine effectiveness, we examined the studies by the different age groups and methods of analysis utilized. We present results as adjusted vaccine effectiveness (VE) when available or as ratio measures, which include risk ratios (RR), incidence rate ratios (IRR), hazard ratios (HR), prevalence ratios (PR), or odds ratios (OR). If a ratio measure was not provided, it was inferred from vaccine effectiveness estimates for the purposes of comparison across studies.

The study protocol was registered on PROSPERO prior to conducting the search and followed PRISMA guidance (Appendix III).[22,23]

Results

Search results

Across both searches, we identified 1,007 potentially eligible articles published in Medline or Embase between 2007 and December 31st, 2022, after de-duplication (Figure 1). After title and abstract screening, 111 articles were included for full-text review. Of those, 18 articles met the criteria for inclusion.[13,24–40] An additional seven articles were identified through backwards citation-chasing, three of which met the criteria for inclusion[14,41,42] for a total of 21 eligible articles

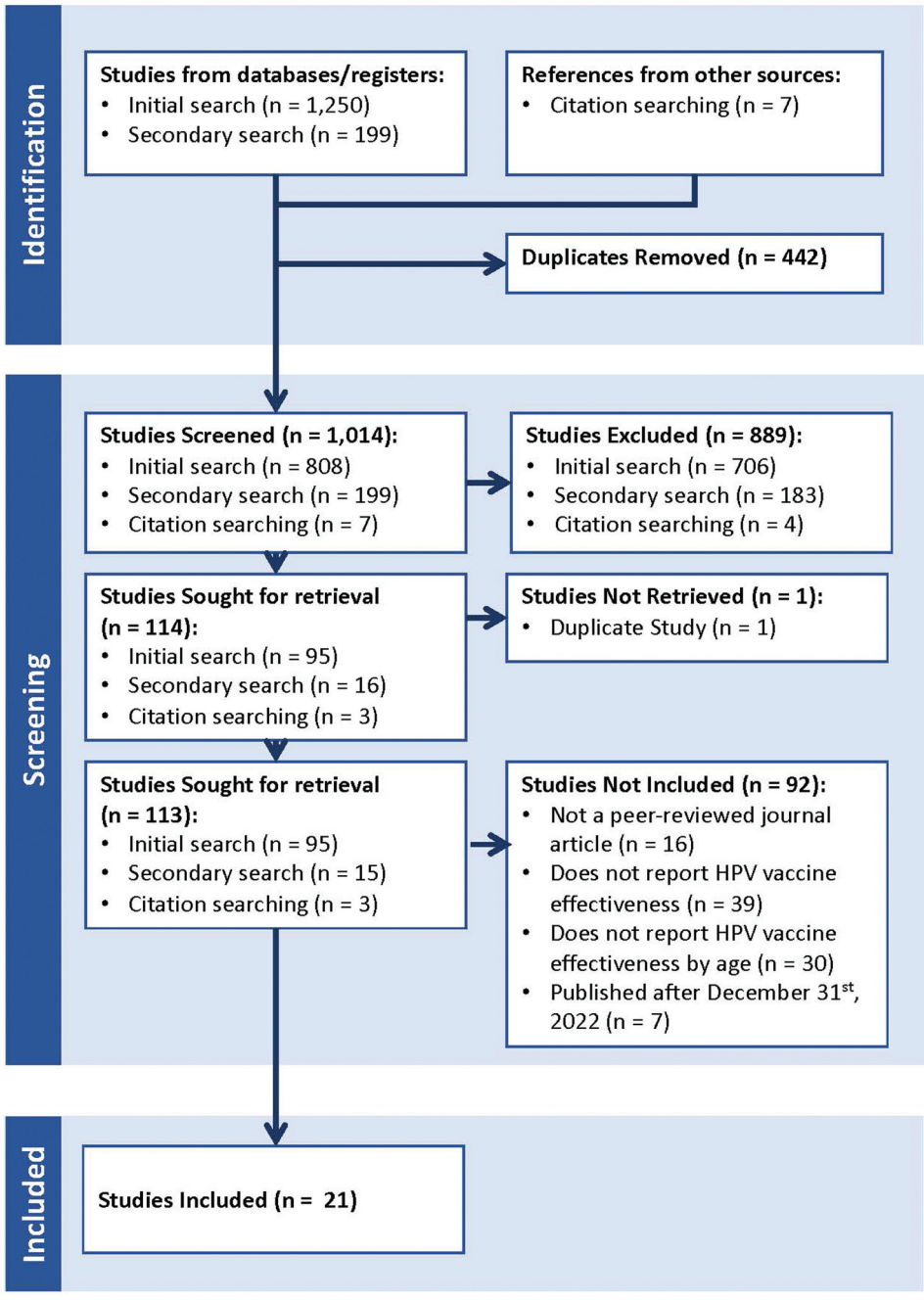

Figure 1. PRISMA diagram.

included in the review. Twelve of the 21 studies evaluated the effectiveness of a specific HPV-vaccine (bivalent or quadrivalent), one evaluated the effectiveness of receipt of any of the HPV vaccines and the remaining eight studies did not specify the vaccine. The studies were predominantly conducted in North America and Europe – eight studies were conducted in the United States,[26,27,30,32,35,38,40,41] four in Sweden[14,34,39,42] and three in Denmark,[13,24,42] three in Canada,[33,36,37] two in Scotland[31,43] and one in Belgium. Additionally, one study was conducted in New Zealand (Table 1).[44]

Four studies used vaccine-type HPV infection (types 6, 11, 16 and 18) as the outcome of interest.[28,30,35,40] Five studies evaluated vaccine effectiveness against anogenital warts.[24,25,33,34,38] In the nine studies evaluating vaccine effectiveness against vaccine-type HPV infection and anogenital warts, three included men and/or transgender women in the analysis.[35,38,40] The most common outcome studied was cervical abnormalities.[26,27,31,32,36,37,39,41,42,44] Two studies used diagnosis of cervical cancer as the endpoint of interest (Table 1).[13,14]

The majority of studies stratified by age at vaccine initiation ($n = 20$), although the age groups evaluated varied widely. The range of age groups studied was 2 to 6. One study stratified by age at the final dose of the HPV vaccine, evaluating participants who completed the vaccine series before the age of 15, between 15 and 19, and after 19 years of age.[38]

Table 1. Study characteristics.

	Study	Country	Study design	Age stratification	Case definition	Vaccine	Funding	Overall risk of bias assessment
HPV infection								
	Kavanagh 2017	Scotland	Cross-sectional study – screening registry data	Age at initiation – 12–13 years, 14 years, 15 years, 16 years, 17 years, ≥18 years	HPV DNA Positivity types 16 and 18 in liquid-based cytology samples	N/A	Scottish Government and Chief Scientists Office	High
	Markowitz 2020	United States	Cross-sectional study – women in network-based healthcare system	Age at initiation - ≤ 18 years, >18 years	HPV DNA Positivity types 6, 11, 16 and 18 in liquid-based cytology samples	N/A	Centers for Disease Control and Prevention	Moderate
	Meites 2020	United States	Cross-sectional study – men	Age at initiation - ≤ 18 years, >18 years	HPV DNA Positivity types 6, 11, 16 and 18 in self-collected anal, oral and blood samples	N/A	Centers for Disease Control and Prevention	High
	Winer 2021	United States	Cross-sectional study – men	Age at initiation - ≤ 18 years, >18 years	HPV DNA Positivity types 6, 11, 16 and 18 in self-collected penile samples	N/A	Centers for Disease Control and Prevention	High
Anogenital warts								
	Baandrup 2021	Denmark	Retrospective Cohort Study – Population Based Health Registry	Age at initiation – 12–14 years, 15–16 years, 17–18 years or ≥19 years	A case of GWs was defined as a composite measure of a redeemed perscription for podophyllotoxin and/or a diagnosis of genital warts in the Danish National Health Registry	qHPV	Mermaid Project	Moderate
	Dominiak-Felden 2015	Belgium	Retrospective Cohort Study – Insurance Reimbursment Database	Age at initiation - <15 years, 15–17 years, ≥18 years	A first case of GWs was defined as an agreement for a first perscription of imiquimod with a level of reimbursement specific to GWs	qHPV	Sanofi Pasteur	Moderate
	Leval 2013	Sweden	Retrospective Cohort Study – Population Based Health Registry	Age at initiation – 10–13 years, 14–16 years, 17–19 years, 20–22 years, 23–26 years and 27–44 years	A first case of GWs was defined as either a first diagnosis in the population registry or a first perscription for GW treatment in the population registry	qHPV	Merck	Moderate
	Willows 2018	Canada	Retrospective Cohort Study – Linkage between vaccine registry and hospital, physician and prescription claims databases	Age at initiation – 9–18 years old, > 18 years old	History of medically attended GWs in claims database	qHPV	Merck	High
	Zeybek 2019	United States	Retrospective Cohort Study – Insurance Claims Database	Age at last dose - < 15 years, 15–19 years, ≥20 years	Diagnosis of GWs in claims database at least 3 months following last dose of HPV vaccine	qHPV	William & Mary McGanity Research Fund Award from the Department of Obstetrics & Gynecology at The University of Texas Medical Branch at Galveston	Moderate
Cervical abnormalities								
	Dehlendorff 2018	Denmark and Sweden	Retrospective Cohort Study – Population Based Health Registries	Age at initiation - ≤ 16 years, 17–19 years, ≥ 20 years	Histology: CIN2+	qHPV	Mermaid Project (Mermaid 2), the Swedish Foundation for Strategic Research, the Swedish Research Council and the Swedish Cancer Society	Moderate
	Gargano 2022	United States	Retrospective Cohort Study – Linked regional registries	Age at initiation - < 20 years, ≥ 20 years	Histology: CIN3+, AIS+	All	Immunization Grant Funds, National Program of Cancer Registries Grant Funds	Moderate

(*Continued*)

Table 1. (Continued).

	Study	Country	Study design	Age stratification	Case definition	Vaccine	Funding	Overall risk of bias assessment
	Herweijer 2016	Sweden	Prospective Cohort Study – Population Based Health Registry	Age at initiation – 16 years, 17–19 years, 20–29 years	Histology: CIN2+, CIN3+, AIS+	qHPV	Swedish Foundation for Strategic Research	Moderate
	Hofstetter 2016	United States	Retrospective Cohort Study – Hospital records and regional immunization registry data	Age at initiation 11–14 years, 15–16 years, 17–18 years, 19–20 years	Cytology: Any abnormal and high grade	N/A	Merck	High
	Innes 2020	New Zealand	Retrospective Cohort Study – Linked national registries	Age at initiation - <18 years, ≥ 18 years	Histology: CIN2+ or glandular lesions	N/A	None reported	High
	Palmer 2019	Scotland	Retrospective Cohort Study – Linked national registries	Age at initiation – 12–13 years, 14 years, 15 years, 16 years, 17 years and ≥18 years	Histology: CIN1, CIN2, CIN3+	bHPV	Scottish National Health Service	High
	Racey 2020	Canada	Retrospective Cohort Study – Linked regional registries	Age at initiation – 9–14 years, ≥ 15 years	Histology: CIN2, CIN2+, CIN3	N/A	Canadian Institutes of Health Research	Moderate
	Righolt 2019	Canada	Retrospective Cohort Study – Linked regional registries	Age at initiation – 14–17 years, ≥ 18 years	Cytology: ASCUS, HSIL, LSIL	qHPV	Merck	High
	Rodriguez 2020	United States	Matched retrospective cohort study – insurance claims data	Age at initiation - <15 years, 15–19 years, ≥ 20 years	Histology: CIN2/CIN3	qHPV	National Institutes of Health, Cancer Prevention Research Institute of Texas	Moderate
	Silverberg 2018	United States	Nested case-control study of women enrolled in an integrated health-care delivery system	Age at initiation – 14–17 years, 18–20 years, ≥ 21 years	Histology: CIN2+ or CIN3+	qHPV	US National Cancer Institute	Moderate
Cervical cancer								
	Kjaer 2021	Denmark	Retrospective Cohort Study – Population Based Health Registry	Age at initiation - < 16 years, 17–19 years, 20–30 years	First diagnoses of cervical cancer in Danish Pathology Registry	N/A	Mermaid project	Moderate
	Lei 2020	Sweden	Retrospective Cohort Study – Population Based Health Registry	Age at initiation - <17 years, ≥ 17 years	Diagnosis with invasive cervical cancer in Swedish Cancer Registry	qHPV	Swedish Foundation for Strategic Research, the Swedish Cancer Society, and the Swedish Research Council and by the China Scholarship Council.	Moderate

Quality assessment

All of the included studies were deemed to have at least moderate risk of bias, and seven of the 21 included studies were deemed to be at high risk of bias (Table 1). Most studies considered at high risk of bias only had one or two domains considered high risk (either information bias related to outcome assessment or confounding) (Appendix II). Most studies included some method of controlling for confounding associated with prevalent infections, usually by excluding participants without a proper buffer period between vaccine receipt and the outcome of interest. Three studies were considered at high risk of bias due to confounding associated with prevalent infections as they did not include a buffer period between vaccination and outcome. One study was deemed to be at high risk of bias due to potential misclassification of outcome status.

Many of the studies were considered at low risk of selection bias or information bias related to the intervention (vaccination status). Many of the included studies were population-based retrospective cohort studies with broad inclusion criteria limiting the risk of selection bias. The majority of studies utilized regional or national vaccine registries for information related to vaccination status. Studies that utilized other sources of data for vaccination histories (medical records or self-report) were considered at moderate risk for information bias related to intervention assessment.

All of the studies were at least moderate risk of bias due to confounding related to HPV acquisition. Given the latency period between infection and development of disease, a challenge investigators face when aiming to quantify the effectiveness of HPV vaccine is the need to control for confounding around whether or not the individual had prevalent HPV infection at the time of vaccination. Given the retrospective or cross-sectional nature of all of the included studies, it is impossible to determine whether or not individuals were infected with HPV at the time of vaccination. To address this, some studies required buffer time periods between vaccination and outcome assessment in order to control for the risk of prevalent infection. Studies that did not account for the risk of prevalent infections at the time of vaccination were considered at high risk of bias. Another important consideration in observational studies of HPV vaccine effectiveness is controlling for confounding due to baseline differences in risk of HPV acquisition between vaccinated and unvaccinated individuals. Some of the studies included in this review collected information on sexual activity and were able to control for baseline risk of HPV acquisition by controlling for markers of sexual activity. However, many of the included studies did not have any available information on the sexual activity of participants. There was a low risk of bias due to confounding related to health-seeking behaviors for all the studies for which it was relevant (those that did not utilize national population health registries).

HPV infection

Four studies reported HPV vaccine effectiveness against vaccine-type HPV infection.[28,30,35,40] Across all four studies, a gradient effect was seen with higher vaccine effectiveness among those who received the vaccine at younger ages. One was conducted in Scotland and reported the effectiveness of the bivalent vaccine against types 16 and 18. The other three were conducted in the United States and reported HPV vaccine effectiveness against the four types included in the quadrivalent vaccine.[30,35,40] All four studies were cross-sectional studies. The study conducted in Scotland utilized national screening registry data.[28] Markowitz et al. utilized data from two integrated healthcare networks in northern California and the Pacific Northwest, while Meites et al. analyzed data collected as part of a cross-sectional study of vaccine impact in men who have sex with men (MSM) and transgender women in three US cities (Seattle, Washington, Chicago, Illinois and Los Angeles, California). Winer et al. similarly evaluated data from a cross-section study of MSM and transgender women conducted in Seattle, Washington.[30,35,40]

Kavanagh et al. reported statistically significant vaccine effectiveness of three doses of the bivalent vaccine compared to unvaccinated individuals across six ages at vaccine initiation groups, with decreasing vaccine effectiveness the later the vaccine series was initiated adjusted for a composite measure of deprivation (Table 2; Figure 2).[28] Vaccine effectiveness was highest in the youngest age group evaluated, 89.1% (95% confidence Interval (CI) 85.1–92.3%) among those who initiated between 12 and 13 years of age and decreased slightly for each year later the vaccine was administered to 28.9% effective among those who received the vaccine after age 18 (95% CI = 4.5–47.8%).[28] Markowitz et al. found statistically significant vaccine effectiveness of at least one dose of the quadrivalent vaccine among those who initiated vaccination prior to age 18 (aPR = 0.06; 95% CI = 0.04–0.11) but no statistically significant effect among those who initiated vaccination after age 18.[30] In Meites et al. and Winer et al., the population of interest was men who have sex with men (MSM). In Meites et al., at least one dose of the quadrivalent vaccine was statistically significantly effective among those who initiated it before and after the age of 18; however, vaccine effectiveness was much higher in those who initiated vaccination prior to age 18 (≤18 years aPR = 0.41, 95% CI = 0.25–0.57; >18 years aPR = 0.82, 95% CI = 0.67–0.98).[35] Winer et al. similarly found high, statistically significant vaccine effectiveness against penile infection among MSM and transgender women who initiated vaccination prior to age 18 (aPR = 0.15; 95% CI = 0.04–0.62); however, they did not find a statistically significant effect in participants who initiated vaccination after age 18.[40] Markowitz et al., Meites et al., and Winer et al. presented analyses adjusted for age and race/ethnicity, and Meites et al. and Winer et al. adjusted for additional factors related to sexual activity, including the number of sexual partners and HIV status.[30,35]

Anogenital warts

Five studies reported vaccine effectiveness of the quadrivalent HPV vaccine (qHPV) against anogenital warts.[24,25,33,34,38] Four of the five studies stratified analyses by age at vaccine initiation with varying sub-

Table 2. Analyses and main findings of studies that evaluated HPV vaccine effectiveness by age at vaccination.

Study	N (overall)	Comparison with unvaccinated	Age groups analyzed	N (age group)	Comparison with unvaccinated by age group	Adjustment
		Effect (95% CI)			Effect (95% CI)	
Vaccine-type HPV infection						
Kavanagh 2017[a]		*Three doses*			*Three doses*	
	8,584	aOR = 0.40 (0.33–0.48)	12–13 years	971	VE = 89.1% (85.1–92.3)	Scottish Index of Multiple Deprivation quintile
			14 years	269	87.7% (78.9–93.5)	
			15 years	880	82.3% (76.8–86.7)	
			16 years	1,156	75.9% (70.2–80.8)	
			17 years	422	58.1% (44.8–68.8)	
			≥18 years	264	28.9% (4.5–47.8)	
Markowitz 2020		*At least one dose*			*At least one dose*	
	4,269	aPR = 0.14 (0.10–0.21)	≤18 years	2,785	aPR = 0.06 (0.04–0.11)	Race/Ethnicity, Age at Screening
			>18 years	432	0.65 (0.40–1.05)	
Meites 2020[b]		*At least one dose*			*At least one dose*	
	1,767	aPR = 0.71 (0.59–0.83)	≤18 years	289	aPR = 0.41 (0.24–0.57)	Age, race/ethnicity, city, number of sex partners, HIV status
			>18 years	366	0.82 (0.67–0.98)	
Winer 2021[b]		*At least one dose*			*At least one dose*	
	751	aPR = 0.69 (0.47–1.01)	≤18 years	83	aPR = 0.15 (0.04–0.62)	Age, history of ever taking PrEP, HIV status, lifetime number of sex partners
			>18 years	217	0.80 (0.52–1.22)	
Anogenital warts						
Baandrup 2021[c]					*Three doses*	
	1,904,895 PYs	N/A	12–14 years	1,609,179 PYs	aIRR = 0.16 (0.15–0.18)	Attained age, socioeconomic status, calendar time
			15–16 years	313,276 PYs	0.20 (0.18–0.22)	
			17–18 years	93,925 PYs	0.29 (0.25–0.33)	
			≥19 years	614,840 PYs	0.76 (0.71–0.81)	
Dominiak-Felden 2015[d]		*Three doses*			*At least one dose*[e]	
	334,903 PYs	VE = 85.9 (74.8, 92.1)	<15 years	57,595	VE = 89.0% (73.2–95.5)	Age
			15–17 years	53,149	90.4% (78.3–95.7)	
			≥18 years	5,636	68.5% (1.2, 89.9)	
Leval 2013[f]					*Three doses*	
	2,209,263	N/A	10–13 years	2	0.07 (0.02–0.27)	Age, parental education
			14–16 years	105	0.20 (0.17–0.25)	
			17–19 years	110	0.29 (0.24–0.35)	
			20–22 years	24	0.52 (0.35–0.78)	
			23–26 years	14	0.79 (0.47–1.33)	
			27–44 years	4	2.32 (0.87–6.18)	
Willows 2018[g]					*At least one dose*	
	31,464	N/A	9–18 years	65,432 PYs	aHR = 0.6 (0.4–0.8)	Birth date, neighborhood of residence, previous hospitalization, previous physician visit
			>19 years, not sexually active	1,820 PYs	1.8 (0.5–5.8)	
			>19 years, sexually active	21,244 PYs	2.8 (2.1–3.7)	
Zeybek 2019[h]			*Age at Last Dose*		*Three doses*	
	440,532 females	N/A	<15 years	60,299	aHR = 0.78 (0.46, 1.35)	Gender, region, history of STDs
	133,394 males		15–19 years	87,235	0.58 (0.49, 0.70)	
			>20 years	29,517	1.11 (0.91, 1.35)	
Cervical abnormalities						
Dehlendorff 2018					*Three doses*	
	2,272,586		≤16 years	453,859	0.23 (0.11–0.49)	Attained age, mother's education, country
			17–19 years	78,432	0.65 (0.41–1.03)	
			≥20 years	180,297	1.31 (0.97–1.76)	
Gargano 2022		*At least one dose*			*At least one dose*	
	773,193	aRR = 0.46 (0.41–0.52)	<20 years	171,156	aRR = 0.35 (0.30–0.40)	Birth year, race
			≥20 years	213,404	0.64 (0.55–0.75)	
Herweijer 2016					*Three doses*	
	1,333,691	N/A	<16 years	441,355 PYs	aIRR = 0.16 (0.08–0.32)	Attained age, parental education
			17–19 years	139,156 PYs	0.43 (0.33–0.57)	
			20–29 years	24,644 PYs	0.75 (0.59–0.95)	
Hofstetter 2016		*At least one dose*			*At least one dose*	

(*Continued*)

Table 2. (Continued).

Study	N (overall)	Comparison with unvaccinated	Age groups analyzed	N (age group)	Comparison with unvaccinated by age group	Adjustment
	13,253	0.77 (0.67–0.89)	11–14 years	178	aHR = 0.24 (0.10–0.59)	Number of doses, age as of Jan 1, 2007, language, insurance, clinic, abnormal baseline cervical cytology result, baseline *Chlamydia* screening
			15–16 years	762	0.63 (0.45–0.89)	
			17–18 years	1341	0.81 (0.64–1.01)	
			19–20 years	328	0.85 (0.68–1.05)	
Innes 2020					*At least one dose*	
	135,273	N/A	<18 years	133,895 PYs	IRR = 0.75 (0.70–0.80)	
			≥18 years	65,761 PYs	0.86 (0.76–0.94)	
Palmer 2019		*Two doses*			*Three doses*	
	138,692	aOR = 0.77 (0.48–1.24)	12–13 years	16,200	aOR = 0.14 (0.08–0.25)	Deprivation, rurality
			14 years	5,409	0.18 (0.07–0.43)	
			15 years	16,532	0.29 (0.19–0.44)	
			16 years	17,511	0.27 (0.18–0.41)	
			17 years	8,711	0.55 (0.36–0.83)	
			≥18 years	4,117	0.85 (0.52–1.37)	
Racey 2020					*At least one dose*	
	38,304	N/A	9–14 years	20,738	VE = 73.6% (57.5%-84.1%)	Birth age, age at first screen
			≥15 years	3,436	32.0% (0.0%-65.3%)	
Righolt 2019[i]					*At least one dose*	
	31,442	N/A	14–17 years		VE = 12% (−37%-43%)	Household income, hospitalization in previous five years, have more than 12 physician visits in the previous year, history of a pap smear
			≥18 years		−37% (−93%-3%)	
Rodriguez 2020					*Three doses*	
	133,082 vaccinated cohort	N/A	<15 years	3,784	aHR = 0.71 (0.37–1.38)	Region, history of STDs, history of pregnancy
	66,541 unvaccinated cohort		15–19 years	24,018	0.66 (0.55–0.80)	
			≥20 years	11,021	0.96 (0.77–1.20)	
Silverberg 2018		*At least one dose*			*At least one dose*	
	4,357 cases 21,773 controls	aOR = 0.82 (0.73–0.93)	14–17 years	293	aOR = 0.61 (0.46–0.81)	Smoking, hormonal contraceptives, race/ethnicity, recent sexually transmitted infections, parity, prior outpatient visits, immunosupression status
			18–20 years	799	0.72 (0.58–0.90)	
			≥21 years	1,445	0.94 (0.81–1.09)	
Cervical cancer						
Kjaer 2021					*At least one dose*	
	867,689	N/A	≤16 years	314,862	aIRR = 0.14 (0.04–0.53)	Age, maximum educational level of own, mother or father, ethnicity
			17–19 years	20,063	0.32 (0.08–1.28)	
			≥20 years	167,607	1.19 (0.80–1.79)	
Lei 2020		*At least one dose*			*At least one dose*	
	1,672,983	aIRR = 0.37 (0.21–0.57)	<17 years		aIRR = 0.12 (0.00–0.34)	Age, county of residence, calendar year, mother's country of birth, highest parental education level, highest annual household income level, previous diagnosis in mother of CIN3+, previous diagnosis in mother of cancers other than cervical cancer.
			≥17 years		0.47 (0.27–0.75)	

HPV = human papillomavirus; CI = confidence interval; aOR = adjusted odds ratio; aIRR = adjusted incidence rate ratio; aHR = adjusted hazard ratio; VE = vaccine effectiveness; aRR = adjusted relative risk; PY = person-year; N/A = not applicable.

[a]Additional analyses compared vaccine effectiveness by dose, birth cohort and Scottish Index of Mutiple Deprivation.

[b]Population studied was men who have sex with men and transgender women.

[c]Additional vaccine effectiveness analyses were conducted stratified by age and by dose.

[d]Person-years of follow-up contributed by fully vaccinated and unvaccinated. Additional analyses evaluated vaccine effectiveness among those who received one or two doses.

[e]Age stratified analyses considered individuals completely vaccinated with one dose.

[f]N's are observed number of cases of genital warts in fully vaccinated group.

[g]Person-Years contributed by vaccinated group. Additional analyses looked at effectiveness by dose.

[h]Analyses include males and females. Additional vaccine effectiveness analyses conducted by dose.

[i]Limited to women with no history of abnormal pap. N's for age analyses not provided.

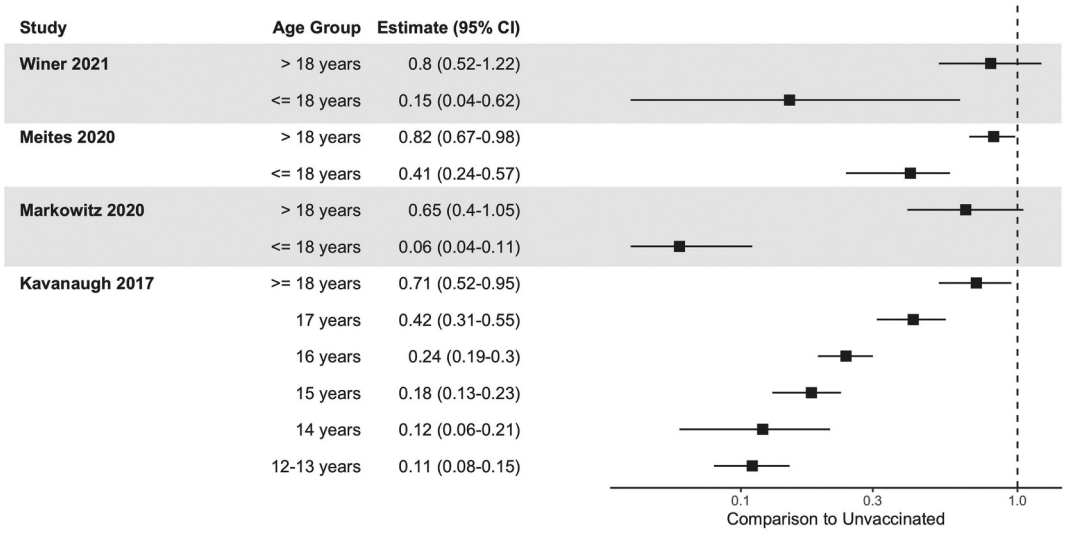

Figure 2. Effectiveness of HPV vaccination against vaccine-type HPV infection by age at vaccination.

groups.[24,25,33,34] The remaining study evaluated vaccine effectiveness stratified by age at which the final dose of the vaccine was received.[38] All five studies were retrospective cohort studies (Table 1).

Three of the five studies had a clear gradient pattern, with the highest vaccine effectiveness among those who received the vaccine at younger ages (Table 2; Figure 3). The youngest age group evaluated was initiation between 10 and 13 years of age in Leval et al., which found that three doses of the quadrivalent vaccine was 93% effective (95% CI = 73–98%) at preventing anogenital warts, compared to 48% among those who received the vaccine after age 19 (95% CI = 22–65%).[34] Baandrup et al. found that for those who initiated vaccination between ages 12–14, the incidence rate of anogenital warts was 0.16 (95% CI = 0.15–0.18) that of those who were unvaccinated compared to 24% effectiveness among those who received the vaccine after age 18 (95% CI = 19–29%).[24] Both Baandrup et al. and Leval et al. utilized population health registries in Denmark and Sweden, respectively, and found a general pattern of decreasing vaccine effectiveness at a later age at initiation.[24,34] Dominiak-Felden et al. found similar vaccine effectiveness of at least one dose of the quadrivalent vaccine for those who initiated vaccination before 15 years of age (VE = 89.0%; 95% CI = 73.2–95.5%) and between age 15 and 17 (VE = 90.4%; 95% CI = 78.3–95.7%) followed by a fairly substantial decrease in vaccine effectiveness among those who initiated after age 18 (VE = 68.5%; 95% CI = 1.2–89.9%).[25]

Willows et al. stratified their analyses both by age and, for those over the age of 18, by sexual activity. Among those who initiated vaccination before age 18, the vaccine was statistically

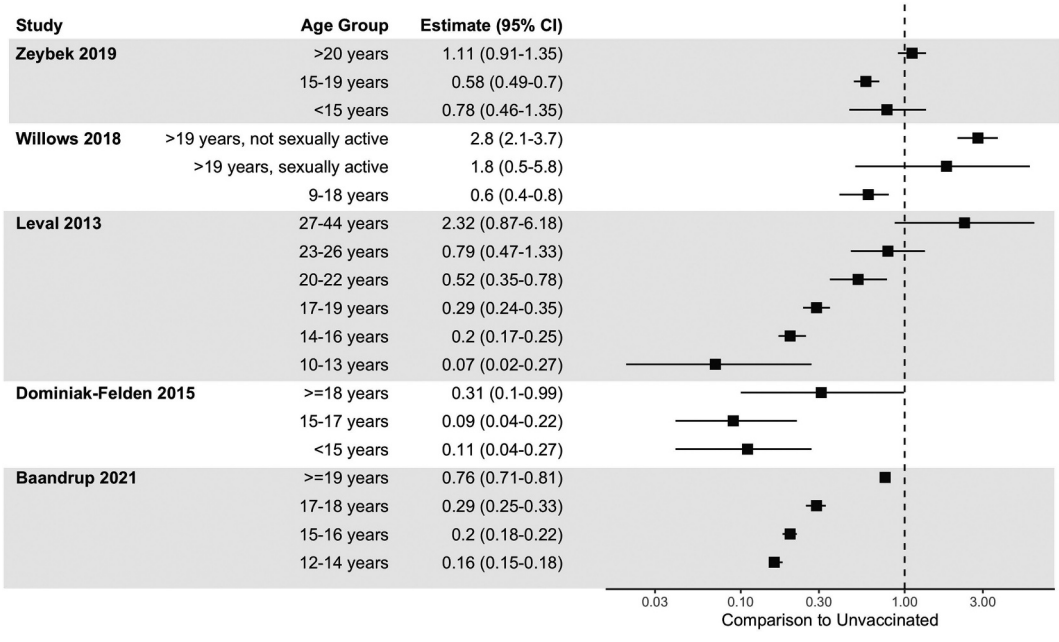

Figure 3. Effectiveness of HPV vaccination against anogenital warts by age at vaccination.

significantly effective (aHR = 0.6; 95% CI = 0.4–0.8). However, regardless of sexual activity, Willows et al. found that the vaccine was not effective in reducing the incidence of genital warts among those who initiated vaccination after age 18 (not sexually active aHR = 1.8; 95% CI = 0.5–5.8; sexually active aHR = 2.8; 95% CI = 2.1–3.7).[33] Zeybek et al. evaluated the effectiveness of the quadrivalent vaccine against genital warts among both men and women stratified by age at which the final dose was received. Among those who received the final dose before the age of 15, Zeybek et al. reported no effect of the vaccine (aHR = 0.78; 95% CI = 0.46–1.35).[38] But among those who completed the vaccine series between the ages of 15 and 19, the vaccine was statistically significantly effective (aHR = 0.58; 95% CI = 0.49–0.70).[38] All of the studies accounted for participant age.[24,25,33,34,38]

Cervical abnormalities

Ten studies evaluated vaccine effectiveness against cervical abnormalities. In all but two studies, the outcome of interest was abnormal high-grade histology results (CIN2+), and many evaluated multiple outcomes (Table 1).[26,31,32,36,39,41,42,44] The remaining two studies evaluated high-grade abnormal cytology as the primary outcome of interest.[27,37] Figure 4 presents vaccine effectiveness against the highest grade cytology or histology outcome reported in the study. Nine of the 10 studies were retrospective cohort studies, utilizing national health registries, regional immunization or screening registries, or insurance claims databases. The remaining study presented the results of a case-control study of women enrolled in an integrated healthcare delivery in the United States.[32]

All of these studies found a general pattern of decreasing vaccine effectiveness as age at initiation or completion increased, particularly when initiated after the age of 18 (Table 2; Figure 4). Palmer et al. found that the HPV vaccine was 86% (95% CI = 75–90%) effective at preventing cervical abnormalities (CIN3+) among girls who initiated vaccination between 12 and 13 years old in Scotland.[31] The vaccine remained statistically significantly effective when initiated up until age 17, after which the effectiveness was limited (aOR = 0.85; 95% CI = 0.52–1.37).[31] Similarly, Hofstetter et al. found that girls and young women who initiated vaccination between ages 11–14 years in New York City in the United States had a 76% lower risk of being diagnosed with a cervical abnormality compared to those who did not initiate vaccination (aHR = 0.24; 95% CI = 0.10–0.59) but that effectiveness was limited when initiated after age 18 (aHR = 0.85; 95% CI = 0.68–1.05).[27]

Two studies did find statistically significant vaccine effectiveness for participants who initiated after the age of 18 in adjusted analyses. Gargano et al. utilized regional registries in Michigan (USA) to evaluate effectiveness against cervical abnormalities (CIN3+) and found that while the vaccine was more effective when initiated prior to the age of 20 (aRR = 0.35; 95% CI = 0.30–0.40), it still had an effect when administered after the age of 20 (aRR = 0.64; 95% CI = 0.55–0.75) adjusted for participant age and race.[26] Similarly, Herweijer et al. found that the vaccine was most effective when initiated prior to age 16 (aIRR = 0.16; 95% CI 0.08–0.32) but also effective when administered at older ages (aIRR 17–19 = 0.43; 95%

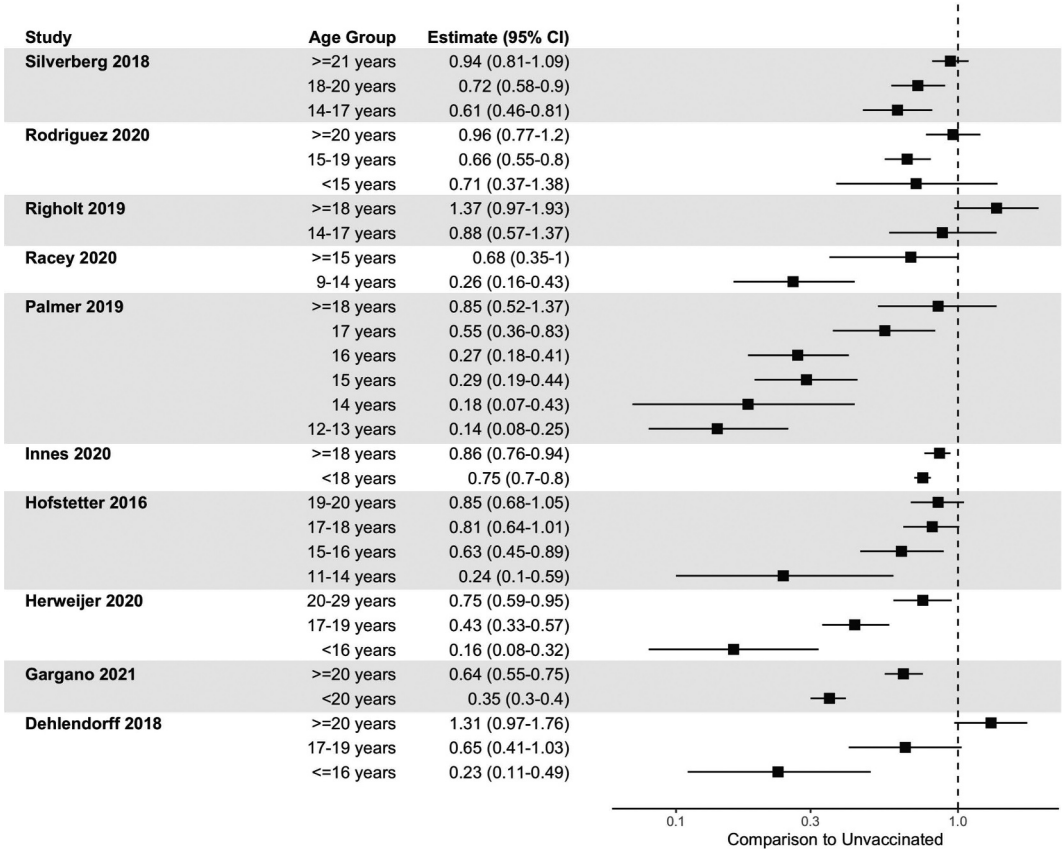

Figure 4. Effectiveness of HPV vaccination against cervical abnormalities by age at vaccination.

CI = 0.33–0.57; aIRR 20+ = 0.75; 95% CI = 0.59–0.95).[39] Innes et al. found statistically significant vaccine effectiveness among participants who initiated vaccination after 18 years of age (IRR = 0.75; 95% CI = 0.70–0.80), however did not conduct any adjusted analyses.[44] Righolt et al. found limited vaccine effectiveness against cervical abnormalities regardless of age (Ages 14–17: VE = 12%; 95% CI = −37–43%; Ages 18+: VE = −37%; 95% CI = −93%-3%).

Cervical cancer

Two retrospective cohort studies evaluated HPV vaccine effectiveness against cervical cancer utilizing national population health registries (Table 1).[13,14] In Denmark, Kjaer et al. found that the vaccine was effective against cervical cancer among those who initiated the vaccine series prior to age 17 (aIRR = 0.14; 95% CI = 0.04, 0.53), adjusting for age, education, and ethnicity (Table 2, Figure 5). In Sweden, Lei et al. found that the vaccine was statistically significantly effective against cervical cancer when administered both before and after age 17 but that the vaccine was more effective when administered prior to age 17 (aIRR <17 years = 0.12, 95% CI = 0.00, 0.34; aIRR ≥17 years = 0.47, 95% CI = 0.27–0.75) adjusted for age, residence, income, education and family history of cervical abnormalities.

Discussion

In this systematic review, we identified 21 observational studies that evaluated HPV vaccine effectiveness against different HPV-related disease outcomes by age at which the vaccine series was either initiated or completed. Seventeen of the 21 studies found the greatest vaccine effectiveness in the youngest age group evaluated,[13,14,24,26–28,30–36,39,40,42,44] with many of those studies also finding decreased vaccine effectiveness by later age at vaccine series initiation. Greater effectiveness of HPV vaccines at younger ages is likely due to administration of these prophylactic vaccines prior to natural exposure to HPV from sexual activity rather than a biologic mechanism independent of natural exposure. Though younger adolescents do produce higher levels of antibodies after vaccination, older adolescents and adults also have a robust immune response that produces antibody levels much higher than natural infection that likely confers substantial protection.

All but one study[37] found statistically significant vaccine effectiveness in at least one age group evaluated.[13,14,24–28,30–36,38–42,44] In the studies that did not find that the vaccine was most effective in the youngest age group or did not find evidence of vaccine effectiveness there were generally very low rates of the disease outcome of interest, particularly in younger age groups, resulting in limited statistical power to detect a difference in disease outcomes between the vaccinated and unvaccinated. For example, in Zeybek et al., the outcome of interest was diagnosis with anogenital warts starting 3 months after completion of the final dose of the HPV vaccine series. Participants were followed for up to 5 years. For those participants who completed vaccination prior to the age of 15, particularly those who completed the vaccine series as recommended (ages 11–12), it is possible that they were at limited to no risk of exposure to HPV during the study period.[38] Similarly, in Righolt et al., which found no evidence of vaccine effectiveness, a short follow-up period for younger participants meant that there was likely both lower risk of exposure and outcome in the younger age groups among both vaccinated and unvaccinated participants.[37]

The HPV vaccine is recommended between ages 9 and 14 years for girls by the World Health Organization and for all adolescents at ages 11–12 by the ACIP in the United States. However, many individuals do not initiate the recommended vaccine series in this window, starting vaccination later in adolescence or in young adulthood. By age 18, approximately 60% of US adolescents will have initiated sexual activity, increasing their risk of exposure to HPV.[45] Many studies used late adolescence (18–20 years of age) as a cutoff point between different age groups, likely reflecting the average age of sexual debut.[14,24–26,28,30,31,33,35,37,40,41,44] While some studies did find that the vaccine was still effective when administered after the age of 18, in general, the vaccine was substantially more effective in those who received the vaccine prior to the age of 18 against all outcomes, reflecting findings from clinical trials that have demonstrated higher efficacy when the vaccine is administered prior to exposure to HPV.

Given that many adolescents do not initiate vaccination on time, in the US, both the American Cancer Society (ACS) and the American Academy of Pediatrics (AAP) recommend initiating the HPV vaccination series as early as 9 years of age in order to complete vaccination prior to initiation of sexual

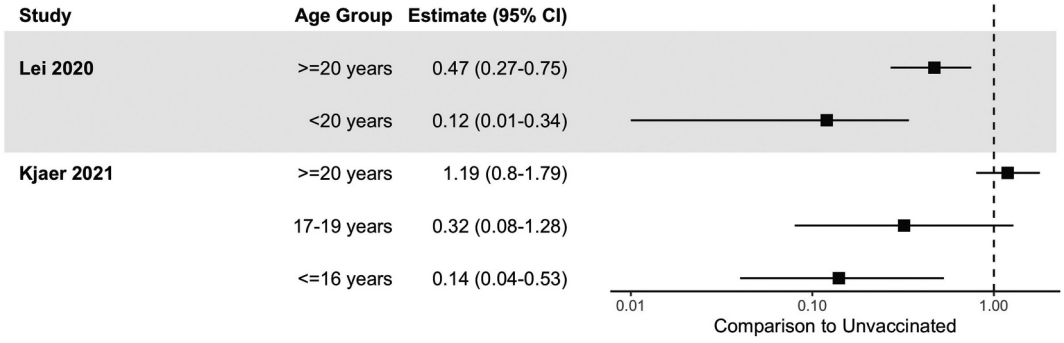

Figure 5. Effectiveness of HPV vaccination against cervical cancer by age at vaccination.

activity.[46,47] There is also evidence that initiating the vaccine series earlier in childhood (at ages 9 or 10) can lead to greater series completion.[46,48] In the studies that evaluated vaccine effectiveness when administered in early adolescence (ages 10–14), vaccine effectiveness estimates against the different outcomes of interest ranged from approximately 74% to 93%.[24,28,31,34,36,38,39]

Our inclusion criteria were specific to studies that reported HPV vaccine effectiveness for comparisons between vaccinated and unvaccinated individuals. Other studies that compared vaccine effectiveness by different ages at vaccination did not meet our inclusion criteria but provide further evidence for the importance of younger ages at vaccination. For example, Cameron et al. evaluated HPV positivity following the introduction of the HPV vaccination program in Scotland and found that individuals who were vaccinated after the age of 18 were more than three times as likely to be positive for HPV types 16 or 18 compared to individuals who were vaccinated at ages 15–16 (aOR = 3.41; 95% CI = 1.98–5.82).[49] Other studies compared the proportions of participants with the outcome between vaccinated and unvaccinated individuals but did not conduct a vaccine effectiveness analysis and therefore also did not meet out inclusion criteria. For example, Onuki et al. found a greater frequency of high grade cervical lesion diagnoses among women vaccinated after age 18 when compared to women vaccinated prior to the age of 18 ($p < 0.001$).[50] These findings also support the conclusion that the HPV vaccine is more effective when initiated at younger ages.

Additionally, we excluded studies that evaluated vaccine effectiveness by birth cohort or age in relation to when the vaccine was licensed and/or recommended given that these studies did not have individual-level data on age at vaccination. During the review process, we identified a number of studies on HPV vaccine effectiveness among women who were above or below a certain age when the vaccine was licensed in 2007.[51–53] In cases when information is not available on the age that an individual received the vaccine, a birth cohort can be a useful proxy as it can indicate whether or not women had the opportunity to be vaccinated at a certain age. In general, these studies found that women who had the opportunity to be vaccinated at younger ages (i.e., were eligible for routine vaccination at ages 11–12) were less likely to have HPV-related disease outcomes compared to women who would have been vaccinated at later ages.[51–53] Our search strategy also restricted the search to studies that included the terms "vaccine" and "effectiveness" within four words of each other in title or abstract, under the assumption that studies that conducted a vaccine effectiveness analysis would include the term in the title or abstract. It is possible that this strategy did not capture every relevant article. However, we did conduct backwards citation chasing in order to limit the possibility of missing articles.

Most of the included studies were deemed to have at least moderate risk of bias. This was generally due to the inherent limitations that may be present in any observational epidemiologic study. However, it is important to note that after the prelicensure randomized trials, observational studies are necessary to assess real-world impact and in many cases as the only ethical approach. Though these studies do have the acknowledged limitations, the consistency across the majority of studies that used different approaches is reassuring about the robustness of the general conclusion about greater effectiveness at younger ages.

All of the studies were conducted in high-income countries and were primarily conducted in North America and Europe, reflecting a lack of studies that evaluate HPV vaccine impact and effectiveness in low- and middle-income countries (LMIC).[6] Overall vaccine effectiveness is affected by vaccine efficacy, real-world conditions of administration, and population-level vaccine coverage. In a study conducted in Bhutan, classified as a lower-middle income country with high HPV vaccine coverage, overall effectiveness estimates were similar to those in high-income countries with high vaccine coverage.[54] However, additional studies may be needed in countries with lower vaccine coverage to understand vaccine effectiveness. Additionally, as demonstrated through this review, HPV vaccine effectiveness by age is influenced by age of initiation of sexual activity, which may also vary by country. The consistency of the findings across setting is encouraging, however it may still be beneficial for other countries, particularly LMIC, to conduct additional vaccine effectiveness studies to better understand vaccine impact and promote vaccine programs.

Vaccine effectiveness studies are vital for understanding how impactful a vaccine is in the real world. For many vaccinations and HPV vaccine in particular, actual patterns of vaccine uptake often vary from the vaccine recommendation in terms of age at administration. Understanding how this variation impacts the effectiveness of the vaccine in different populations is important for informing future vaccine recommendations, vaccine policy and implementation of vaccination programs. This review demonstrates that in high-income settings, the HPV vaccine is more effective when the vaccine series is initiated at younger ages. However, gaps remain. Few studies evaluated disease outcomes in men. Furthermore, few studies included HPV-associated cancers; this will be increasingly feasible in the coming years and should be a research priority. Additional studies that evaluate vaccine effectiveness in the youngest recommended age groups (ages 9 and 10) will help improve our understanding the effectiveness of HPV vaccine by age. In all future research, the importance of controlling for confounding by factors related to vaccination and outcomes (e.g., sexual activity) will be important. Collectively, these findings can be used to bolster current recommendations encouraging parents to begin vaccinating their children at the earliest recommended age.

Disclosure statement

Dr. Niccolai serves as a scientific advisor for Merck and Moderna. Drs. Oliveira and Sheikha and Mss. Ellingson and Nyhan have no conflicts of interest to declare.

Funding

This work was supported in part by the National Institutes of Health (NIH) [grant number R01AI123204] (Drs. Niccolai, Oliveira and Sheikha) and [5F31AI167626] (Ellingson). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

ORCID

Mallory K. Ellingson http://orcid.org/0000-0003-2729-0661

References

1. How Many Cancers Are Linked with HPV Each Year? | CDC. Published 2022 Oct 4. [accessed 2023 Feb 20]. https://www.cdc.gov/cancer/hpv/statistics/cases.htm
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. doi:10.3322/caac.21660.
3. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180–e90. doi:10.1016/S2214-109X(19)30488-7.
4. Human Papillomavirus (HPV) Vaccines - NCI. Published 2021 Jun 18. [accessed 2023 Jun 26]. https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet
5. Cervical cancer. [accessed 2023 Feb 20]. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer
6. Oliveira CR, Niccolai LM. Monitoring HPV vaccine impact on cervical disease: status and future directions for the era of cervical cancer elimination. Prev Med. 2021;144:106363. doi:10.1016/j.ypmed.2020.106363.
7. Markowitz LE, Schiller JT. Human papillomavirus vaccines. J Infect Dis. 2021;224(12 Suppl 2):S367–S78. doi:10.1093/infdis/jiaa621.
8. Huh WK, Joura EA, Giuliano AR, Iversen O-E, de Andrade RP, Ault KA, Bartholomew D, Cestero RM, Fedrizzi EN, Hirschberg AL, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. Lancet Lond Engl. 2017;390(10108):2143–59. doi:10.1016/S0140-6736(17)31821-4.
9. Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boily M-C, Baldo V, Brassard P, Brotherton JML, Callander D, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394(10197):497–509. doi:10.1016/S0140-6736(19)30298-3.
10. Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Bernal J, Elliss-Brookes L, Sasieni P. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet. 2021;398(10316):2084–92. doi:10.1016/S0140-6736(21)02178-4.
11. Wang W Vivian, Kothari S, Skufca J, Giuliano, AR, Sundström, K, Nygård, M, Koro, C, Baay, M, Verstraeten, T, Luxembourg, A. Real-world impact and effectiveness of the quadrivalent HPV vaccine: an updated systematic literature review. Expert Rev Vaccines. 2022;1–19. doi:10.1080/14760584.2022.2129615.
12. Markowitz LE, Drolet M, Lewis RM, Lemieux-Mellouki P, Pérez N, Jit M, Brotherton JM, Ogilvie G, Kreimer AR, Brisson M, et al. Human papillomavirus vaccine effectiveness by number of doses: updated systematic review of data from national immunization programs. Vaccine. 2022;40(37):5413–32. doi:10.1016/j.vaccine.2022.06.065.
13. Kjaer SK, Dehlendorff C, Belmonte F, Baandrup L. Real-world effectiveness of human papillomavirus vaccination against cervical cancer. J Natl Cancer Inst. 2021;113(10):1329–35. doi:10.1093/jnci/djab080.
14. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383(14):1340–8. doi:10.1056/NEJMoa1917338.
15. Mix JM, Van Dyne EA, Saraiya M, Hallowell BD, Thomas CC. Assessing Impact of HPV vaccination on cervical cancer incidence among women aged 15–29 years in the United States, 1999–2017: an ecologic study. Cancer Epidemiol Biomarkers Prev. 2021;30(1):30–7. doi:10.1158/1055-9965.EPI-20-0846.
16. Human papillomavirus vaccines: WHO position paper (2022 Update). Wkly Epidemiol Rec. 2022;97(50):645–72.
17. Meites E. Use of a 2-dose schedule for human papillomavirus vaccination — Updated recommendations of the advisory committee on immunization practices. Morb Mortal Wkly Rep. 2016;65(49):1405–8. doi:10.15585/mmwr.mm6549a5.
18. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the advisory committee on immunization practices. Morb Mortal Wkly Rep. 2019;68(32):698–702. doi:10.15585/mmwr.mm6832a3.
19. Dobson SRM, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, Sauvageau C, Scheifele DW, Kollmann TR, Halperin SA, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013;309(17):1793–802. doi:10.1001/jama.2013.1625.
20. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, Block SL, Skrivanek A, Nur Azurah AG, Fong SM, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. JAMA. 2016;316(22):2411–21. doi:10.1001/jama.2016.17615.
21. Covidence - Better systematic review management. Covidence. [accessed 2023 Mar 20]. https://www.covidence.org/
22. Ellingson MK, Sheikha H. Human papillomavirus vaccine effectiveness by age at vaccination: a systematic review; 2022.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
24. Baandrup L, Dehlendorff C, Kjaer SK. One-dose human papillomavirus vaccination and the risk of genital warts: a Danish nationwide population-based study. Clin Infect Dis. 2021;73(9):e3220–e6. doi:10.1093/cid/ciaa1067.
25. Dominiak-Felden G, Gobbo C, Simondon F, Liu X. Evaluating the early benefit of quadrivalent HPV vaccine on genital warts in Belgium: A cohort study. PLoS One. 2015;10(7):e0132404. doi:10.1371/journal.pone.0132404.
26. Gargano JW, You M, Potter R, Alverson, G, Swanson, R, Saraiya, M, Markowitz, LE, Copeland, G. An evaluation of dose-related HPV vaccine effectiveness using central registries in Michigan. Cancer Epidemiol Biomarkers Prev. 2022;31(1):183–91. doi:10.1158/1055-9965.EPI-21-0625.
27. Hofstetter AM, Ompad DC, Stockwell MS, Rosenthal SL, Soren K. Human papillomavirus vaccination and cervical cytology outcomes among urban low-income minority females. JAMA Pediatr. 2016;170(5):445–52. doi:10.1001/jamapediatrics.2015.3926.
28. Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, Bhatia R, Moore C, Cubie H, Cruickshank M, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis. 2017;17(12):1293–302. doi:10.1016/S1473-3099(17)30468-1.
29. Lamb F, Herweijer, E, Ploner, A, Uhnoo, I, Sundström, K, Sparén, P, Arnheim-Dahlström, L. Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: a nationwide cohort study. BMJ Open. 2017;7(6):e015021. doi:10.1136/bmjopen-2016-015021.
30. Markowitz LE, Naleway AL, Klein NP, Lewis RM, Crane B, Querec TD, Hsiao A, Aukes L, Timbol J, Weinmann S, et al. Human papillomavirus vaccine effectiveness against HPV infection: evaluation of one, two, and three doses. J Infect Dis. 2020;221(6):910–8. doi:10.1093/infdis/jiz555.

31. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, Cruickshank M. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019;365:l1161. doi:10.1136/bmj.l1161.
32. Silverberg MJ, Leyden WA, Lam JO, Gregorich SE, Huchko MJ, Kulasingam S, Kuppermann M, Smith-McCune KK, Sawaya GF. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. Lancet Child Adolesc Health. 2018;2(10):707–14. doi:10.1016/S2352-4642(18)30220-7.
33. Willows K, Bozat-Emre S, Righolt CH, Kliewer EV, Mahmud SM. Early evidence of the effectiveness of the human papillomavirus vaccination program against anogenital warts in Manitoba, Canada: a registry cohort study. Sex Transm Dis. 2018;45(4):254–9. doi:10.1097/OLQ.0000000000000742.
34. Leval A, Herweijer E, Ploner A, Eloranta S, Fridman Simard J, Dillner J, Young C, Netterlid E, Sparén P, Arnheim-Dahlström L, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. JNCI J Natl Cancer Inst. 2013;105(7):469–74. doi:10.1093/jnci/djt032.
35. Meites E, Winer RL, Newcomb ME, Gorbach PM, Querec TD, Rudd J, Collins T, Lin J, Moore J, Remble T, et al. Vaccine effectiveness against prevalent anal and oral human papillomavirus infection among men who have sex with men—United States, 2016–2018. J Infect Dis. 2020;222(12):2052–60. doi:10.1093/infdis/jiaa306.
36. Racey CS, Albert A, Donken R, Smith L, Spinelli JJ, Pedersen H, de Bruin P, Masaro C, Mitchell-Foster S, Sadarangani M, et al. Cervical intraepithelial Neoplasia rates in British Columbia women: a population-level data linkage evaluation of the school-based HPV immunization program. J Infect Dis. 2020;221(1):81–90. doi:10.1093/infdis/jiz422.
37. Righolt CH, Bozat-Emre S, Mahmud SM. Effectiveness of school-based and high-risk human papillomavirus vaccination programs against cervical dysplasia in Manitoba, Canada. Int J Cancer. 2019;145(3):671–7. doi:10.1002/ijc.32135.
38. Zeybek B, Lin YL, Kuo YF, Rodriguez AM. The impact of varying numbers of quadrivalent human papillomavirus vaccine doses on anogenital warts in the United States: a database study. J Low Genit Tract Dis. 2018;22(3):189–94. doi:10.1097/LGT.0000000000000401.
39. Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. Int J Cancer. 2016;138(12):2867–74. doi:10.1002/ijc.30035.
40. Winer RL, Lin J, Querec TD, Unger ER, Stern JE, Rudd JM, Golden MR, Swanson F, Markowitz LE, Meites E, et al. Effectiveness of Human Papillomavirus (HPV) vaccination against penile HPV infection in men who have sex with men and transgender women. J Infect Dis. 2022;225(3):422–30. doi:10.1093/infdis/jiab390.
41. Rodriguez AM, Zeybek B, Vaughn M, Westra J, Kaul S, Montealegre JR, Lin Y-L, Kuo Y-F. Comparison of the long-term impact and clinical outcomes of fewer doses and standard doses of human papillomavirus vaccine in the United States: a database study. Cancer. 2020;126(8):1656–67. doi:10.1002/cncr.32700.
42. Dehlendorff C, Sparén P, Baldur-Felskov B, Herweijer E, Arnheim-Dahlström L, Ploner A, Uhnoo I, Kjaer SK. Effectiveness of varying number of doses and timing between doses of quadrivalent HPV vaccine against severe cervical lesions. Vaccine. 2018;36(43):6373–8. doi:10.1016/j.vaccine.2018.09.011.
43. Kavanagh K, Pollock KGJ, Potts A, Love J, Cuschieri K, Cubie H, Robertson C, Donaghy M. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer. 2014;110(11):2804–11. doi:10.1038/bjc.2014.198.
44. Innes CRH, Williman JA, Simcock BJ, Hider P, Sage M, Dempster-Rivett K, Lawton, BA, Sykes, PH. Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women. N Z Med J. 2020;133(1508):72–84.
45. Products - data briefs - number 366 -May 2020. Published 2020 May 5. [accessed 2023 May 1]. https://www.cdc.gov/nchs/products/databriefs/db366.htm
46. O'Leary ST, Nyquist A-C. Why AAP recommends initiating HPV vaccination as early as age 9. Published online 2019 Oct 4. [accessed 2023 Mar 20]. https://publications.aap.org/aapnews/news/14942/Why-AAP-recommends-initiating-HPV-vaccination-as
47. HPV Vaccination and Cancer Prevention | ACS. [accessed 2023 Mar 30]. https://www.cancer.org/healthy/hpv-vaccine.html
48. O'Leary SC, Frost HM. Does HPV vaccination initiation at age 9, improve HPV initiation and vaccine series completion rates by age 13? Hum Vaccines Immunother. 2023;19(1):2180971. doi:10.1080/21645515.2023.2180971.
49. Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, Ahmed S, Palmer T, Pollock KGJ. Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009–2013 - volume 22, number 1—January 2016- emerging infectious diseases journal - CDC. Emerg Infect Dis. 2016;22(1):56–64. doi:10.3201/eid2201.150736.
50. Onuki M, Yamamoto K, Yahata H, Kanao H, Yokota H, Kato H, Shimamoto K, Takehara K, Kamiura S, Tsuda N, et al. Human papillomavirus vaccine effectiveness by age at first vaccination among Japanese women. Cancer Sci. 2022;113(4):1428–34. doi:10.1111/cas.15270.
51. Brotherton JML, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: observational cohort of young women in Australia. Papillomavirus Res. 2015;1:59–73. doi:10.1016/j.pvr.2015.05.005.
52. Acuti Martellucci C, Nomura S, Yoneoka D, Ueda P, Brotherton J, Canfell K, Palmer M, Manzoli L, Giorgi Rossi P, De Togni A, et al. Human papillomavirus vaccine effectiveness within a cervical cancer screening programme: cohort study. BJOG: Int J Obstet Gynaecol. 2021;128(3):532–9. doi:10.1111/1471-0528.16429.
53. Crowe E, Pandeya N, Brotherton JML, Dobson AJ, Kisely S, Lambert SB, Whiteman DC. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ. 2014;348(mar04 2):g1458. doi:10.1136/bmj.g1458.
54. Baussano I, Tshomo U, Tenet V, Heideman DAM, Wangden T, Franceschi S, Clifford GM. Prevalence of human papillomavirus and estimation of human papillomavirus vaccine effectiveness in Thimphu, Bhutan, in 2011–2012 and 2018. Ann Intern Med. 2020;173(11):888–94. doi:10.7326/M20-2849.

Appendices

Appendix I. Search Strategy

Round 1 of searching
Searched 2023-01-10
No publication type filter was used in this search.
Ovid MEDLINE(R) <1996 to December Week 5 2022>
Ovid Embase < 1996 to 2023 January 09>

(1) papillomavirus vaccin×.mp. 14407
(2) HPV vaccine.mp. 12695
(3) Gardasil.mp. 3313
(4) Cervarix.mp. 2297
(5) 1 or 2 or 3 or 4 22,765
(6) (vaccin* adj4 effectiveness).mp. 19750
(7) papillomavirus infections.mp. 33155
(8) HPV.mp. 104236
(9) uterine cervical neoplasm.mp. 233
(10) cervical intraepithelial neoplasia.mp. 22297
(11) HPV-related disease×.mp. 1353
(12) Condylomata acuminate.mp. 62
(13) Genital warts.mp. 5112
(14) 7 or 8 or 9 or 10 or 11 or 12 or 13 122,093
(15) 5 and 6 and 14 1250

Round 2 of searching
Ovid Medline
Searched 2023-04-14
No date filter and no publication type filter was used in this search.

Ovid MEDLINE(R) ALL <1946 to April 13, 2023>		
1	papillomavirus vaccin*.mp. or exp papillomavirus vaccines/	10835
2	HPV vaccin*.mp.	10086
3	Gardasil.mp.	592
4	Cervarix.mp.	341
5	1 or 2 or 3 or 4	13801
6	(vaccin* adj4 effectiveness).mp. or vaccine efficacy/	11411
7	(papillomavirus infection* or papilloma virus infection*).mp.	34941
8	HPV.mp.	51257
9	uterine cervical neoplasm.mp. or Uterine Cervical Neoplasms/or cervical cancer*.mp. or cervical neoplasm*.mp.	104036
10	cervical intraepithelial neoplasia.mp. or exp Uterine Cervical Dysplasia/	17911
11	HPV related disease*.mp.	636
12	Condylomata acuminate.mp. or exp Condylomata Acuminata/or condylomata acuminata.mp.	5898
13	Genital warts.mp.	2668
14	7 or 8 or 9 or 10 or 11 or 12 or 13	142329
15	5 and 6 and 14	707

This query can be rerun by pasting the middle column of the table into the Ovid Search Launcher at https://tools.ovid.com/ovidtools/launcher.html.

Ovid Embase
Searched 2023-04-14
No date filter and no publication type filter was used in this search.

Embase <1974 to 2023 April 13>		
1	papillomavirus vaccin*.mp. or exp Human papilloma virus vaccine/	6022
2	HPV vaccin*.mp.	13899
3	Gardasil.mp.	2856
4	Cervarix.mp.	2030
5	1 or 2 or 3 or 4	17479
6	(vaccin* adj4 effectiveness).mp.	13412
7	(papillomavirus infection* or papilloma virus infection*).mp. or exp papillomavirus infection/	40849
8	HPV.mp.	72190
9	uterine cervical neoplasm.mp. or exp uterine cervix cancer/or cervical cancer*.mp. or cervical neoplasm*.mp.	139131
10	cervical intraepithelial neoplasia.mp.	12085
11	HPV related disease*.mp.	891
12	Condylomata acuminate.mp. or exp condyloma acuminatum/or condylomata acuminata.mp.	9792
13	Genital warts.mp.	3815
14	7 or 8 or 9 or 10 or 11 or 12 or 13	196980
15	5 and 6 and 14	948

This query can be rerun by pasting the middle column of the table into the Ovid Search Launcher at https://tools.ovid.com/ovidtools/launcher.html.

Round 2 totals

source	raw numbers from round 2	after deduplication by Covidence (within the round 2 results and also against round 1 results)
medline	707	86
embase	948	113
total	1655	199

The new records were uploaded to a separate Covidence project for screening.

Appendix II. Bias analysis results

		Information Bias			Confounding	
Study	Selection Bias	Intervention	Outcome	Prevalent Infection	HPV Acquisition	Health Seeking Behavior
HPV Infection						
Kavanagh 2017	Low	Low	Low	High	High	Low
Markowitz 2020	Low	Low	Moderate	Moderate	Moderate	Low
Meites 2020	Moderate	Moderate	Moderate	High	Moderate	Low
Winer 2020	Moderate	Moderate	Moderate	High	Moderate	Low
Anogenital Warts						
Baandrup 2021	Low	Low	Low	Low	Moderate	N/A
Dominiak-Felden 2015	Low	Low	Low	Low	Moderate	N/A
Leval 2013	Low	Low	Low	Moderate	Moderate	N/A
Willows 2018	Moderate	Low	High	High	Low	Low
Zeybek 2019	Moderate	Low	Low	Low	Moderate	N/A
Cervical Abnormalities						
Dehlendorff 2018	Low	Low	Moderate	Moderate	Moderate	N/A
Gargano 2022	Moderate	Low	Low	Moderate	Moderate	Low
Herweijer 2016	Low	Low	Moderate	Low	Moderate	N/A
Hofstetter 2016	Moderate	Moderate	High	Low	Moderate	Low
Innes 2020	Low	Low	Moderate	Moderate	High	Low
Palmer 2019	Low	Low	Low	Low	High	Low
Racey 2020	Moderate	Low	Moderate	Low	Moderate	Low
Righolt 2019	Moderate	Low	High	Moderate	High	Low
Rodriguez 2020	Moderate	Low	Moderate	Low	Moderate	Low
Silverberg 2018	Moderate	Low	Moderate	Low	Moderate	Low
Cervical Cancer						
Kjaer 2021	Low	Low	Moderate	Low	Moderate	N/A
Lei 2020	Low	Low	Moderate	Low	Moderate	N/A

Appendix III

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.2 (word count limited, could not include all required information)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3–4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5, p. 7
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.4–5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix I
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.5–6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6–7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p. 17

(*Continued*)

(Continued).

Section and Topic	Item #	Checklist item	Location where item is reported
Study characteristics	17	Cite each included study and present its characteristics.	p. 7–15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 8–9, Table 1, Appendix II
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p.7–15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.15–20
	23b	Discuss any limitations of the evidence included in the review.	p. 18–19
	23c	Discuss any limitations of the review processes used.	p. 18–19
	23d	Discuss implications of the results for practice, policy, and future research.	p. 19–20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 21
Competing interests	26	Declare any competing interests of review authors.	p. 21
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
For more information, visit: http://www.prisma-statement.org/.