Summary of the evidence on the safety, efficacy, and effectiveness of human papillomavirus vaccines

Umbrella review of systematic reviews

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Supplemental material is available online.

ABSTRACT

Background. This objective of this umbrella review was to summarize the evidence on safety, efficacy, and effectiveness of human papillomavirus (HPV) vaccines in the general population.

Methods. The authors conducted a literature search and selected systematic reviews if they were published from January 2006 through November 2018, included randomized controlled trials or observational studies, related to the general population, and evaluated HPV vaccine–related clinical outcomes. The authors independently and in duplicate screened literature, extracted data, and appraised reviews using AMSTAR 2, a critical appraisal tool for systematic reviews.

Results. The authors selected 30 systematic reviews that included male and female participants aged 9 through 76 years from multiple countries. Reviews evaluated postvaccine seroconversion, HPV infection rates, precancerous or benign lesions, and adverse events; none of the researchers reported on oral or oropharyngeal lesions. Results from the reviews showed that, compared with those who received a placebo or non–HPV-type vaccine, HPV-vaccinated participants had statistically significantly higher rates of seroconversion and local adverse events, statistically significantly lower rates of HPV infection and condylomata lesions, and decreased rates of HPV-related precancerous lesions, which did not always attain statistical significance.

Conclusions. Systematic reviews have found evidence that the available HPV vaccines are safe, effective, and efficacious against vaccine-type HPV infection and HPV-associated cellular changes, including precancerous and benign lesions.

Practical Implications. Dentists may use this resource to better understand the literature on the potential harms and benefits of HPV vaccination.

Key Words. Human papillomavirus; human papillomavirus vaccines; condylomata; precancerous cervical cancer; oropharyngeal cancer; adverse events.

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Human papillomavirus (HPV) is a nonenveloped double-stranded DNA virus with more than 100 different genotypes isolated to date.[1] It is the most common sexually transmitted infection in the United States, with a prevalence of 70 million and an incidence of 14 million cases per year.[2] HPV is detected in oral rinses or gargles in 6.9% of people aged 14 through 69 years[3-5]; the rate is 3-fold higher in men than women (11.5% versus 3.3%).[6] Most (90%) mucosal HPV infections, whether cervical or oral or oropharyngeal, resolve asymptomatically within 1 through 2 years.[7] HPV types are categorized into low risk (types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) or high risk (types 16, 18, 31, 33, 35, 45, 51, 52, 56, and 58) on the basis of their oncogenic potential at the cervix, which is the most thoroughly studied anatomic site.

Persistent (nonclearing) infections with one of the high-risk HPV types can lead to cancer in a number of anatomic sites over many years, including the oropharynx.[8] Low-risk HPV types are associated with benign lesions, including condylomata acuminata lesions, verruca vulgaris, papillomas, and recurrent respiratory papillomatosis.[1,9,10]

Epidemiology of HPV-associated precancerous and cancerous lesions

High-risk HPV types (especially types 16 and 18) are known causes of cervical cancer and some anal, oropharyngeal, penile, vaginal, and vulvar cancers.[8] The Centers for Disease Control and Prevention estimates that as of 2015, 12.1 of every 100,000 adults have received a diagnosis of HPV-associated cancer. Rates of different HPV-associated cancers have changed over time. Incidence of cervical carcinoma, once the most common HPV-associated cancer, has declined since 1999, while the incidence of anal, oropharyngeal, and vulvar squamous cell carcinomas (SCCs) have increased.[8-11] HPV 16 is estimated to be responsible for most (> 90%) oropharyngeal, cervical, and anal cancers.[12]

In 2015, oropharyngeal SCC was the most common HPV-associated cancer, surpassing cervical carcinoma.[8] The largest increases in rates of HPV-associated oropharyngeal SCC (HPVOSCC) were in white middle-aged men.[8] Oral cavity and oropharyngeal SCC incidence rates related to tobacco and alcohol declined from 1988 through 2004.[13,14] However, the overall incidence of oropharyngeal SCC has risen over the past 3 decades, and this is attributed to a 225% increase in HPVOSCC.[14] As a result, HPVOSCC now represents 70% through 80% of oropharyngeal SCCs in the United States.[15] The lingual and palatine tonsils, specifically, are hot spots for HPV infection. It is expected that oropharyngeal cancer incidence will continue to increase,[16] stimulating interest in prevention of HPV infection and subsequent development of HPVOSCC.[17]

HPV vaccines

The US Food and Drug Administration has approved 3 HPV vaccines, all of which protect against high-risk HPV types 16 and 18.[18] Cervarix (GlaxoSmithKline), a bivalent vaccine, contains L1 proteins specific to HPV types 16 and 18. Gardasil (Merck), a quadrivalent vaccine, contains L1 proteins for HPV 6, 11, 16, and 18. Gardasil 9 (Merck), a nonavalent vaccine, contains L1 proteins specific to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Since 2017, only the nonavalent HPV vaccine is distributed in the United States.

Review objective

Research published in 2018 shows that there is a need to develop scientific and educational resources to help dentists understand the evidence about HPV vaccines.[19,20] Just as systematic reviews synthesize the data from existing individual studies, an umbrella review summarizes the evidence from existing systematic reviews. Umbrella reviews can provide a summary of evidence from multiple systematic reviews that cover different populations, research questions, or time periods, so that a single paper provides an overview of the best available evidence to clinical decision makers.[21] The purpose of this umbrella review was to summarize the evidence available about the HPV vaccine in terms of its safety as well as its efficacy and effectiveness on HPV infection, HPV-related noncancerous lesions, and HPV-related precancerous lesions at any anatomic site in men or women of any age. This overview can serve as a guide for readers looking for a high-quality systematic review on a particular outcome, patient population, or vaccine type. In addition, it highlights contradictions and areas of consistency within the evidence base of HPV vaccination, as well as research gaps.

ABBREVIATION KEY

AE:	Adverse events.
CINAHL:	Cumulative Index to Nursing and Allied Health Literature.
HPV:	Human papillomavirus.
HPVOSCC:	Human papillomavirus–associated oropharyngeal squamous cell carcinoma.
PICO:	Patient/population, intervention, comparison, outcome.
SCC:	Squamous cell carcinoma.

METHODS

We registered the review protocol in PROSPERO, the International Prospective Register of Systematic Reviews (registration 118971) and followed the literature search, screen, appraisal, and synthesis that were established a priori. We used a previously described method to develop this umbrella review.[22]

Eligibility criteria

Type of Studies

We included systematic reviews in which researchers evaluated outcomes related to the safety, efficacy, and effectiveness of HPV vaccines. If umbrella reviews had been found, we would have

excluded them. To be considered a systematic review, the study needed to include a reproducible search methodology for identifying eligible studies and an explicit set of inclusion and exclusion criteria. We considered double-blind, randomized controlled trials to measure HPV vaccine efficacy or the effect of the vaccine under controlled conditions. We considered observational studies to measure HPV vaccine effectiveness, which can be thought of as the effects of the vaccine in less-controlled conditions that are more generalizable to the general population.[23]

Type of Participants

We included systematic reviews with data on men or women, of any age, in any geographical location, to focus the umbrella review on HPV vaccine outcomes among the general population as opposed to those for a specific health condition.

Type of Interventions

We included systematic reviews that studied any type of HPV vaccine.

Outcome Measures

We included the following outcome measures at any anatomic site: HPV incident or persistent infection, prevalence of oral antibodies to HPV; HPV infection (oral); HPV infection (other); condylomata acuminata lesions; HPV-associated precancerous intraepithelial lesions; and adverse events (AEs). Specifics regarding measurement and definition of these outcomes can be found in the Appendix (available online at the end of this article). We included systematic reviews regardless of whether their researchers reported outcomes by per protocol or intention to treat. No restriction was placed on time in which measured outcomes were reported. We defined AEs as reported by the review authors.

Literature Search Strategy

An informationist (K.K.O.) developed a search strategy to retrieve relevant literature from MEDLINE via PubMed, Embase via embase.com, Cumulative Index to Nursing and Allied Health Literature Complete via EBSCO, and the Cochrane Database of Systematic Reviews from January 2006 through November 2018 (eTable 1, available online at the end of this article). We used the Clinical Queries systematic review filter in PubMed[24] and the Scottish Intercollegiate Guidelines Network filter in Embase and Cumulative Index to Nursing and Allied Health Literature.[25] We searched the reference sections of all included systematic reviews and searched PROSPERO and the Database of Abstracts of Reviews of Effects. We did not exclude any reviews on the basis of status or the language of publication.

Selection of Studies, Data Extraction, and Evaluation

We (C.G.E., R.D.L.) independently screened citation titles and abstracts for eligibility using Covidence systematic review software (Veritas Health Innovation) and then screened the full texts. We (C.G.E., S.C.P., R.D.L.) extracted data independently in duplicate from each systematic review to 2 standardized forms. We contacted authors when information was unclear or missing. The first form captured the review aim or PICO (Patient/population, intervention, comparison, outcome) questions, databases searched, language restriction, literature search time, primary studies' inclusion criteria, design of included studies, number of included studies, total number of participants, participant demographics, vaccines used, comparators, outcome measures, and whether meta-analysis, formal risk of bias assessment, or an evaluation of the certainty of the evidence were presented. The second standardized form collected the following information from the included reviews' results: whether outcomes were presented under an intention-to-treat or per-protocol analysis, the summary treatment estimates, and the 95% confidence interval (CI) for each outcome. Outcomes are presented as calculated by the authors of the reviews. The statistical significance of each review's meta-analyses are graphically summarized.

We (C.G.E., R.D.L.) independently evaluated each systematic review included by using the online version of AMSTAR 2, a tool for assessing the methodological quality of systematic reviews,[26] and solved disagreements via discussion.

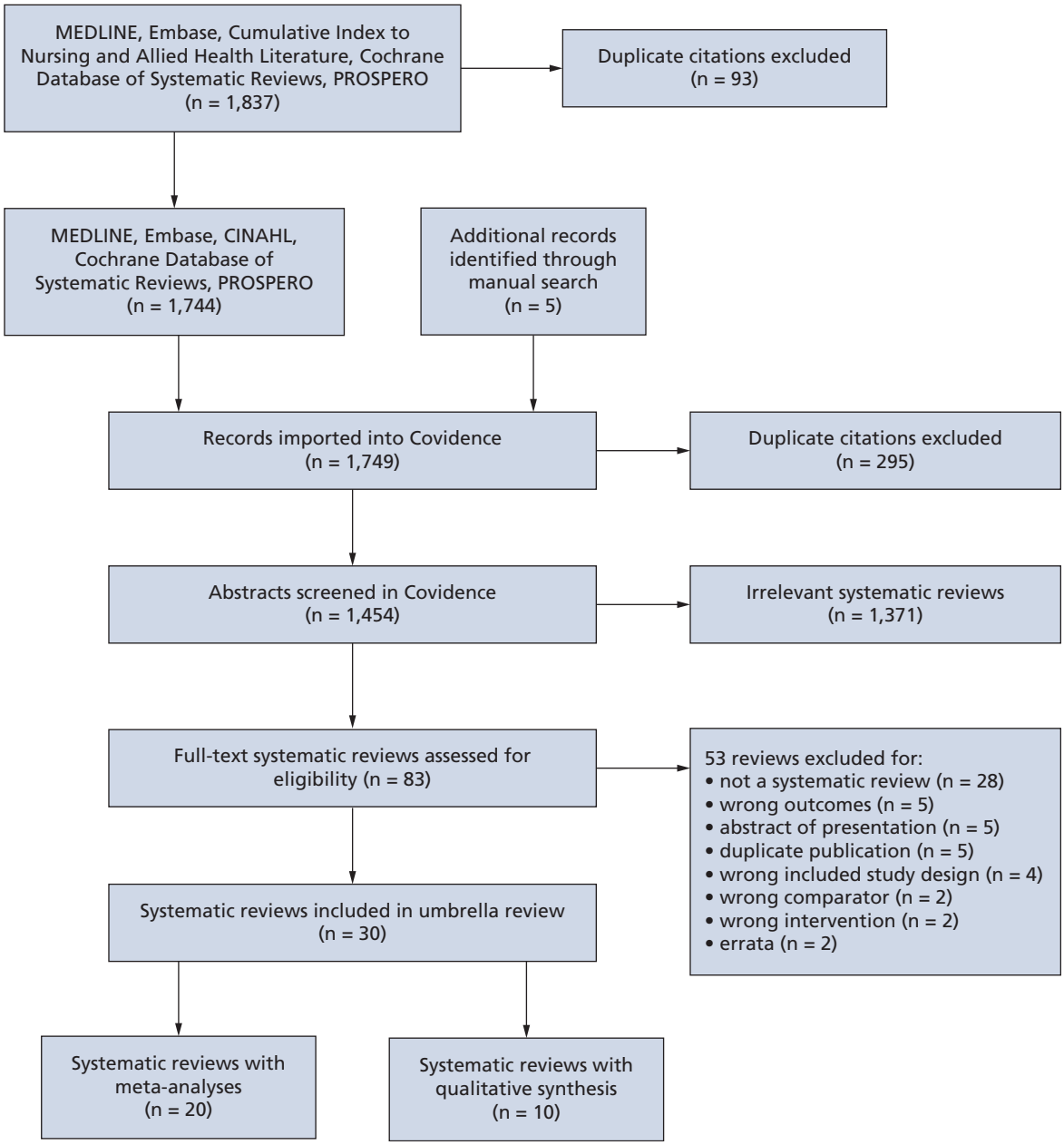

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search.[27] Covidence is manufactured by Veritas Health Innovation.

RESULTS

Results of the search

After eliminating duplicate citations, we identified 1,454 unique references for screening (Figure 1). After title and abstract review, we screened 83 potentially eligible articles using full texts. A total of 30 reviews[28-57] met the selection criteria. A full list of the 53 reviews excluded at the full-text level and the reasons for their exclusion are presented in eTable 2 (available online at the end of this article).

Characteristics of the included systematic reviews

We found that the number of studies from which results were summarized in the published systematic reviews ranged from 3 through 58 and included study participants aged 9 through 76 years (eTable 3, available online at the end of this article). The number of study participants involved ranged from a little over 1,000 to more than 1 million. Further characteristics can be found in the Appendix (available online at the end of this article). The systematic reviewers aimed to answer a

variety of research questions (eTable 3). Some reported only about the safety of HPV vaccines,[28,31,36,41,42,45,48,51] while others evaluated only the potential benefits of the vaccines.[29,33-35,38,43,44,47,55,56] Some focused on a single outcome, such as cervical persistent HPV infection[38] or anogenital warts.[55,56] Three reviews summarized outcomes for men or boys only[37,54,57] and 15 for women or girls only,[28-30,32-35,38,39,43,46-51] and researchers in the remaining 12 reviews included data for men and boys, women and girls.[31,35,36,40-42,44,45,52,53,55,56] Others limited their search and findings by age group,[31,32] vaccine,[53,57] vaccination schedule or doses,[33,44] or nation.[52,56] We found no systematic reviews in which the authors summarized the available evidence for safety, efficacy, and effectiveness in the general population without 1 of the aforementioned restrictions.

Systematic review methodological quality

Twelve of the included systematic reviews had no critical weaknesses according to AMSTAR 2 criteria.[29,30,33,34,37,38,40,43,46,47,49,55] The remaining 18 reviews had at least 1 critical flaw, meaning they may not provide an accurate and comprehensive summary of the available evidence.[26] The most common critical flaws were lack of a registered protocol before start of the review[28,29,31,32,35,36,38-48,50-54,57] and an assessment of the risk of publication bias.[20,33,34,36,40,43,46,48-51] Reviews with critical flaws were no different from those without them in terms of year of publication, demographics of included participants, number of studies included, vaccine type, or whether the systematic review authors had any reported conflicts of interest (eTable 3). Critically flawed systematic reviews were more likely to provide qualitative summaries of the evidence rather than conduct meta-analysis, and most reported on AEs only (eTable 3).

Outcomes in systematic reviews

Risk of Bias, Methodological Quality, and Assessments of the Certainty of the Evidence

In most of the included systematic reviews, the authors assessed the risk of bias in their included studies[29-34,37-40,43,44,46,48-50,52,55,56] using the Cochrane risk-of-bias tool designed for randomized controlled trials,[30,32,34,37,40,48,52,55,58] the Jadad scale,[31,38,49,59] or their own set of criteria.[29,39,43,44,46,50,56] Of the systematic reviews that summarized the risk of bias, most assessed all of their included studies as being of low risk of bias or high methodological quality, with the exception of 1 study in which the researchers followed participants for more than 5 years[33] and 1 nonrandomized study (eTable 3).[37] In 6 of the included systematic reviews, the authors evaluated the certainty of their included evidence,[28,30,32-34,37] in 4 of them using Grading of Recommendations Assessment, Development, and Evaluation[60] (eTable 3).[30,32,33,37] The most common reason given for rating down the certainty of the evidence was imprecision caused by wide CIs around the effect measure (eTable 4, available online at the end of this article).

Seroconversion or Infection Efficacy

Four systematic reviews reported immunogenicity,[40,52,54,57] of which 3 calculated summary statistics on HPV antibody titers.[40,52,54] Tan and colleagues[54] calculated seroconversion rates exceeding 99% for HPV types 6, 11, 16, and 18. Participants vaccinated with HPV vaccines had a higher chance of seroconversion for HPV types 6 (odds ratio [OR], 128.54; 95% CI, 37.22 to 443.9), 11 (OR, 89.6; 95% CI, 32.53 to 246.03), 16 (systematic review estimates ranged from relative risk [RR], 44.86; 95% CI, 11.90 to 169.5 to OR, 303.92; 95% CI, 46.41 to 1,990.23), and 18 (ranging from RR, 8.13; 95% CI, 5.96 to 11.11 to RR, 96.04; 95% CI, 33.87 to 272.34) compared with those receiving a placebo or hepatitis A vaccine (Figure 1; eTable 3, available online at the end of this article).[40,52] Eleven systematic reviews evaluated HPV infection rates,[29,30,33,35,37-39,43,44,46,49] of which 7 conducted meta-analysis.[29,30,33,38,39,46,49] All showed reductions in rates of incident (ranging from OR, 0.09; 95% CI, 0.05 to 0.15 to RR, 0.23; 95% CI, 0.14 to 0.37) or persistent infection (ranging from RR, 0.05; 95% CI, 0.03 to 0.09 to RR, 0.52; 95% CI, 0.42 to 0.65) among those vaccinated with an HPV vaccine compared with those who were not (Figure 2 and eTable 4, available online at the end of this article, display meta-analysis results; eTable 5, available online at the end of this article, displays qualitative synthesis results). A single review evaluated efficacy against persistent oral infection and found an 88% reduction in persistent oral infection (95% CI, 2% to 98%).[37]

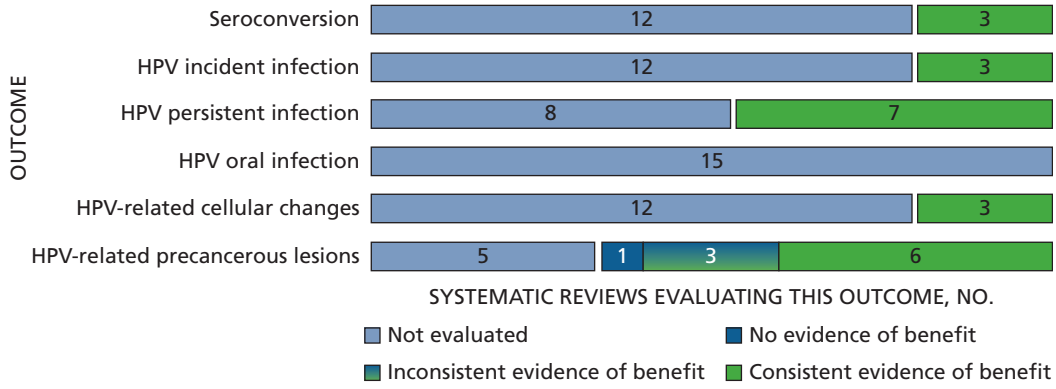

Figure 2. Human papillomavirus (HPV) vaccine meta-analysis results from included systematic reviews by efficacy outcome type.

HPV-Related Lesion Efficacy

Eight reviews summarized data on condylomata acuminata lesions,[32,35,37,44,46,55-57] of which 6 reported meta-analysis results.[32,37,39,46,49,55] These 6 reviews reported a lower risk of developing condylomata lesions (ranging from RR, 0.05; 95% CI, 0.01 to 0.25 to RR, 0.38; 95% CI, 0.31 to 0.47) (Figure 2, eTable 4, available online at the end of this article) among people receiving an HPV vaccine. Fifteen reviews summarized data on precancerous intraepithelial lesions,[29,30,32-35,37,39,43,44,46,47,49,50,57] of which 10 reported results from a meta-analysis,[29,30,32-34,39,46,47,49,50] commonly reporting data from multiple lesion types as separate outcomes. Although in every meta-analysis HPV vaccination showed a protective effect against development of precancerous intraepithelial lesions with HPV vaccination, the effect was not always statistically significant for each lesion type studied. The effect sizes ranged from an RR of 0.01 (95% CI, 0.0 to 0.1) for cervical intraepithelial neoplasia 3+ to an RR of 0.8 (95% CI, 0.62 to 1.02) for cervical intraepithelial neoplasia 2+ (Figure 2 and eTable 4, available online at the end of this article, display meta-analysis results; eTable 5, available online at the end of this article, displays qualitative synthesis results). One review analyzed results only from the subgroup of women with evidence of high-risk types of HPV previous to vaccination; this was the sole meta-analysis not to find a protective effect of the vaccine against a precancerous lesion, in this case for vulvar intraepithelial neoplasia 2-3/vaginal intraepithelial neoplasia 2-3 (OR, 2.25; 95% CI, 0.78 to 6.50).[47] None of the reviews included data on nonmalignant or precancerous oral or oropharyngeal lesions.

HPV Vaccine Effectiveness

Five systematic reviews described data on vaccine effectiveness in men, boys, women, or girls, aged at least 9 years and living in Australia, Belgium, Canada, Denmark, England, France, Germany, New Zealand, Scotland, Spain, Sweden, and the United States (eTable 5, available online at the end of this article).[33,35,37,44,56] None of these reviews conducted meta-analyses and instead qualitatively described their findings as consistent decreases in HPV infection, condylomata, cervical intraepithelial neoplasia 2+, adenocarcinomas in situ, and low- and high-grade cytologic abnormalities in HPV-vaccinated populations compared with those unvaccinated (eTable 5, available online at the end of this article). One review included data on effectiveness against oral HPV infection from clinical trials that enrolled immunocompromised and immunocompetent men. In this review, HPV vaccines were associated with a 91% lower incident oral infection rate (95% CI, −59% to 99.5%) in men.[37]

AEs

The investigators in the included systematic reviews commonly categorized AEs as local (such as pain, swelling, or redness at the injection site), systemic (such as fever, headache, or fatigue), or serious (such as negative pregnancy outcomes or death). Of the 19 reviews that included information regarding AEs, 17 presented insight about local AEs,[30,31,36,39-42,44,46,48-55] 16 included separate mention of systemic AEs,[30,31,36,39-42,44,46,48,49,51-55] and 14 reported serious AEs, including

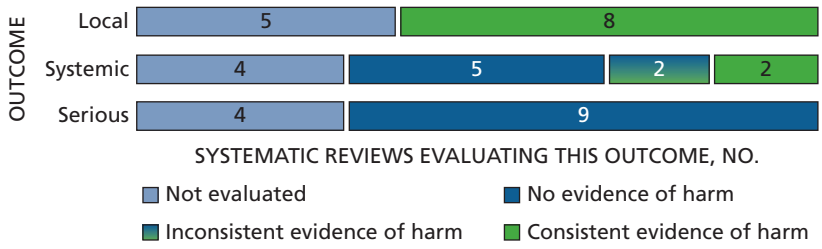

Figure 3. Human papillomavirus vaccine meta-analysis results from included systematic reviews by adverse outcome type.

death.[30,31,36,39-42,44,46,48-55] (There were no deaths attributable to the HPV vaccine.) Eight systematic reviews conducted meta-analyses on local AEs, such as pain, swelling, or redness at the injection site; all found that the risk of developing local AEs was higher for those vaccinated with an HPV vaccine compared with placebo, hepatitis A, or hepatitis B vaccine (Figure 3).[31,36,40,46,48,51,52,54] The chance of local AEs after vaccination ranged from an RR of 1.12 (95% CI, 1.06 to 1.18)[54] to an OR of 2.33 (95% CI, 1.61 to 3.36).[36] Nine systematic reviews meta-analyzed data on systemic AEs.[31,36,39,40,48,50,53,54,56] The meta-analyses differed on the magnitude and statistical significance of the chance of systemic AEs, from the risk of developing new onset of a chronic disease (RR, 0.5; 95% CI, 0.28 to 1.10)[51] to the odds of myalgia (OR, 1.97; 95% CI, 1.77 to 2.20)[36] (Figure 3). Nine reviews conducted meta-analysis for serious AEs, with estimates ranging from an RR of 0.66 (95% CI, 0.35 to 1.27)[51] to an RR of 1.29 (95% CI, 0.85 to 1.98)[30]; none found a statistically significant difference in risks of serious AEs in those vaccinated with an HPV vaccine compared with those who were not (Figure 3).[30,32,37,39,40,46,49,51,54] Evidence that was qualitatively synthesized rather than meta-analyzed by systematic review authors is summarized in eTable 4 (available online at the end of this article).

DISCUSSION

Summary of main findings

In this umbrella review, we compiled the data and evidence available in publications since the introduction of HPV vaccines. Our findings indicate that available HPV vaccines are effective against vaccine-type HPV infection and HPV-associated cellular changes, including precancerous and benign lesions. Compared with other vaccines, there may be higher rates of local or systemic AEs associated with HPV vaccination, but rates of serious AEs were similar between vaccinated and placebo groups. These overall findings did not vary by participants' sex, age, or trial location. Although only 1 systematic review[37] included data on the impact of HPV vaccination on oral HPV infection, the observed effect was consistent with that observed for HPV infection elsewhere in the body. The certainty of the evidence of the systematic reviews varied from high to very low, and the investigators in most of the reviews did not assess or report on the certainty of the evidence. Neither the quality of the included systematic reviews nor their results were associated with potential sources of conflict of interest reported by the authors of the systematic reviews.

Strengths and limitations

Existing systematic reviews on HPV vaccine safety, efficacy, and effectiveness present distinctive selection criteria for their primary studies. To effectively inform their practices, dentists would have to read multiple systematic reviews, each with variations in patient populations, outcomes presented, and vaccine types and doses. In contrast, conducting an umbrella review allowed us to develop a comprehensive summary of the available data to address a broad range of questions that dentists may have about HPV vaccines. Strengths of this review include its design and methodological rigor, as we used systematic methods to retrieve, select, and evaluate the available evidence. Our search included gray literature and was not restricted by language, which minimized the possibility that relevant reviews would have been missed. In addition, a panel with expertise in dentistry, oral pathology, human papilloma virology and epidemiology helped to define the scope of the work and interpretation of available evidence.

An important limitation of this review is that the number of studies and thus reviews that included data regarding oral infection was limited, precluding stringent analysis of this end point. As we further found, there are not yet reviews in which the investigators include data regarding the efficacy of HPV vaccines on oral or oropharyngeal cancers. In addition, given that many of the systematic reviews had similar aims and were conducted in a relatively limited time, some reviews included the same trials, so that their findings were derived from overlapping primary studies.

Implications for practice

The American Dental Association urges dentists to support the use and administration of the HPV vaccine as recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.[61] As Glick[62] noted, not only do dental offices provide an additional point at which to advocate for patients to follow immunization standards, but with state legislative approval and additional training, dentists could administer vaccinations. When it passed legislation in 2019 adding prescription and administration of vaccines into a dentist's scope of practice, Oregon became the first state in which dentists with appropriate training can administer the HPV vaccine.[63] Dentists with questions about the evidence on HPV vaccination may find their questions answered by this umbrella review or may use it as a guide to find a systemic review that addresses their specific query.

Implications for research

A knowledge gap exists regarding the direct effect of the HPV vaccine on HPV-associated oropharyngeal cancers. For those already infected with HPV, there is a need for further study of the HPV vaccination's effect on oral clearance of the virus and risk of developing HPV-associated lesions, including oropharyngeal cancer. There is still a need to improve identification of precursor lesions and biomarkers to facilitate early detection of oropharyngeal cancer. Lastly, best-practice strategies, which can be implemented by dentists and will serve to increase HPV vaccination rates in accord with guidance from the Centers for Disease Control and Prevention, need to be defined. Further research is needed to determine the effect of HPV vaccination on prevention of oral or oropharyngeal cancers.

CONCLUSIONS

The collective evidence of the efficacy of the HPV vaccines, which comes from systematic reviews of randomized controlled trials, demonstrates that HPV vaccines are effective against vaccine-type HPV infection and HPV-associated cellular changes, including precancerous and benign lesions. Furthermore, while the collective evidence from systematic reviews of safety data from randomized controlled trials and observational studies shows a consistent association between the HPV vaccine and local AEs, it also shows no increased risk of developing serious AEs. Systematic reviews of observational studies find evidence of HPV vaccine effectiveness. However, although existing research on oral infection and oral or oropharyngeal cancers is limited, there is sufficient evidence available for dentists to answer questions or concerns that they or their patients may have about HPV vaccines. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2019.10.010.

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SUPPLEMENTAL METHODS

In accordance with the World Health Organization expert consensus, we defined incident human papillomavirus (HPV) infection as new detection of HPV DNA in cells in people previously found to be HPV negative, and persistent HPV infection as detection of the same HPV DNA in specimens obtained after at least 6 months in those who were naïve to that HPV type at baseline.[e1,e2]

Antibodies to HPV types 6, 11, 16, or 18 were detected by using either enzyme-linked immunosorbent assay (ELISA) or anti-HPV serum competitive Luminex immunoassay (R&D Systems), with seroconversion determined by comparing patients' individual antibody profiles before and after HPV vaccination.[40,52,54] For competitive Luminex immunoassay, the levels were defined as at least 20 milli-Merck units for HPV 6; 16 for HPV 11; 20 for HPV 16; and 24 for HPV 18. For ELISA, the levels were 8 ELISA units per milliliter for HPV 16 and 7 ELISA units per milliliter for HPV 18.

Given the relatively low incidence and the long time to progression (> 10 years) for the HPV-associated cancers developing from the epithelium, the World Health Organization expert consensus is that trial investigators should use incident high-grade proliferative lesions (for example, high-grade cervical intraepithelial neoplasia and adenocarcinomas in situ) as the clinical end points of HPV trials.[e1,e2,30]

Characteristics of included studies

In all but 6 of the systematic reviews,[37,40,51,53,56,57] researchers reported on outcomes when administering more than 1 HPV vaccine. In 7 studies, researchers reported outcomes after administration of the monovalent HPV vaccine,[30,32,38,39,47,49,54] in 25 after administration of the bivalent HPV vaccine,[28-36,38,39,41-52,54,55] in 28 after administration of the quadrivalent HPV vaccine,[28-50,52,54-57] and in 3 after administration of the nonavalent HPV vaccine.[45,48,53] Researchers in 13 reviews did not indicate whether the results presented were based on intention-to-treat or per-protocol analysis.[28,31,35,36,40-42,44,45,47,48,56,57] In 4 reviews researchers summarized and reported intention-to-treat analysis only,[34,37,46,50] in 3 reviews researchers presented per-protocol analysis only,[38,51,54] and in 10 reviews researchers presented both intention-to-treat and per-protocol analyses.[29,30,32,33,39,43,49,52,53,55]

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eTable 1. Search strategy for umbrella review.

PubMed	
"Papillomavirus Vaccines"[Mesh] OR (("Papillomavirus Infections"[Mesh] OR "Papillomaviridae"[Mesh] OR HPV* OR hrHPV† OR HPV16/18 OR HPV6 OR HPV16 OR HPV18 OR "Human papillomavirus" OR "Human papillomaviruses" OR "Human papilloma virus" OR "Human papilloma viruses" OR Gardasil OR Cervarix OR 4vHPV‡ OR 9vHPV§) AND ("Vaccination"[Mesh] OR Vaccine OR Vaccines OR Vaccinate OR Vaccinated OR Vaccination OR immunize OR Immunization OR Immunizations OR immunized)) Database supplied limits: 2006 onward; Systematic reviews Filters: none	
Embase	
#43	#9 AND #41 AND [2006-2018]/py‖
#42	#9 AND #41
#41	#40 NOT #39
#40	#13 OR #22 OR #28 OR #33
#39	#34 OR #35 OR #38
#38	#36 NOT (#36 AND #37)
#37	'human'/exp¶
#36	'animal'/exp
#35	'editorial':it#
#34	'letter':it
#33	#31 AND #32
#32	'review':it
#31	#29 OR #30
#30	'selection criteria':ab**
#29	'data extraction':ab
#28	#23 OR #24 OR #25 OR #26 OR #27
#27	'relevant journals':ab
#26	'manual search*':ab
#25	'hand-search*':ab
#24	'bibliograph*':ab
#23	'reference lists':ab
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#21	'bids':ab
#20	'science citation index':ab
#19	('cinahl':ab OR 'cinhal':ab)
#18	('psychinfo':ab OR 'psycinfo':ab)
#17	('psychlit':ab OR 'psyclit':ab)
#16	'embase':ab
#15	'cochrane':ab
#14	'cancerlit':ab
#13	#10 OR #11 OR #12
#12	systematic NEXT/1 (review* OR overview*)
#11	(meta NEXT/1 analy*) OR metaanalys*
#10	'meta analysis'/exp
#9	#1 OR #8
#8	#6 AND #7
#7	#4 OR #5

* HPV: Human papillomavirus. † hrHPV: High-risk HPV. ‡ 4vHPV: Quadrivalent HPV vaccine. § 9vHPV: Nonavalent HPV vaccine. ‖ py: Publication year. ¶ exp: Explode. # it: Publication type. ** ab: Abstract. †† SIGN: Scottish Intercollegiate Guidelines Network. ‡‡ MH: MeSH Heading. §§ TX: All text (in Cumulative Index to Nursing and Allied Health Literature). ¶¶ PT: Publication type. ## MeSH: Medical Subject Headings. *** CRD: National Institute for Health Research Centre for Reviews and Dissemination.

eTable 1. Continued

#6	#2 OR #3
#5	vaccine OR vaccines OR vaccinate OR vaccinated OR vaccination OR immunize OR immunization OR immunizations OR immunized
#4	'vaccination'/exp
#3	hpv OR hrhpv OR hpv1618 OR hpv6 OR hpv16 OR hpv18 OR 'human papillomavirus' OR 'human papillomaviruses' OR 'human papilloma virus' OR 'human papilloma viruses' OR gardasil OR cervarix OR 4vhpv OR 9vhpv
#2	'papillomavirus infection'/exp OR 'papillomaviridae'/exp
#1	'wart virus vaccine'/exp
Database supplied limits: 2006 onward	
Filters: SIGN[††] Systematic reviews filter incorporated into search strategy	

CUMULATIVE INDEX TO NURSING AND ALLIED HEALTH LITERATURE	
S1	(MH[‡‡] "Papillomavirus Vaccine")
S2	(MH "Papillomavirus Infections+")
S3	HPV OR hrHPV OR HPV16/18 OR HPV6 OR HPV16 OR HPV18 OR "Human papillomavirus" OR "Human papillomaviruses" OR "Human papilloma virus" OR "Human papilloma viruses" OR Gardasil OR Cervarix OR 4vHPV OR 9vHPV
S4	S2 OR S3
S5	(MH "Immunization+")
S6	Vaccine OR Vaccines OR Vaccinate OR Vaccinated OR Vaccination OR immunize OR Immunization OR Immunizations OR immunized
S7	S5 OR S6
S8	S4 AND S7
S9	S1 OR S8
S10	(MH "Meta Analysis")
S11	TX[§§] Meta analys*
S12	TX Metaanaly*
S13	(MH "Literature Review+")
S14	TX systematic N1 (review or overview)
S15	S10 OR S11 OR S12 OR S13 OR S14
S16	PT[¶¶] commentary
S17	PT letter
S18	PT editorial
S19	(MH "Animals")
S20	S16 OR S17 OR S18 OR S19
S21	S15 NOT S20
S22	S9 AND S21
Database supplied limits: 2006 onward	
Filters: SIGN Systematic reviews filter incorporated into search strategy	

Cochrane Database of Systematic Reviews	
#1	MeSH[##] descriptor: [Papillomavirus Vaccines] explode all trees
#2	MeSH descriptor: [Papillomavirus Infections] explode all trees
#3	MeSH descriptor: [Papillomaviridae] explode all trees
#4	HPV OR hrHPV OR HPV16/18 OR HPV6 OR HPV16 OR HPV18 OR "Human papillomavirus" OR "Human papillomaviruses" OR "Human papilloma virus" OR "Human papilloma viruses" OR Gardasil OR Cervarix OR 4vHPV OR 9vHPV
#5	#2 OR #3 OR #4
#6	MeSH descriptor: [Vaccination] explode all trees
#7	Vaccine OR Vaccines OR Vaccinate OR Vaccinated OR Vaccination OR immunize OR Immunization OR Immunizations OR immunized
#8	#6 OR #7

eTable 1. Continued

#9	#5 AND #8
#10	#1 OR #9

Database supplied limits: 2006 onward

Filters: none

Prospective Register for Systematic Reviews

(("human papillomavirus" OR "human papilloma virus" OR HPV) AND (vaccin* OR immun*))
Database supplied limits: none (limited by date within EndNote)
Filters: none

Database of Abstracts of Reviews of Effects

HPV vaccine OR Papillomavirus Vaccines
Database supplied limits: Limited to items from CRD*** (CRD assessed review bibliographic and full abstract) (limited by date within EndNote)
Filters: none

eTable 2. Excluded systematic reviews and reason for exclusion.

PRIMARY AUTHOR, DATE	ARTICLE TITLE	REASON FOR EXCLUSION
Ault, 2006	Vaccines for the prevention of human papillomavirus and associated gynecologic diseases: a review	Not a systematic review
Damm, 2009	Human papillomavirus (HPV) vaccination for the prevention of HPV 16/18 induced cervical cancer and its precursors	Abstract of presentation only
Jeurissen, 2009	Epidemiological and economic impact of human papillomavirus vaccines	Wrong outcomes
Marra, 2009	Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review	Wrong outcomes
Mougin, 2009	[HPV immunization for the prevention of cervical cancer]	Not a systematic review
La Torre, 2010	The health technology assessment of bivalent HPV vaccine Cervarix in Italy	Not a systematic review
McCormack, 2010	Quadrivalent human papillomavirus (types 6,11,16,18) recombinant vaccine (Gardasil®): a review of its use in the prevention of premalignant genital lesions, genital cancer and genital warts in women	Not a systematic review
Pomfret, 2011	Quadrivalent human papillomavirus (HPV) vaccine: a review of safety, efficacy, and pharmacoeconomics	Not a systematic review
Romanowski, 2011	Long term protection against cervical infection with the human papillomavirus: review of currently available vaccines	Not a systematic review
Riaz, 2012	The efficacy of bivalent and tetravalent HPV vaccination against cervical intraepithelial neoplasia and persistent HPV 16 and 18 infection	Abstract of presentation only
Schiller, 2012	A review of clinical trials of human papillomavirus prophylactic vaccines	Not a systematic review
Araujo, 2013	[Efficacy of Commercially Available Vaccines Against HPV Infection in Women: A Systematic Review and Meta-Analysis]	Duplicate
Miltz, 2013	Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure	Abstract of presentation only
Tomljenovic, 2013	Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (how) effective and safe?	Not a systematic review
Yvonne, 2013	Duration of protection after vaccination against human papillomavirus	Not a systematic review
Angelo, 2014	Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme	Not a systematic review
Deleré, 2014	The efficacy and duration of vaccine protection against human papillomavirus	Duplicate
DeVincenzo, 2014	Long-term efficacy and safety of human papillomavirus vaccination	Not a systematic review
Erickson, 2014	Update on vaccination clinical trials for HPV-related disease	Not a systematic review
Huang, 2014	Can HPV vaccine have other health benefits more than cancer prevention? A systematic review of association between cervical HPV infection and preterm birth	Wrong intervention; wrong outcomes
BoTerning, 2015	HPV vaccination status and changes in sexual behavior: a systematic review	Not a systematic review
Konstantyner, 2015	Safety of human papillomavirus 6, 11, 16 and 18 (recombinant): systematic review and meta-analysis	Duplicate
Mariani, 2015	Early direct and indirect impact of quadrivalent HPV (4HPV) vaccine on genital warts: a systematic review	Wrong study design
Stillo, 2015	Safety of human papillomavirus vaccines: a review	Not a systematic review
Vichnin, 2015	An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015	Not a systematic review
Alexandra, 2016	Sociodemographic differences in human papillomavirus vaccine impact: a systematic review	Wrong study design
Brisson, 2016	Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models	Wrong outcomes
Hatice, 2016	The efficacy of the human papillomavirus vaccine against cervical dysplasia and safety of the vaccine: a systematic review and meta-analysis	Not a systematic review
Jordão, 2016	Adverse events following HPV vaccination: a systematic review	Not a systematic review
Mofrad, 2016	The role of human papilloma virus (HPV) vaccines in prevention of cervical cancer	Not a systematic review
Thomas, 2016	Efficacy, effectiveness and safety of vaccination against human papillomavirus in males	Not a systematic review
Ventimiglia, 2016	Human papillomavirus infection and vaccination in males	Wrong outcomes
Yang, 2016	Update on the new 9-valent vaccine for human papillomavirus prevention	Not a systematic review
Bissett, 2017	Seropositivity to non-vaccine incorporated genotypes induced by the bivalent and quadrivalent HPV vaccines: a systematic review and meta-analysis	Wrong outcomes
Caroline, 2017	Safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia (CIN 2/3) associated with human papillomavirus (HPV): a systematic review	Not a systematic review
Costa, 2017	Safety of human papillomavirus 9-valent vaccine: a meta-analysis of randomized trials	Wrong comparator

eTable 2. Continued

PRIMARY AUTHOR, DATE	ARTICLE TITLE	REASON FOR EXCLUSION
D'Addario, 2017	Two-dose schedules for human papillomavirus vaccine: systematic review and meta-analysis	Wrong comparator
Di Mario, 2017	Corrigendum to "Are the two human papillomavirus vaccines really similar? A systematic review of available evidence: efficacy of the two vaccines against HPV"	Erratum
DiMario, 2017	Corrigendum to "Are the two human papillomavirus vaccines really similar? A systematic review of available evidence: efficacy of the two vaccines against HPV"	Duplicate and erratum
Herney, 2017	The effects of vaccination on papillomavirus infection prevalence and incidence: a systematic review and meta-analysis	Not a systematic review
Lars, 2017	Benefits and harms of human papillomavirus vaccines: systematic review of industry clinical study reports and non-industry published and unpublished reports	Not a systematic review
Martinez-Lavin, 2017	Erratum to: serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series	Erratum
Prudence, 2017	Human papillomavirus prevalence in women following HPV vaccine introduction: a systematic review	Not a systematic review
Tine, 2017	Therapeutic HPV vaccination and recurrent respiratory papillomatosis: a systematic review and meta-analysis	Not a systematic review
Anita, 2018	Trends in genital warts due to the quadrivalent human papillomavirus vaccination: a meta-analysis	Not a systematic review
Arbyn, 2018	Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors	Duplicate
Hutcherson, 2018	Systematic review of clinical and pharmacoeconomic outcomes of the human papillomavirus nonavalent recombinant vaccine	Abstract of presentation only
Muusha, 2018	Human papillomavirus prevalence among women following HPV vaccine introduction: a systematic review	Abstract of presentation only
Phillips, 2018	Safety of human papillomavirus vaccines: an updated review	Not a systematic review
Schneider, 2018	Therapeutic human papillomavirus vaccines in head and neck cancer: a systematic review of current clinical trials	Wrong intervention
Stacey, 2018	A systematic review of human papillomavirus (HPV) vaccine in the treatment of HPV related vulval and vaginal intraepithelial neoplasia	Not a systematic review
Steben, 2018	A review of the impact and effectiveness of the quadrivalent human papillomavirus vaccine: 10 years of clinical experience in Canada	Wrong study design
Yakely, 2018	Impact and effectiveness of the human papillomavirus (HPV) vaccine on anogenital warts in United States and Canada: a systematic review	Duplicate

eTable 3. Description of included systematic reviews.

STUDY	REVIEW AIM OR PICO* QUESTION	SEARCH STRATEGY	TIME INCLUDED IN LITERATURE SEARCH	INCLUSION CRITERIA	NO. OF STUDIES INCLUDED	TOTAL NO. OF PARTICIPANTS
La Torre and Colleagues, 2007[38]	Review scientific literature regarding HPV vaccine efficacy in preventing cervical persistent infection	PubMed, Embase, Cochrane Library; gave search terms; no language restriction	1990-August 15, 2007	RCTs‡; females; evaluated cervical persistent infection	5	22,630
Rambout and Colleagues, 2007[49]	Determine whether females who receive prophylactic HPV vaccination have a lower incidence of HPV persistent infection and precancerous lesions than females who are not vaccinated	MEDLINE, Embase, Cochrane Registry, Cochrane Library, Google Scholar, Clinical Trial Registry, Public Health Announcements, conference proceedings, manufacturer's information; searched reference lists, bibliographies; no language restriction	1950-2007	RCTs; females; any HPV vaccine; any dosing; placebo or no vaccine comparator; only outcomes related to oncogenic strains	6	40,323
Agorastos and Colleagues, 2009[28]	Report the international experience on safety of prophylactic HPV vaccines to date	MEDLINE, bibliography of selected articles, conference abstracts, position statements, gray literature	Through January 31, 2009, for articles; through April 10, 2009 for other materials	Not stated	13 published reports; 7 reports from public health agencies	> 60,000
Medeiros and Colleagues, 2009[46]	Systematically review RCTs in which HPV vaccine was compared with placebo regarding safety, efficacy, and immunogenicity	MEDLINE, CANCERLIT, LILACS,** Embase, Cochrane Library (2007 issue 2); included search terms; no language restrictions; searched reference lists	1/1997-9/2007	No language criteria; humans; placebo-controlled RCTs; females; excluded cohort and case-control studies and studies that did not describe final histologic results	6	47,236
Yancey and Colleagues, 2010[57]	Evaluate immunogenicity, efficacy, and safety of the 4vHPV vaccine in males	PubMed and searched reference lists; English language only	1966-March 2010	HPV 4vHPV vaccine; males	3	1,147
Lu and Colleagues, 2011[39]	Provide a comprehensive assessment of vaccine safety and efficacy against multiple virologic and clinical end points	MEDLINE, Cochrane Library, Cochrane Central Register of Controlled Trials; included search terms; searched bibliographies and hand searched conference abstract books; English only	2006-August 31, 2009	RCTs; English language; on L1 VLP¶¶-based HPV vaccines; female participants	13 studies representing 7 RCTs	44,142
Malagón and Colleagues, 2012[43]	Summarize and compare evidence from clinical trials about the cross-protective efficacy of the 2vHPV and 4vHPV vaccines in HPV-naïve populations	MEDLINE, Embase; included search terms; searched reference lists; searched abstracts of HPV conferences; vaccine Web sites; contacted manufacturers for unpublished results; no mention of language restriction	Through January 2012	RCTs; 2vHPV or 4vHPV vaccine; any population; reported on efficacy against cervical or genital infection or disease	12 (4 RCTs)	22,559

* PICO: Patient/population, intervention, comparison, outcome. † HPV: Human papillomavirus. ‡ RCT: Randomized controlled trial. § 1vHPV: Monovalent HPV vaccine. ¶ 2vHPV: Bivalent HPV vaccine. # 4vHPV: Quadrivalent HPV vaccine. ** LILACS: Latin American and Caribbean Health Sciences Literature. †† VIN: Vulvar intraepithelial neoplasia. ‡‡ VaIN: Vaginal intraepithelial neoplasia. §§ CIN: Cervical intraepithelial neoplasia. ¶¶ VLP: Viruslike particle. ## AIS: Adenoma in situ. *** Nonavalent HPV vaccine.

eTable 3. Continued

PARTICIPANT DEMOGRAPHICS	HPV[†] VACCINE	COMPARATOR	REPORTED OUTCOMES	DATA ANALYSIS TYPE	POTENTIAL SOURCES OF CONFLICT OF INTEREST	AMSTAR 2
Females aged 13-25 y	1vHPV,[§] 2vHPV,[¶] 4vHPV[#]	Placebo; HPV 11 vaccine, hepatitis A vaccine	Persistent (6 mo) cervical infection with HPV 16	Meta-analysis	Did not report	Moderate
Females 15-25 y	1vHPV, 2vHPV, 4vHPV	Placebo, unvaccinated	Cervical lesions; persistent HPV infections; external genital disease; adverse events	Meta-analysis	Yes	High
Females 12 y or older, multisite, multicountry	2vHPV, 4vHPV	Placebo for prelicensure data; not stated for other studies	Local and systemic adverse events	Qualitative synthesis	Yes	Critically low
Females aged 9-26 y	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Adverse events; condyloma; VIN[††] I-III; VaIN[‡‡] I-III; CIN[§§] 1-3	Meta-analysis	No	Moderate
Males aged 9-17 y, multicenter	4vHPV	Placebo	Immunogenicity, external genital lesions, warts, genital intraepithelial neoplasia, adverse events	Qualitative synthesis	No	Critically low
Females aged 15-45 y, multicenter	1vHPV, 2vHPV, 4vHPV	Placebo, hepatitis A vaccine, hepatitis B vaccine	Persistent infection (6 mo), CIN 1+, adverse events	Meta-analysis	Yes	Low
Females aged 15-26 y, multicenter	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Persistent infection (6 mo), CIN 2+	Meta-analysis	Yes	Moderate

eTable 3. Description of included systematic reviews.

STUDY	REVIEW AIM OR PICO* QUESTION	SEARCH STRATEGY	TIME INCLUDED IN LITERATURE SEARCH	INCLUSION CRITERIA	NO. OF STUDIES INCLUDED	TOTAL NO. OF PARTICIPANTS
Rey-Ares and Colleagues, 2012[50]	Conduct a systematic review and meta-analysis to evaluate the efficacy and safety of HPV vaccines in preventing CIN grades 2 and 3, AIS[#,##] (CIN 2+) and cervical cancer	MEDLINE, Cochrane Central Registry of Controlled Trials, Database of Abstract Reviews of Effects, National Health Service Economic Evaluation Database, LILACS, Embase "generic Internet search"; no language restriction	Through July 2011	Clinical trials; 2vHPV or tetravalent vaccines; included CIN 2+ lesions or cervical cancer as outcomes	4 articles on 3 trials	190,534
Araujo and Colleagues, 2013[29]	Determine the efficacy of 2vHPV and quadrivalent vaccine to reduce the risk of CIN 2 and CIN 3 in females	MEDLINE, LILACS, Cochrane Library; Professional librarian's help with search terms; no language restriction	2000-November 2009	RCTs; efficacy of commercially available 2vHPV or 4vHPV HPV vaccines; females only	6	41,750
Macartney and Colleagues, 2013[41]	Assess all available published safety data on both HPV vaccines	MEDLINE, Embase; no language restriction; searched reference lists bibliographies; searched Internet	Through May 2012	Reported safety data from 2 available HPV vaccines	12 trials; 21 case series; 4 postlicensure studies; 8 postlicensure population-based studies	> 21,000
Couto and Colleagues, 2014[32]	Determine efficacy of vaccinating females against HPV starting at 16 y or older	Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, PubMed, ISI Web of Science, Google Scholar; search strategy in appendix; contacted pharmaceutical companies for additional information; no mention of language restriction	1999-October 2012	RCTs; examined efficacy of HPV vaccination in females 16 y or older	46 articles on 13 studies	40,800
Deleré and Colleagues, 2014[33]	Evaluate the duration of protection after HPV vaccination and clarify whether people vaccinated in childhood are protected against HPV years later	MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstract Reviews of Effects; full search strategy in eAppendix; no restriction based on publication status or language	Through November 19, 2013	Immunization with licensed vaccine according to schedule 0-1-(-2)-6 mo or similar, without booster doses after primary vaccination; must have comparison group	15	46,436
Goncalves and Colleagues, 2014[36]	Evaluate safety and adverse events of HPV vaccines.	PubMed, Embase, Scientific Electronic Library Online, CANCERLIT; gave heading terms and text words; no language restriction	Through March 2013	Double-blind RCT; evaluate 2vHPV or 4vHPV HPV vaccines; participants aged > 9 y; excluded pregnant females and those at high risk of contracting HPV	12	29,540
Miltz and Colleagues, 2014[47]	Review the efficacy of the HPV vaccine in females with evidence of prior HPV exposure	MEDLINE; Embase; Web of Science; PubMed; Cochrane Central Register of Controlled Trials; English only	Through August 30, 2013	RCT and post-RCT; investigated HPV vaccine efficacy against associated CIN 3+ or VIN 2-3/VaIN 2-3; studies where females had prior exposure to vaccine-type HPV exposure	5	8,387

eTable 3. Continued

PARTICIPANT DEMOGRAPHICS	HPV† VACCINE	COMPARATOR	REPORTED OUTCOMES	DATA ANALYSIS TYPE	POTENTIAL SOURCES OF CONFLICT OF INTEREST	AMSTAR 2
Healthy females aged 15-26 y	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	CIN 2+, AIS, cervical cancer, adverse events	Meta-analysis	Did not report	Low
Females aged 12-45 y	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Persistent infection, CIN 2+, AIS	Meta-analysis	No	Moderate
Both sexes, aged 9-26 y	2vHPV, 4vHPV	Unvaccinated	Adverse events	Qualitative synthesis	No	Critically low
Healthy females with 0-6 sexual partners, aged 16-45 y	1vHPV, 2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Mortality; CIN 2+; genital warts; VIN 2+; VaIN 2+; condyloma; serious adverse events	Meta-analysis	No	Low
Females aged 9-26 y, generally healthy, any country	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Incident or persistent HPV infection; CIN 2+	Meta-analysis	Yes	Moderate
Predominantly but not exclusively females; aged 9-45 y	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Adverse events	Meta-analysis	No	Low
Females mean aged 20-43 y	1vHPV, 2vHPV, 4vHPV	Placebo, hepatitis A vaccine	CIN 3+, VIN 2+	Meta-analysis	No	Moderate

eTable 3. Description of included systematic reviews.

STUDY	REVIEW AIM OR PICO* QUESTION	SEARCH STRATEGY	TIME INCLUDED IN LITERATURE SEARCH	INCLUSION CRITERIA	NO. OF STUDIES INCLUDED	TOTAL NO. OF PARTICIPANTS
Coelho and Colleagues, 2015[31]	Identify and quantify the adverse effects associated with the recombinant HPV (types 6, 11, 16 and 18) vaccine in adolescents	PubMed, LILACS, Scientific Electronic Library Online; searched for HPV vaccines and adverse effects; no language or date restrictions	Through April 2014	RCTs; adolescents; no patients with cervical diseases, HIV, or had already received HPV vaccine	14	40,458
Di Mario and Colleagues, 2015[34]	Assess the efficacy of the 2vHPV and 4vHPV vaccines against cervical cancer	Cochrane Library, MEDLINE, Embase; also searched Internet for prepublication presentations; experts and vaccine manufacturers contacted; searched reference lists; no language or time restriction	Through March 2014	RCTs; compared HPV 2vHPV or 4vHPV vaccines with placebo or any other control; must include females	9 articles based on 5 trials	38,419
Luo and Colleagues, 2015[40]	Systematically review the safety and immunogenicity of 4vHPV vaccine among healthy population	PubMed, Embase, Chinese Biomedical Literature Database, Cochrane Library, China National Knowledge Infrastructure, Web of Science, Wang Fang Data; searched reference lists; included search terms; no language restriction	Through October 2013	RCTs	9	39,688
Sangar and Colleagues, 2015[51]	Evaluate HPV vaccine safety	MEDLINE, Cochrane Library, Cochrane Central Register of Controlled Trials; included search terms; no mention of searching reference lists or gray literature; English only	June 1996-November 2014	Double-blind RCTs; healthy females; 2vHPV or 4vHPV vaccines	4	1,427
Tan and Colleagues, 2015[54]	Systematically assess the current evidence regarding the efficacy and safety of HPV vaccination in healthy males	PubMed, Embase, MEDLINE, Web of Science, ClinicalTrials.gov; restricted to English; searched reference lists; looked for trials and conference abstracts	Through November 2014	Males; healthy study population; clinical trials, prospective cohort studies or vaccine intervention studies; ≥ 10 patients/study	3 safety, 8 in total	4,139 for safety, 6,079 in total
Garland and Colleagues, 2016[35]	Quantify reported effectiveness and impact of 4vHPV vaccination on HPV infection, anogenital warts, and cervical cytologic and histologic abnormalities	PubMed and Embase; full search terms in eAppendix; no language restriction; searched reference lists	January 1, 2007-February 29, 2016	RCT or observational studies; must relate to 2vHPV or 4vHPV HPV vaccines	58	Millions
Macki and Colleagues, 2016[42]	Determine safety of the HPV vaccine.	PubMed; search term was *human papillomavirus vaccine*, no language restriction mentioned; no searched reference lists mentioned	Through October 2014	RCTs; compared 2vHPV or 4vHPV vaccines with control (trials with hepatitis A or B comparators were excluded)	13	31,289
Martínez-Lavín and Colleagues, 2017[45]	Critically review HPV vaccine serious adverse events described in prelicensure RTs and postmarketing case series	PubMed; search term was *HPV vaccine*; no mention of language; no search of reference lists	Through January 31, 2017	RCTs or postmarketing studies	16 RCTs, 12 postmarketing case series	60,729

eTable 3. Continued

PARTICIPANT DEMOGRAPHICS	HPV† VACCINE	COMPARATOR	REPORTED OUTCOMES	DATA ANALYSIS TYPE	POTENTIAL SOURCES OF CONFLICT OF INTEREST	AMSTAR 2
Females aged 9-45 y; males aged 9-26 y	2vHPV, 4vHPV	Placebo, non-HPV vaccine, different HPV vaccine dose schedule or type	Adverse events	Meta-analysis	No	Low
Healthy, nonpregnant females aged 15-26 y, multiple sites	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	CIN 2+, CIN 3+, AIS	Meta-analysis	No	High
Both sexes, aged 9-45 y	4vHPV	Placebo	Adverse events, immunogenicity	Meta-analysis	Did not report	Moderate
Females aged 10-35 y; Asian and African sites	2vHPV	Placebo	Adverse events	Meta-analysis	Yes	Critically low
Males aged 9-55 y	1vHPV, 2vHPV, 4vHPV	Placebo, hepatitis B vaccine	Immunogenicity, adverse events	Meta-analysis	No	Critically low
Primarily but not exclusively females; 9 y or older	2vHPV, 4vHPV	Prevaccination period, unvaccinated	HPV June 11, 2018 infection prevalence; genital warts; cervical cytologic and histologic abnormalities	Qualitative synthesis	Yes	Critically low
All sexes but predominantly females; multicenter; aged 9-45 y	2vHPV, 4vHPV	Placebo	Adverse events	Qualitative synthesis	No	Critically low
All sexes, aged 9-45 y, multicenter	2vHPV, 4vHPV, 9vHPV***	Placebo, hepatitis A vaccine	Adverse events	Qualitative synthesis	No	Critically low

eTable 3. Description of included systematic reviews.

STUDY	REVIEW AIM OR PICO* QUESTION	SEARCH STRATEGY	TIME INCLUDED IN LITERATURE SEARCH	INCLUSION CRITERIA	NO. OF STUDIES INCLUDED	TOTAL NO. OF PARTICIPANTS
Ogawa and Colleagues, 2017[48]	Evaluate the safety of the HPV vaccine in healthy young females	MEDLINE, Cochrane Central Register of Controlled Trials, Japana Centra Revuo Medicina, Pharmaceuticals and Medicines Devices Agency; no language restriction	1966-February 2017	Prospective controlled studies; young, healthy females; 2vHPV, 4vHPV, or 9vHPV	22 articles, 24 studies	23,570
Setiawan and Colleagues, 2017[52]	Investigate the immunogenicity and safety profiles of HPV vaccines among both uninfected and infected populations in Asian countries	PubMed, Embase, Cochrane Library, ClinicalTrials.gov; gave search terms; no mention of searching reference lists or gray literature; English only	Through November 21, 2014	RCTs; conducted in Asia; immunogenicity or safety as outcomes	10	9,400
Signorelli and Colleagues, 2017[53]	Systematically assess all available evidence from RCTs on 9vHPV	MEDLINE, Embase, Cochrane Library registered clinical trials; searched reference lists; consulted with experts; search strategies in supplement; English language only	Through August 25, 2016	Clinical trials; 9vHPV vaccine; any age group, study population, comparison, dose, or outcome	10 included, 1 looked at vaccine versus placebo	28,608 in total, 924 from single trial with placebo control
Tejada and Colleagues, 2017[55]	Summarize available evidence on the efficacy of HPV vaccines in preventing nononcological lesions	MEDLINE, Embase, Cochrane Library, Scopus, LILACS, Scientific Electronic Library Online, Web of Knowledge; reviewed conference abstracts, National Institutes of Health and Europe clinical registries, searched reference lists; search strategies available online; no language restriction	Through July 2015	RCTs; nononcological lesions evaluated as outcome	6	27,079
Arbyn and Colleagues, 2018[30]	Evaluate the harms and protection of HPV vaccines against cervical precancer and HPV 16/18 infection in adolescent and older females	The Cochrane Central Register of Controlled Trials, MEDLINE, Embase Search terms in appendixes No language restriction	2002-July 2017	Phase II and III RCTs; female participants; placebo comparator	26	73,428
Harder and Colleagues, 2018[37]	Assess the currently available evidence on the efficacy, effectiveness, and safety of HPV vaccination in males	MEDLINE, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, conference abstracts, searched reference lists; no language or publication status restriction	Through April 18, 2017	Males; report clinically relevant outcome	7	5,294
Markowitz and Colleagues, 2018[44]	Systematically review HPV vaccine effectiveness by number of doses.	MEDLINE; Embase; provided search terms; no language restriction; no mention of searched reference lists	January 1, 2007-June 15, 2017	Reported effectiveness of HPV vaccination on infection, warts, or cervical abnormalities; assessed effectiveness of HPV vaccination by number of doses; excluded RCTs	14	3,104,053
Yakely and Colleagues, 2018[56]	Assess real-world impact and effectiveness of the HPV vaccine as it relates to anogenital warts	PubMed, MEDLINE, Embase; search terms in Supplement; English language restriction; no reference list search	January 1, 2006-March 12, 2018	Must include 4vHPV or 9vHPV vaccine; must include anogenital warts as outcome; US setting	3 effectiveness, 8 in total	109,123,079 for impact studies; 452,736 for effectiveness studies

eTable 3. Continued

PARTICIPANT DEMOGRAPHICS	HPV† VACCINE	COMPARATOR	REPORTED OUTCOMES	DATA ANALYSIS TYPE	POTENTIAL SOURCES OF CONFLICT OF INTEREST	AMSTAR 2
Healthy females aged 12-37 y	2vHPV, 4vHPV, 9vHPV	Placebo, hepatitis A vaccine, hepatitis B vaccine, other HPV vaccine (2vHPV compared with 4vHPV, 4vHPV compared with 9vHPV)	Adverse events	Meta-analysis	No	Low
Both sexes but predominantly female; aged 9-45 y; multiple Asian countries	2vHPV, 4vHPV	Placebo, hepatitis A vaccine	Immunogenicity and adverse events	Meta-analysis	No	Critically low
Males and females aged 9-26 y	9vHPV	Placebo	Immunogenicity; high-grade cervical, vulvar, and vaginal disease or cancer; adverse events	Qualitative synthesis	No	Critically low
Both sexes, adults, multicenter	2vHPV, 4vHPV	Placebo	Anogenital warts	Meta-analysis	No	High
Females aged 15-45 y	1vHPV, 2vHPV, 4vHPV	Placebo with no active product or non–HPV vaccine	CIN 2+; AIS; adverse events; HPV infection (16 and 18 or 6, 11, 16, and 18)	Meta-analysis	Did not report	Moderate
Men aged 12-76 y, multicenter, multicountry	4vHPV	Placebo, unvaccinated	Incident or persistent oral or anogenital infection; anogenital warts; anal intraepithelial neoplasia 2+, penile intraepithelial neoplasia 2+, severe adverse events	Qualitative synthesis	No	Moderate
Aged 9-26 y, multicountry	2vHPV, 4vHPV	Other number of doses of HPV vaccine	Vaccine-type HPV infection; anogenital warts; CIN 1-3+; AIS	Qualitative synthesis	No	Low
Both sexes, 9 y or older, entirely US-based	4vHPV	Unvaccinated	Anogenital warts	Qualitative synthesis	Yes	Critically low

eTable 4. Meta-analysis results from included systematic reviews.

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTION EFFICACY	HPV PERSISTENT (> 6 MO) INFECTION EFFICACY	HPV ORAL INFECTION EFFICACY	HPV-RELATED WART EFFICACY	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	AE† RATE
La Torre and Colleagues, 2007[38]	Not evaluated	Not evaluated	HPV 16 persistent cervical infection: RR,‡ 0.10 (95% CI,§ 0.07 to 0.15); HPV 18 persistent cervical infection: RR, 0.22 (95% CI, 0.13 to 0.38)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Rambout and Colleagues, 2007[49]	Not evaluated	Not evaluated	Peto-OR,¶ 0.14 (95% CI, 0.10 to 0.19) per protocol; Peto-OR,0.22 (95% CI, 0.18 to 0.27) per ITT#	Not evaluated	Peto-OR, 0.13 (95% CI, 0.08 −0.22) per protocol; Peto-OR, 0.30 (95% CI, 0.22 to 0.43) per ITT	Per protocol: CIN** 2+: Peto-OR, 0.14 (95% CI, 0.09 to 0.21) Any CIN: Peto-OR, 0.13 (95% CI, 0.09 to 0.20) Modified ITT: CIN 2+: Peto-OR, 0.52 (95% CI, 0.43 to 0.63) Any CIN: Peto-OR, 0.36 (95% CI, 0.29 to 0.45)	Not evaluated	More than 1 AE: Peto-OR, 1.00 (95% CI, 0.87 to 1.14) Death: Peto-OR, 0.91 (95% CI, 0.39 to 2.14)
Medeiros and Colleagues, 2009[46]	Not evaluated	HPV 16/18: OR, 0.09 (95% CI, 0.05 to 0.15)	HPV 16/18: OR, 0.26 (95% CI, 0.07 to 0.99)	Not evaluated	OR, 0.24 (95% CI, 0.17 to 0.33)	2vHPV†† vaccine on low- or high-grade SIL‡‡: OR, 0.07 (95% CI, 0.04 to 0.14); 4vHPV§§ vaccine on low-grade SIL: OR, 0.13 (95% CI, 0.01 to 2.04); 4vHPV vaccine on high-grade SIL: OR, 0.54 (95% CI, 0.30 to 0.98); adenocarcinoma in situ: OR, 0.45 (95% CI, 0.12 to 1.73); VIN¶¶ 1 or VaIN## 1: OR, 0.37 (95% CI, 0.15 to 0.96); VIN 2-3 or VaIN 2-3: OR, 0.38 (95% CI, 0.14 to 1.08)	Not evaluated	2vHPV: injection site: OR, 1.74 (95% CI, 1.27 to 2.40) Systemic: OR, 1.18 (95% CI, 0.07 to 1.99) Serious AE: OR, 1.05 (95% CI, 0.91 to 1.21) Death: not estimable Total: OR, 1.35 (95% CI, 1.05 to 1.73) 4vHPV: any AE: OR, 1.16 (95% CI, 0.94 to 1.43)
Lu and Colleagues, 2011[39]	Not evaluated	Not evaluated	HPV 16: ITT RR, 0.15 (95% CI, 0.10 to 0.23) and per-protocol RR, 0.06 (95% CI, 0.04 to 0.09); HPV 18: ITT RR, 0.24 (95% CI, 0.14 to 0.42) and per-protocol RR, 0.05 (95% CI, 0.03 to 0.09)	Not evaluated	Not evaluated	ITT CIN 2+ associated with HPV 16: RR, 0.47 (95% CI, 0.36 to 0.61) or 53% efficacy; perprotocol CIN 2+ associated with HPV 16 RR, 0.04 (95% CI, 0.01 to 0.11) or 96% efficacy; ITT CIN 2+ associated with HPV 18: RR, 0.16 (95% CI, 0.08 to 0.34) or 84% efficacy; per protocol CIN 2+ associated with HPV 18: RR, 0.10 (95% CI, 0.03 to 0.38) or 90% efficacy	Not evaluated	Serious AE: RR, 1.00 (95% CI, 0.91 to 1.09); injection-related serious AE: RR, 1.82 (95% CI, 0.79 to 4.20)

* HPV: Human papillomavirus. † AE: Adverse event. ‡ RR: Relative risk. § CI: Confidence interval. ¶ OR: Odds ratio. # ITT: Intention to treat. ** CIN: Cervical intraepithelial neoplasia. †† 2vHPV: Bivalent HPV vaccine. ‡‡ SIL: Squamous intraepithelial lesion. §§ 4vHPV: Quadrivalent HPV vaccine. ¶¶ VIN: Vulval intraepithelial neoplasia. ## VaIN: Vaginal intraepithelial neoplasia. *** GRADE: Grading of Recommendations Assessment, Development, and Evaluation. ††† RD: Risk difference.

eTable 4. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTION EFFICACY	HPV PERSISTENT (> 6 MO) INFECTION EFFICACY	HPV ORAL INFECTION EFFICACY	HPV-RELATED WART EFFICACY	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	AE† RATE
Rey-Ares and Colleagues, 2012[50]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	CIN 2+ associated with HPV 16: RR, 0.45 (95% CI, 0.38 to 0.54); CIN 2+ associated with HPV 18: RR, 0.14 (95% CI, 0.08 to 0.25)	Not evaluated	Not evaluated
Araujo and Colleagues, 2013[29]	Not evaluated	Not evaluated	RR, 0.07 (95% CI, 0.03 to 0.16) by protocol; RR, 0.52 (95% CI, 0.42 to 0.65) by ITT	Not evaluated	Not evaluated	CIN 2: RR, 0.03 (95% CI, 0.01 to 0.1) by protocol; RR, 0.37 (95% CI, 0.29 to 0.48) by ITT; CIN 3: RR, 0.04 (95% CI, 0.01 to 0.11) by protocol; RR, 0.58 (95% CI, 0.45 to 0.74) by ITT	Not evaluated	Not evaluated
Couto and Colleagues, 2014[32]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Any HPV type: RR, 0.38 (95% CI, 0.31 to 0.47), GRADE***: high; HPV 6/11: RR, 0.28 (95% CI, 0.12 to 0.65), GRADE: high	CIN 2+ any HPV type at 4 y: RR, 0.8 (95% CI, 0.62 to 1.02), GRADE: moderate; VIN 2+ and VaIN 2+ any HPV type at 4 y: RR, 0.49 (95% CI, 0.32 to 0.76), GRADE: moderate; VIN 2+ and VaIN 2+ HPV-related at 4-5 y: RR, 0.72 (95% CI, 0.03 to 15.02), GRADE: low	Not evaluated	Serious AE at > 7 mo: RR, 0.99 (95% CI, 0.91 to 1.08), GRADE: moderate
Deleré and Colleagues, 2014[33]	Not evaluated	Incident HPV 16/18 infections RR, 0.17 (95% CI, 0.10 to 0.30), GRADE: high	HPV 16/18 RR, 0.10 (95% CI, 0.05 to 0.21), GRADE: high	Not evaluated	Not evaluated	CIN 2+ (any HPV type at median follow-up 27 mo) RR, 0.16 (95% CI, 0.05 to 0.50), GRADE: moderate; CIN 3+ (any HPV type at median follow-up 27 mo) RR, 0.06 (95% CI, 0.02 to 0.17), GRADE: high	Not evaluated	Not evaluated

eTable 4. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTION EFFICACY	HPV PERSISTENT (> 6 MO) INFECTION EFFICACY	HPV ORAL INFECTION EFFICACY	HPV-RELATED WART EFFICACY	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	AE† RATE
Goncalves and Colleagues, 2014[36]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	HPV 16/18: injection site pain OR, 3.29 (95% CI, 3.00 to 3.60); redness OR, 2.41 (95% CI, 2.17 to 2.68); swelling OR, 3.14 (95% CI, 2.79 to 3.53); fever OR, 1.21 (95% CI, 1.03 to 1.42); local symptoms OR, 2.33 (95% CI, 1.61 to 3.36); fatigue OR, 1.29 (95% CI, 1.18 to 1.42); gastrointestinal symptoms OR, 1.13 (95% CI, 1.00 to 1.28); headache OR, 1.17 (95% CI, 1.06 to 1.28); myalgia OR, 1.97 (95% CI, 1.77 to 2.20); arthralgia OR, 1.40 (95% CI, 1.20 to 1.64); general symptoms OR, 1.07 (95% CI, 0.82 to 1.41); HPV 6/11/16/18: pain OR, 2.88 (95% CI, 2.42 to 3.43); swelling OR, 2.65 (95% CI, 2.04 to 3.44); general symptoms OR, 1.11 (95% CI, 1.00 to 1.23)
Miltz and Colleagues, 2014[47]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	CIN 3+ associated with 16/18: OR, 0.90 (95% CI, 0.56 to 1.44); VIN 2-3/VaIN 2-3 associated with 16/18: OR, 2.25 (95% CI, 0.78 to 6.50)	Not evaluated	Not evaluated
Coelho and Colleagues, 2015[31]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Local pain: RD,††† 0.11 (95% CI, 0.09 to 0.13); edema: RD, 0.08 (95% CI, 0.06 to 0.09); erythema: RD, 0.05 (95% CI, 0.04 to 0.07); fever: RD, 0.02 (95% CI, 0.01 to 0.03)
Di Mario and Colleagues, 2015[34]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	CIN 2: hazard ratio, 0.74 (95% CI, 0.61 to 0.89); CIN 3: hazard ratio, 0.68 (95% CI, 0.44 to 1.06)	Not evaluated	Not evaluated
Luo and Colleagues, 2015[40]	HPV 6 OR, 128.54 (95% CI, 37.22 to 443.9); HPV 11 OR, 89.6 (95% CI, 32.53 to 246.03); HPV 16 OR, 303.92 (95% CI, 46.41 to 1990.23); HPV 18 OR, 97.17 (95% CI, 33.91 to 278.40)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Injection site: swelling and red spots: RR, 1.22 (95% CI, 1.13 to 1.32); systemic AE: RR, 1.03 (95% CI, 0.99 to 1.07); serious AE: RR, 1.06 (95% CI, 0.75 to 1.50)

eTable 4. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTION EFFICACY	HPV PERSISTENT (> 6 MO) INFECTION EFFICACY	HPV ORAL INFECTION EFFICACY	HPV-RELATED WART EFFICACY	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	AE† RATE
Sangar and Colleagues, 2015[51]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Pain at injection site: RR, 1.17 (95% CI, 1.10 to 1.25); redness at injection site: RR, 2.30 (95% CI, 1.14 to 4.62); swelling at injection site: RR, 1.84 (95% CI, 1.47 to 2.3); arthralgia: RR, 1.39 (95% CI, 1.09 to 1.78); fatigue: RR, 1.18 (95% CI, 1.02 to 1.36); fever: RR, 1.07 (95% CI, 0.90 to 1.29); gastrointestinal: RR, 1.11 (95% CI, 0.89 to 1.4); headache: RR, 0.99 (95% CI, 0.85 to 1.14); myalgia: RR, 1.40 (95% CI, 1.16 to 1.68); rash: RR, 1.13 (95% CI, 0.73 to 1.73); urticaria: RR, 1.29 (95% CI, 0.89 to 1.88); new onset of chronic disease: RR, 0.56 (95% CI, 0.28 to 1.10); medically significant condition: RR, 0.93 (95% CI, 0.65 to 1.34); serious AE: RR, 0.66 (95% CI, 0.35 to 1.27)
Tan and Colleagues, 2015[54]	HPV 6 seroconversion rate: 99.5% (95% CI, 98.9% to 100%); HPV 11 seroconversion rate: 99.7% (95% CI, 99.4% to 100%); HPV 16 seroconversion rate: 99.6% (95% CI, 99.2% to 100%); HPV 18 seroconversion rate: 99.3% (95% CI, 98.4% to 100%)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Injection site AE: RR, 1.12 (95% CI, 1.06 to 1.18); systemic AE: RR, 0.99 (95% CI, 0.91 to 1.1); no serious AE in either group
Ogawa and Colleagues, 2017[48]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Solicited local symptoms: RR, 1.20 (95% CI, 1.13 to 1.27); solicited systemic symptoms: RR, 1.04 (95% CI, 0.99 to 1.09); unsolicited symptoms: RR, 1.28 (95% CI, 1.01 to 1.63) compared with placebo but not different than hepatitis vaccine

eTable 4. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTION EFFICACY	HPV PERSISTENT (> 6 MO) INFECTION EFFICACY	HPV ORAL INFECTION EFFICACY	HPV-RELATED WART EFFICACY	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	AE† RATE
Setiawan and Colleagues, 2017[52]	HPV 16: uninfected population: 2vHPV RR, 44.86 (95% CI, 11.90 to 169.5); 4vHPV RR, 252.65 (95% CI, 35.77 to 1,784.59); combined RR, 62.52 (95% CI, 16.29 to 239.96); infected and uninfected populations RR, 8.6 (95% CI, 6.95 to 10.94); HPV 18: uninfected population: 2vHPV RR, 43.22 (95% CI, 25.52 to 73.68); 4vHPV RR, 96.04 (95% CI, 33.87 to 272.34); combined RR, 50.14 (95% CI, 31.17 to 50.68); infected and uninfected populations RR, 8.13 (95% CI, 5.96 to 11.11)	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Local AE: RR, 1.89 (95% CI, 1.65 to 2.17); systemic AE: RR, 1.33 (95% CI, 1.33 to 1.50)
Tejada and Colleagues, 2017[55]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	ITT: RR, 0.38 (95% CI, 0.32 to 0.45); per protocol: RR, 0.05 (95% CI, 0.01 to 0.25)	Not evaluated	Not evaluated	Not evaluated
Arbyn and Colleagues, 2018[30]	Not evaluated	HPV 16/18 incident infection: RR, 0.23 (95% CI, 0.14 to 0.37), GRADE: high	HPV 16/18 RR, 0.07 (95% CI, 0.05 to 0.09), GRADE: moderate; HPV 6/ 11/16/18 RR, 0.13 (95% CI, 0.05 to 0.37), GRADE: moderate	Not evaluated	Not evaluated	CIN 2+ associated with HPV 16/18 at 3-5 y: RR, 0.1 (95% CI, 0.0 to 0.05), GRADE: high; CIN 3+ associated with HPV16/18 at 3-5 y: RR, 0.01 (95% CI, 0.0 to 0.10), GRADE: high; adenocarcinoma in situ associated with HPV 16/18 at 3-5 y: RR, 0.10 (95% CI, 0.01 to 0.76), GRADE: moderate	Not evaluated	Serious AE at 6 mo to 7 y: RR, 0.98 (95% CI, 0.92 to 1.05), GRADE: high; death at 7 mo to 10 y: RR, 1.29 (95% CI, 0.85 to 1.98), GRADE: low
Harder and Colleagues, 2018[37]	Not evaluated	Not evaluated	Anogenital infection: Vaccine efficacy 46.9% (95% CI, 28.6 to 60.8), GRADE: moderate	Incident oral infection HPV 16 and/or 18: Vaccine efficacy 91% (95% CI, −59 to 99.5%), GRADE: very low; persisting oral infection: Vaccine efficacy 88% (95% CI, 2 to 98%), GRADE: moderate	Genital: Vaccine efficacy 89.4% (95% CI, 65.5 to 97.9%), GRADE: high; anal: Vaccine efficacy 100% (95% CI, 8.2 to 100%), GRADE: high	Anal intraepithelial neoplasia 2: Vaccine efficacy 61.9% (95% CI, 21.4 to 82.8), GRADE: moderate; anal intraepithelial neoplasia 3: Vaccine efficacy 46.8% (95% CI, −20 to 77.9), GRADE: low	Not evaluated	Not judged to be vaccine related but AE RR, 0.73 (95% CI, 0.25 to 1.99), GRADE: moderate

eTable 5. Qualitative synthesis results from included systematic reviews.

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTIONS	HPV PERSISTENT (> 6 MO) INFECTIONS	HPV ORAL INFECTIONS	HPV-RELATED WARTS	HPV EFFECTIVENESS	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	ADVERSE EVENTS
Agorastos and Colleagues, 2009[28]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Risk difference between vaccinated and placebo group ranged from 9.4% (95% CI,† 7.3% to 11.5%) to 22.2% (95% CI, 19.7% to 24.7%) (local); 1.8% (95% CI, 0.3% to 3.2%) to 12.0% (95% CI, 10.8% to 13.2%) (systemic); 0% (95% CI, −0.1% to 0.1%) to 0.05% (95% CI, −0.03% to 0.1%) (serious). In surveillance data, 32 deaths (none judged likely to be caused by the vaccine) out of > 31.7 million vaccine doses
Yancey and Colleagues, 2010[57]	Compared 4vHPV‡ vaccinated and 2vHPV§ vaccinated, 4vHPV geometric mean titers were noninferior to 2vHPV ($P < .01$) For 4vHPV, seroconversion rates were > 99.5% for HPV 6/11/16/18 at 1 month and > 92% at 1 y	Not evaluated	Compared vaccinated with placebo, risk difference of 40.9%	Not evaluated	Compared vaccinated with placebo, lower rate of condyloma: 10.6% (95% CI, 65.5% to 97.9%)	Not evaluated	Not evaluated	Not evaluated	Rate of 53.9 AEs¶ per 100,000 doses, of which 6% were considered serious
Malagón and Colleagues, 2012[43]	Not evaluated	Not evaluated	Compared vaccinated with non–HPV-vaccinated, vaccine efficacy against persistent infection with nonvaccine HPV types 31/33/45/52/58 ranged from −52.7% (95% CI, −883.5% to 70.3%) to 79.9% (95% CI, 61.3% to 89.4%)	Not evaluated	Not evaluated	Not evaluated	Compared vaccinated with non–HPV-vaccinated, vaccine efficacy against CIN# 2+ with nonvaccine HPV types 31/33/45/52/58 ranged from −132.3% (95% CI, −637.5% to 16.2%) to 100% (95% CI, 41.7% to 100%)	Not evaluated	Not evaluated

* HPV: Human papillomavirus. † CI: Confidence interval. ‡ 4vHPV: Quadrivalent HPV vaccine. § 2vHPV: Bivalent HPV vaccine. ¶ AE: Adverse event. # CIN: Cervical intraepithelial neoplasia. ** 9vHPV: Nonavalent HPV vaccine. †† AIN: Anal intraepithelial neoplasia. ‡‡ aOR: Adjusted odds ratio. §§ aRR: Adjusted relative risk. ¶¶ HR: Hazard ratio.

eTable 5. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTIONS	HPV PERSISTENT (> 6 MO) INFECTIONS	HPV ORAL INFECTIONS	HPV-RELATED WARTS	HPV EFFECTIVENESS	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	ADVERSE EVENTS
Macartney and Colleagues, 2013[41]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Risk differences between vaccinated and placebo group ranged from 0.5% to 34% (local); 0% to 12% (systemic); 0%, with no death judged related to the vaccine (serious). Inconsistent differences in local or systemic AEs by age; no statistically significant difference between males and females; higher rate of local AEs in 2vHPV vaccine compared with 4vHPV but no difference in systemic or serious AEs
Deleré and Colleagues, 2014[33]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Compared vaccine era with prevaccine era, decrease in incidence of HPV infections or CIN 2+ lesions	Not evaluated	Not evaluated	Not evaluated

eTable 5. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTIONS	HPV PERSISTENT (> 6 MO) INFECTIONS	HPV ORAL INFECTIONS	HPV-RELATED WARTS	HPV EFFECTIVENESS	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	ADVERSE EVENTS
Garland and Colleagues, 2016[35]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Compared vaccinated with at least 1 dose with unvaccinated, 76% to 89% decrease in prevalent HPV 6/11/16/18 infections Greatest decreases in those who received more than 1 dose 14%-88% decreases in prevalent HPV 16/18 in age cohort of those vaccinated compared with those in prevaccine era 45%-92.6% reduction in incidence of genital warts among those vaccinated compared with unvaccinated, with greater reduction in those vaccinated in youngest age groups 16%-60% declines in cervical cytologic abnormalities in those vaccinated compared with those unvaccinated Highest declines among those of younger ages when vaccinated or who received more than 1 dose	Not evaluated	Not evaluated	Not evaluated
Macki and Colleagues, 2016[42]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Risk differences between vaccinated and placebo group ranged from 1.7% to 27.8% (local); −13.7% to 29.6% (systemic); −0.6% to 0.6% (serious)

eTable 5. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTIONS	HPV PERSISTENT (> 6 MO) INFECTIONS	HPV ORAL INFECTIONS	HPV-RELATED WARTS	HPV EFFECTIVENESS	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	ADVERSE EVENTS
Martínez-Lavín and Colleagues, 2017[45]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Risk difference between vaccinated and unvaccinated ranged from −0.9% to 8% (systemic); −1.2% to 5% (serious) Risk difference between 9vHPV and 4vHPV vaccine ranged from −4.5% to 3.9% (systemic); −0.5% to 0.7% (serious)
Signorelli and Colleagues, 2017[53]	Compared 9vHPV** vaccinated and 4vHPV vaccinated, statistically similar geometric mean titers for HPV 6/11/16/18 3 mo after participants vaccinated with 9vHPV, > 95% of participants seroconverted for HPV 31/33/45/52/58.	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Compared 9vHPV vaccinated with 4vHPV vaccinated, risk difference, 0.7 (95% CI, −15.7 to 14.8)	Not evaluated	Risk difference between 9vHPV and placebo was 4.5% (local); 4% (systemic); 0.5% (serious) Risk difference between 9vHPV and 4vHPV ranged from 3.3% to 7% (local); −4.5% to 0.9% (systemic); −0.4% to 0.7% (serious)
Harder and Colleagues, 2018[37]	Not evaluated	Compared vaccinated with placebo, vaccine efficacy against incident anogenital HPV 16: ranged from 28.0% (95% CI, 12.9% to 40.7%) to 45.1% (95% CI, 18.0% to 63.7%); HPV 18: ranged from 33.9% (95% CI, 13.0% to 50.1%) to 49.5% (95% CI, 11.3% to 72.1%)	Compared vaccinated with placebo, vaccine efficacy against persisting anogenital infection with HPV 16 ranged from 46.9% (95% CI, 28.6% to 60.8%) to 54% (95% CI, 23.9% to 72.9%); with HPV 18 ranged from 56.0% (95% CI, 28.8% to 73.7%) to 73.6% (95% CI, 37.5% to 90.3%)	Compared vaccinated with placebo, vaccine efficacy against persisting oral infection was 88% (95% CI, 2% to 98%); against incident oral infection with HPV 16/18 was 91% (95% CI, −59.0% to 99.5%)	Compared vaccinated with placebo, vaccine efficacy against condylomata acuminata ranged from −26% (95% CI, −130% to 31%) to 67.2% (95% CI, 47.3% to 80.3%)	Not evaluated	Compared vaccinated with placebo, vaccine efficacy against AIN†† 2+ ranged from 46.8% (95% CI, −20% to 77.9%) to 61.9% (95% CI, 21.4% to 82.8%)	Not evaluated	Risk difference between vaccinated and unvaccinated, −0.15

eTable 5. Continued

STUDY	SEROCONVERSION	HPV* INCIDENT INFECTIONS	HPV PERSISTENT (> 6 MO) INFECTIONS	HPV ORAL INFECTIONS	HPV-RELATED WARTS	HPV EFFECTIVENESS	HPV-RELATED PRECANCEROUS LESIONS	HPV-RELATED ORAL CANCER	ADVERSE EVENTS
Markowitz and Colleagues, 2018[44]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Compared vaccinated with unvaccinated: decreased aOR‡‡ of HPV 16/18 ranged from aOR, 0.27 (95% CI, 0.20 to 0.37) to aOR, 0.95 (95% CI, 0.51 to 1.76); decreased aRR§§ for anogenital warts ranged from aRR, 0.12 (95% CI, CI 0.07 to 0.21) to aRR, 0.54 (95% CI, 0.46 to 0.56); aRR of CIN 3/ adenocarcinoma in situ ranged from aRR, 0.45 (95% CI, 0.35 to 0.77) to aRR, 1.42 (95% CI, 0.89 to 2.28); decreased aOR of high grade histologic lesions ranged from aOR, 0.54 (95% CI, 0.43 to 0.67) to aOR, 0.95 (95% CI, 0.77 to 1.16); decreased change of abnormal cytology ranged from aOR, 0.17 (95% CI, 0.02 to 1.20) to aRR, 1.05 (95% CI, 0.88 to 1.26)	Not evaluated	Not evaluated	Not evaluated
Yakely and Colleagues, 2018[56]	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Compared vaccinated with unvaccinated, reduced HR¶¶ of anogenital warts ranged from HR, 0.23 (95% CI, 0.17 to 0.31) to HR, 0.91 (95% CI, 0.59 to 1.41). There was a dose-response relationship between increasing number of doses and decreased anogenital wart rate	Not evaluated	Not evaluated	Not evaluated