Human Papillomavirus Vaccine Effectiveness by Number of Doses: Updated Systematic Review of Data from National Immunization Programs

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Abstract

Background: Human papillomavirus (HPV) vaccines were first licensed as a three-dose series. Two doses are now widely recommended in some age groups; there are data suggesting high efficacy with one dose. We updated a systematic literature review of HPV vaccine effectiveness by number of doses in observational studies.

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Methods: We searched Medline and Embase databases from January 1, 2007, through September 29, 2021. Data were extracted and summarized in a narrative synthesis. We also conducted quality assessments for bias due to selection, information, and confounding.

Results: Overall, 35 studies were included; all except one were conducted within the context of a recommended three-dose schedule. Evaluations were in countries that used bivalent HPV vaccine (seven), quadrivalent HPV vaccine (27) or both (one). Nine evaluated effectiveness against HPV infection, ten anogenital warts, and 16 cervical abnormalities. All studies were judged to have moderate or serious risk of bias. The biases rated as serious would likely result in lower effectiveness with fewer doses. Investigators attempted to control for or stratify by potentially important variables, such as age at vaccination. Eight studies evaluated impact of buffer periods (lag time) for case counting and 10 evaluated different intervals between doses for two-dose vaccine recipients. Studies that stratified by vaccination age found higher effectiveness with younger age at vaccination, although differences were not all formally tested. Most studies found highest estimates of effectiveness with three doses; significant effectiveness was found among 28/29 studies that evaluated three doses, 19/29 that evaluated two doses, and 18/30 that evaluated one dose. Some studies that adjusted or stratified analyses by age at vaccination found similar effectiveness with three, two and one doses.

Conclusion: Observational studies of HPV vaccine effectiveness have many biases. Studies examining persons vaccinated prior to sexual activity and using methods to reduce sources of bias are needed for valid effectiveness estimates.

1.0 BACKGROUND

All currently available human papillomavirus (HPV) vaccines were originally evaluated in clinical trials, licensed and recommended as a three-dose schedule (0, 1–2 and 6 months). The high efficacy and immunogenicity observed in those trials, as well as a post hoc analysis of one clinical trial, stimulated interest in whether fewer doses would result in similar high efficacy.[1] Subsequently, immunogenicity studies designed to compare two and three doses showed non-inferior antibody response after two doses, administered 6 to 12 months apart, in young adolescent females compared with three doses in women in the age group in which efficacy was demonstrated in clinical trials.[2, 3] These data led to regulatory approval of a two-dose schedule for younger age groups. In 2014 and 2016, respectively, the World Health Organization and the U.S. Advisory Committee on Immunization Practices changed dosing recommendations to two doses for girls starting the series at age 9 through 14 years.[4, 5] Some data that raised interest in two-dose schedules also suggested that one dose might provide long lasting immunity;[6] the biologic plausibility for this has been summarized.[7] Trials were designed to rigorously evaluate the efficacy and immunogenicity of single dose HPV vaccination; results from one were reported in early 2022.[8, 9]

We previously conducted a systematic review of the literature of post-licensure observational studies to summarize evidence regarding effectiveness of HPV vaccination by number of

doses.[10] In that 2018 report, there were 14 studies; most found highest effectiveness with three doses. However, there were many biases in the studies and most included mainly women who had been vaccinated during catch-up vaccination programs at an age older than the routine target age group. We updated our previous report for several reasons: 1) the number of studies examining effectiveness of HPV vaccination by number of doses has increased considerably since our first review; 2) more recent publications include girls vaccinated at a younger age, a population less likely to be affected by biases due to differences between dose groups in the likelihood of prevalent infection at the time of vaccination; and 3) we conducted an extensive quality assessment of all studies to explore the main limitations and challenges of estimating HPV vaccine effectiveness by number of doses using observational studies.

2.0 METHODS

2.1 Study selection

Studies were eligible for inclusion if they fulfilled the following criteria: 1) reported effectiveness of HPV vaccination against infection, anogenital warts, or cervical abnormalities (based on cytological or histological outcomes); 2) assessed effectiveness of HPV vaccination by number of doses received (one, two, or three). We excluded studies if vaccination was administered as part of a clinical trial (e.g., post hoc evaluations of clinical trials).

In the previously published review, we first searched Medline and Embase databases from January 1, 2007, through June 15, 2017. For this review, we updated the search through September 29, 2021. We used the same methodology in the original and updated searches, which was a combination of Medical Subject Headings (MeSH) terms, title or abstract words, without restriction on language of publications: ("papillomavirus vaccines", "HPV vaccine", "HPV vaccination", "papillomavirus vaccine", or "papillomavirus vaccination") and ("program evaluation", "immunization programs", "population surveillance", "sentinel surveillance", "incidence", "prevalence", "rate", "rates", "effectiveness", "doses") and ("papillomavirus infections", "HPV", "uterine cervical neoplasms", "cervical intraepithelial neoplasia", "HPV related diseases", "condylomata acuminata", "genital warts"). The selection of eligible articles was performed first by NP on title and abstract, and second by NP and MD on the full-text article.

2.2 Data extraction

Three authors (NP, LM, RL) independently extracted main study characteristics and outcomes using standardized forms. Discrepancies were resolved by a fourth author (MD). The main study characteristics included country, study design, age at vaccination and at outcome assessment, sample size according to the number of doses received, case definition, and statistical analyses (procedure used to assign the number of doses and adjustment for potential confounders).

2.3 Quality assessment

Two teams that were part of this review (Université Laval and Centers for Disease Control and Prevention (CDC)) independently assessed quality; discrepancies were resolved by consensus. We assessed included studies for selection bias, information bias, and confounding based on the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I). We used the same main sources of biases and ratings as the ROBINS-I, but adapted questions to consider the particularities of reduced dose observational studies. For selection bias, we examined whether selection of participants could be influenced by participants' characteristics or outcome. For information bias, we examined potential biases in measurement of intervention (e.g., validity of data sources to determine dose groups, sufficient interval between first and second dose among two-dose recipients) and in measurement of outcome (e.g., validity of the algorithm used to identify outcomes, use of lag time or buffer period between time of vaccination and counting of outcome to exclude outcomes originating from prevalent infections at a given dose). For confounding, we examined the likelihood of differences between dose groups in: 1) prevalence of HPV infection at first dose, 2) risk of HPV acquisition during study follow-up, and 3) immunogenicity (for studies with formal comparisons between three, two and one doses). We also examined methods used to control for these potential confounders.

For each domain, possible ratings were "Low": confident that there is little chance for bias; "Moderate": unlikely that there is a substantial bias, but a slight bias is possible; "Serious": significant possibility of a substantial bias; "Critical": confident that a substantial bias exists. The risk of bias in each category was assigned based on the highest (worst) domain rating within that category. If more than one age group was used in the analyses, we rated the age group with the lowest risk of bias. Because one aim of this systematic review was to discuss study limitations, no studies were excluded on the basis of methodological quality. Quality assessment findings were compiled in a descriptive synthesis.

2.4 Data synthesis

A narrative synthesis was conducted using data reported in the publications. The main outcome was effectiveness of HPV vaccination comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different numbers of doses (three vs none, two vs none, one vs none, three vs two, three vs one, two vs one) of quadrivalent HPV vaccine (Gardasil, 4vHPV) or bivalent HPV vaccine (Cervarix, 2vHPV). Results are presented as crude or adjusted risk ratios (RR), hazard ratios (HR), incidence rate ratios (IRR), prevalence ratios (PR), or odds ratios (OR). Because eligible studies used different buffer periods or age groups at vaccination and at outcome assessment, heterogeneity between studies was significant. Therefore, it was not possible to pool results from the different studies.

3.0 RESULTS

3.1 Search results

In the updated search from June 16, 2017, through September 29, 2021, 3784 additional articles were identified, 116 full text articles were assessed and 21 included. Overall, there

were 35 articles in the review, 14 from the initial review[11–24] and 21 from the update.[25–45] (Figure 1). The 35 articles were from 12 countries: United States (eleven), Scotland (six), Australia (four), Denmark (three), Sweden (two), Canada (two), and one each from Belgium, Denmark/Sweden, Italy, Mongolia, Netherlands, Spain, and New Zealand (Table 1, Table 2, Table S1).

All studies except one were conducted within the context of a recommended three-dose schedule. Evaluations were in countries that used 2vHPV (seven), 4vHPV (27) or both (one). Nine studies evaluated effectiveness for prevention of prevalent (detected at a single time point) or incident vaccine-type (4vHPV or 2vHPV) HPV infection,[11, 12, 25–31] ten anogenital warts,[13–18, 32–35] and 16 cervical cytological or histological abnormalities[19–24, 36–45].

3.2   Quality assessment

All 35 studies were determined to be at moderate or serious risk of bias (Table 1, Tables S2-S5, Figures S1–S6). No study had a domain rated as critical. Comparisons involving one and two doses were more likely to be affected by serious biases than three doses. Of seven potential sources of biases, three were more likely to be rated at serious risk of bias. These serious biases fell in two broad categories, i.e., information bias and confounding; each are likely to underestimate the effectiveness of one and two doses.

First, the majority of studies were deemed at moderate or serious risk of information bias for measurement of outcome (Figures S1, S4–S6). This is because prevalent infections at a given dose could cause an attribution of outcome to the wrong dose if outcomes are detected after a given dose but originate from an infection acquired before that dose. Studies using buffer periods to exclude outcomes originating from prevalent infections (12 months for infection, six months for anogenital warts, 24 months for cervical abnormalities)[46–48] or restricting analyses to girls vaccinated at an age when they were less likely to have prevalent infections were deemed at lower risk of information bias. Of note, while buffer periods decrease the likelihood that a prevalent infection at the time of a given vaccination was responsible for the outcome detected, they do not guarantee this.

Second, studies examining two-dose effectiveness were deemed at serious risk of information bias in measurement of intervention if the interval between the two doses was less than five months (Figures S2, S4–S6).[2–4] Because the majority of studies were conducted when a three-dose schedule was recommended, the interval between the first and second dose was often only one or two months; longer intervals were found when individuals were late for the second dose in a recommended three-dose series.

Third, the majority of studies were at moderate or serious risk of confounding as a result of differences between dose groups in prevalence of HPV infection at first dose or start of follow-up and/or in risk of HPV acquisition during follow-up (Figures S3–S6). The use of buffer periods or restriction of analysis to younger age groups could control for differences in prevalent infection at first dose between dose groups. More recent studies tend to include individuals vaccinated at a younger age and were less likely to be affected by biases related to prevalent infections at vaccination. Few studies were able to control for the potential

difference in risk of HPV acquisition between dose groups by adjusting for sexual activity during follow-up (Tables S3–S5).

3.3 HPV infection

In the original review, two studies reported vaccine effectiveness for prevention of prevalent vaccine-type infection, both from Scotland where 2vHPV was introduced.[11, 12] In the updated review, seven additional studies were identified, two from countries were 2vHPV was used (Scotland and Netherlands[30, 31]), and five from countries where 4vHPV was used (four from the United States[25–28] and one from Mongolia[29]) (Table 1). In five of the nine studies, three-, two- and one-dose vaccine recipients were compared with those unvaccinated;[11, 12, 27, 28, 30] four included a formal comparison between those with different numbers of doses (Table 2).[25–28] One study was conducted after a 2vHPV two-dose schedule was implemented in the Netherlands.[31] None of the studies assessed effectiveness using different buffer periods or intervals between doses in two-dose vaccine recipients.

Figure 2 shows estimates from eight studies that provided vaccine effectiveness estimates against HPV infection, either overall or limited to persons vaccinated at 18 years. Of five studies that evaluated effectiveness with three doses (compared to no vaccination), all found significant effectiveness.[11, 12, 27, 28, 30] Five of six found some significant effectiveness with two doses,[12, 27, 28, 30, 31] and four of six with one dose.[12, 27–29] Six studies conducted analyses limited to persons vaccinated at a younger age or only included such persons in the study.[11, 12, 28–31] In general, effectiveness estimates were higher with younger age at vaccination. In the one study conducted in the setting of a routine 2vHPV two-dose schedule, girls who were vaccinated at age 12–13 years were followed prospectively with self-collected vaginal swabs for HPV DNA.[31] The adjusted VE of two doses against incident HPV16/18 infection was 84% (95% CI 27.0, 96.5).

The three reports from Scotland used the same data sources, specifically data from assessment of vaccine-type HPV prevalence in women attending their first cervical screen generally at age 20–21 years,[28] immunization records from the Scottish Immunization Recall System, and other national registries. The first Scottish study reported statistically significant effectiveness in adjusted analyses for three doses but not for two or one doses. [11] The two subsequent studies found significant effectiveness for three and two doses.[12, 30] Effectiveness of one dose was observed when one dose vaccinees were oversampled and in some adjusted analyses of a cohort that included girls vaccinated at routine ages as well as those vaccinated during catch-up.[12] The most recent report stratified by age at vaccination for three doses only; higher effectiveness was found with younger age at vaccination.[30] There was no formal comparison of three vs. fewer doses effectiveness in any report from Scotland. For 4vHPV, two studies from the United States both found similar effectiveness for three, two and one doses. One used data from a national survey that obtained vaccination history from self-report.[27] The other used data from women aged 20–29 years continuously enrolled in an integrated health care system with vaccination histories from medical records.[28] The later study found high and similar effectiveness with three, two and one doses when analyses were limited to women who received the first dose

at age 18 years. A study from Mongolia included women who were part of a pilot 4vHPV vaccination campaign[29]; the analysis included 118 women who received only one dose at age 11–15 years compared with 357 unvaccinated women, frequency-matched on age. The adjusted PR was 0.08 (95% CI 0.01, 0.56).

Two articles reported effectiveness in men aged 14–26 years, both from the same U.S. study at different time points; there was no statistically significant effectiveness for prevention of genital or anal vaccine-type HPV among those who received one dose (compared to no vaccination) and no difference in effectiveness by number of doses.[25, 26] The number of vaccinated men was small in both, and almost half had initiated sexual activity at the same age as or before vaccination.

In summary, among nine studies of effectiveness against HPV infection, three, all from Scotland, reported highest point estimates with three doses.[11, 12, 30] Two studies among women in the United States reported similar effectiveness regardless of number of doses.[27, 28] A study from Mongolia only reported single-dose effectiveness (92%),[29] and a study from the Netherlands only reported two-dose effectiveness (84%).[31] Two studies among men included a small number of vaccinated participants; no significant effectiveness was reported with one dose.[25, 26]

3.2 Anogenital warts

The original review included six studies of anogenital wart outcomes.[13–18] In the updated review, four additional studies were identified; one included men and women.[32–35] The 10 studies were from six countries that had introduced 4vHPV. In nine of ten studies, analyses were adjusted or stratified for age at vaccination; all 10 were able to adjust for markers of socioeconomic status, and several attempted to adjust for differences in sexual behavior using composite measures (Table 1).[32–34] Nine studies analyzed at least one of the vaccine dose groups compared with no vaccination; seven conducted a formal comparison of effectiveness between number of doses (Table 2).[13, 14, 16, 18, 32, 33, 35] Three included assessment of effectiveness using different buffer periods,[13, 16, 32] and five evaluated different intervals between doses in two-dose vaccine recipients.[14, 16, 18, 32, 33]

Figure 3 shows estimates from nine studies that provided vaccine effectiveness estimates against anogenital warts and buffer periods used. Of eight studies that formally evaluated effectiveness with three doses (compared to no vaccination), all found significant effectiveness. Six of seven found some significant effectiveness with two doses,[13, 15, 17, 32, 33, 35] and six of eight with one dose.[13, 14, 17, 32, 33, 35] Effectiveness estimates of one and two doses were generally higher when using buffer periods of longer duration. In the three studies that examined different buffer periods,[13, 16, 32] two found that a longer buffer period decreased differences by number of doses. Herweijer et al, used a three-month buffer period in the primary analysis.[13] In analyses adjusted for attained age and parental education, there was statistically significant effectiveness for three, adjusted IRR (aIRR)=0.20 (95% CI 0.17, 0.23); two, aIRR=0.32 (95% CI 0.26, 0.40); and one doses, aIRR=0.54 (95% CI 0.43, 0.68). In analyses stratified by age at vaccination (10–16 years and 17–19 years), with a buffer period > four months, there was no statistically significant

difference between three and two doses, regardless of age at first vaccine dose. With a 12-month buffer period, there was no difference in effectiveness for three (aIRR=0.19 [95% CI 0.14, 0.24]), two (aIRR=0.19 [95% CI 0.13, 0.29]) or one (aIRR=0.24 [95% CI 0.15, 0.39]) doses among those who initiated vaccination at age 10–16 years. In a U.S. study, using data from electronic medical records and chart review, the adjusted HR of a single dose with a 6-month buffer from the last received dose was 0.81 (95% CI 0.60, 1.08) and with a 12-month buffer from the first dose was 0.32 (95% CI 0.20, 0.52).[32]

Seven studies that stratified by age at vaccination found higher vaccine effectiveness with younger compared to older age at vaccination, although differences were not formally tested in all.[13–15, 18, 33–35] Four studies evaluated vaccine effectiveness for three, two and one doses stratified by age at vaccination.[13, 33–35] Herweijer et al conducted the most detailed analysis, stratifying by age at vaccination (10–16 years and 17–19 years) and using different buffer periods.[13] They found higher effectiveness within the younger age at vaccination group, particularly for one-dose recipients when no or short buffer periods were used. Willows et al found higher effectiveness for all dose groups in those vaccinated at younger ages (9–18 years vs   19 years),[34] but differences by number of doses remained in all age at vaccination groups. In contrast, Zeybek et al found similar effectiveness by number of doses with younger age at vaccination.[33] A study by Navarro-Illana et al was limited mainly to girls vaccinated at age 14 years due to the national vaccination program in Spain; that study reported similar point estimates of effectiveness regardless of number of doses.[17]

In the five studies that explored the interval between doses in two-dose vaccine recipients, [14, 16, 18, 32, 33] three found that a longer interval changed effectiveness estimates or resulted in no difference between three and two doses.[14, 18, 32] For example, in a large study in Denmark where 70% of girls had an interval of two months between doses one and two, effectiveness was significantly higher with three doses than two doses in overall analyses.[14] However, there was no statistically significant difference between three and two doses with an interval > four months between doses and the IRR was close to one with an interval of six months.

In summary, among the ten studies evaluating 4vHPV effectiveness against anogenital warts, a range of age groups and different sensitivity analyses were included. Most studies reported highest effectiveness with three doses in the primary analyses. Sensitivity analyses suggested biases that could result from differences in age at vaccination across dose groups. Some found that differences between three and fewer doses decreased in analyses limited to persons vaccinated at younger ages, with longer buffer periods, or with longer intervals between two doses.

3.4   Cervical cytological and histological abnormalities

The original review included six studies that evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities. In the updated review, ten additional studies were included (Tables 1 and 2).[36–45] Of the 16 studies, 12 were from countries that had introduced mainly 4vHPV, three 2vHPV, and one both. By number of doses, eight studies evaluated histological outcomes only, three cytological outcomes only,[22,

23, 45] and five both histological and cytological outcomes.[19–21, 41, 44] Histological abnormalities included cervical intraepithelial neoplasia (CIN) grade 1, 2, 3, CIN2+ (CIN grade 2 or higher or adenocarcinoma in situ [AIS]), and CIN3/AIS. Characteristics of women, including age at first vaccine dose, differed across dose groups in most studies. All studies except one evaluated cytological or histological outcomes irrespective of HPV type.[40]

Among the 16 studies, 15 found significant effectiveness for three doses. Figure 4 shows estimates from 13 studies that provide estimates of vaccine effectiveness against CIN2+. Either in the main analysis, in analyses restricted to certain age groups, or those using longer buffer periods, all 13 found significant effectiveness for prevention of high grade lesions (CIN2+ or CIN3+) with three doses; five of these 13 studies found significant effectiveness with two doses;[20, 38–41] and five with one dose.[20, 38–41] In general, analyses using longer buffer periods found higher effectiveness estimates and smaller differences by number of doses.

Eight studies used no buffer or buffer periods <12 months when evaluating prevention of high grade histological lesions, and five used an explicit buffer 12 months.[20, 21, 39–41] Four explored different buffer periods;[20, 21, 39, 40] of these, two found that longer buffer periods increased estimates of effectiveness for all dose groups.[21, 40] Brotherton et al found that point estimates for effectiveness of three and one doses were similar with a 12-month buffer but not with shorter buffers.[21] Another study using a 12-month buffer found that among those vaccinated at age 15–19 years, effectiveness was similar for three, two and one doses. Although Johnson et al found that effectiveness estimates increased with longer buffer periods, that study also formally compared three and one doses; a significant difference remained even with a 24-month buffer.[40]

Overall, 12 of 16 studies presented data stratified by age at vaccination or birth year group.[20–22, 36–42, 44, 45] Most found higher point estimates of vaccine effectiveness against cytological or histological outcomes with younger age at vaccination or later birth year, although the differences were not all formally tested. In eight studies that evaluated high grade histological lesions by number of doses stratified by age at vaccination, or in studies limited to women vaccinated at younger ages,[20, 21, 37–42] three found similar and significant effectiveness regardless of number of doses.[38, 39, 41] These three studies evaluated women vaccinated at age 16 years in Denmark, age <16 years in Australia and age 15–19 years in the United States. A study from Sweden and Demark also reported similar point estimates by number of doses among those vaccinated at age 16 years and 17–19 years, but only the the effectiveness estimate for three doses was significant among those vaccinated at 16 years.[37]

Most two-dose vaccine recipients received doses at a one- or two-month interval because they received vaccination under recommendations for a three-dose schedule. Four studies using histological outcomes examined intervals between two doses; three found no impact of interval on the estimate of effect,[21, 39, 41] and one found similar effectiveness with three and two doses with an interval five months but not < five months between doses in those vaccinated at age 16 years.[37]

In summary, we identified 16 studies evaluating vaccine effectiveness for prevention of cervical abnormalities. In many studies, baseline characteristics of women who received fewer than three doses were different than three-dose vaccine recipients, and investigators conducted stratified and/or adjusted analyses to control for these differences. All studies except one found effectiveness with three doses compared to no vaccination. While many of the earliest published studies reported highest efficacy with three doses and no significant effectiveness with fewer doses, more recently published studies have reported effectiveness with three, two and one doses, and three of five reported similar effectiveness by number of doses.[38, 39, 41] Limiting analyses to persons vaccinated at younger ages and using buffer periods, factors that impact several different domains in the quality assessments, resulted in higher effectiveness estimates.

4.0 DISCUSSION

Vaccine effectiveness studies are valuable for evaluating vaccination programs and vaccines in real world settings. Because not all persons who start the HPV vaccination schedule complete the series, data from observational studies have been used to provide information on effectiveness with reduced dose schedules. However, differences in persons who complete a recommended three-dose series and those who do not, as well as other methodologic limitations, can result in substantial biases. In this updated systematic review of HPV vaccination effect by number of doses, we included 35 observational studies that evaluated outcomes of vaccine-type HPV infection, anogenital warts or cervical abnormalities. Among 29 studies that evaluated three doses, 28 found evidence of significant effectiveness.[11–13, 15–17, 19–24, 27, 28, 30, 32–37, 39–44] Among 29 studies that evaluated two doses, 19 found significant effectiveness.[12, 13, 15, 17, 19–22, 27, 28, 30–33, 35, 38–41] In 18 of 30 studies, significant effectiveness was observed for one dose in some or all analyses.[12–14, 17, 19–21, 27–29, 32, 33, 35, 38–41, 45] Across all endpoints (infection, anogenital warts, and cervical abnormalities), variation in effectiveness by number of doses was observed in most of the earliest published studies; highest effectiveness was found with three doses. Few studies directly compared three, two, and one doses and some effectiveness estimates had wide confidence intervals due to the small number of outcomes in one- and two-dose vaccine recipients.

In this review we formally assessed the risk of bias; almost all studies were assessed to have serious risk for at least one type of bias or confounding. The most common types of bias identified as serious were information bias, in measurement of the intervention or outcome, and confounding due to differences by number of doses in HPV infection at the time of vaccination and acquisition during follow-up. These multiple potential biases should be considered when interpreting the findings. Except for one study, all post-licensure studies were conducted in settings of a three-dose recommendation; for most two-dose vaccine recipients there was only a one- or two-month interval between doses one and two, leading to information bias in measurement of the intervention. Importantly, girls who received one or two doses differed from those completing the recommended schedule. In countries with catch-up vaccination policies, studies included persons vaccinated in the catch-up age group. Girls who received fewer than three doses were often older at the time of vaccination than three-dose vaccine recipients, had lower socioeconomic status, and/or had indicators

of earlier sexual exposure.[19, 21, 28, 32, 34, 38–41], resulting in these studies being at risk of both information bias related to measurement of the outcome, as misattribution of an outcome to the wrong dose was likely, and bias due to confounding. While some risk factors were measured and analyses adjusted, it is likely that unmeasured confounding remained, particularly for risk of HPV acquisition during the study follow-up. These would likely bias results towards greater effectiveness of three doses compared to one or two.

Although most studies found highest point estimates of effectiveness with three doses, the variation in effectiveness by number of doses was diminished or eliminated in studies when analyses were stratified by age at vaccination. Overall, five studies that found similar effectiveness for three, two and one doses, three evaluating cervical outcomes,[38, 39, 41] one evaluating anogenital warts[33] and one prevalent vaccine-type infection,[28] limited analyses to mainly those vaccinated in teenage years. However, other studies limited to persons vaccinated at ages 12–17 years did not report similar findings.[30, 42]

As more vaccinated persons age into age groups where outcomes are detected, more recent studies have been able to stratify by age at vaccination or limit studies to persons vaccinated at younger ages, which, among other things, improved the overall quality of studies. While less than 50% of studies published before 2019 were rated at only moderate risk of bias or had only one category rated at serious risk of bias, 77% (10/13) of studies published in 2019 or later were rated as such (Table 1).[26, 28, 29, 31, 35, 38–42] Among these ten studies, eight provided effectiveness estimates for three, two, and one doses, and six showed significant effectiveness for all three dose groups.[28, 35, 38–41] Of five studies that compared effectiveness between one and three doses,[28, 35, 38–40] three found similar point estimates with no significant difference in effectiveness.[28, 38, 39] Limiting studies to persons vaccinated at younger ages decreases the likelihood that a detected outcome is due to an infection present at the time of vaccination and minimizes potential biases due to differences in age at vaccination between dose groups.

In these types of observational studies, it is not possible to determine who was infected at the time of vaccination and if the outcome detected was due to infection already present at vaccination. Buffer periods, used in some studies to delay case counting, attempt to address this problem, as the use of buffers makes it more likey that the outcome detected was due to infection acquired after vaccination. Based on HPV natural history, longer buffer periods might be more important for evaluation of vaccine effectiveness against CIN2+ than anogenital warts because progression from infection to disease is shorter for anogenital warts. In our quality assessments, we considered different buffer periods for each outcome: 12 months for infection, six months for anogenital warts and 24 months for cervical abnormalities. In addition, buffer periods could be of greater importance with older age at vaccination because there is a higher likelihood of prevalent infection with increasing age through the twenties. Therefore, the impact of buffer periods would likely vary across studies. Among eight studies that conducted sensitivity analyses using different buffer periods,[13, 16, 20, 21, 32, 39, 40, 45] five found that estimates changed with longer buffer periods including higher effectiveness for one or two doses and a decrease in differences by number of doses.[13, 20, 21, 32, 40] While helpful to reduce some bias,

buffer periods also can reduce the number of person-years with one or two doses, which is small in some studies.

Because most post-licensure studies published to date were conducted in settings of a national three-dose recommendation, the majority of individuals vaccinated with two doses received doses with a one-month or two-month interval, not the interval recommended for a two-dose series. Immunogenicity studies leading to approval of a two-dose schedule found non-inferior results with two doses compared to three doses when the doses were separated by at least five or six months.[2, 3] Although the number of girls vaccinated with two doses separated by at least six months was small in studies identified for this review, ten evaluated interval between doses.[14, 16, 18, 21, 22, 32, 33, 37, 39, 41] Three of five studies evaluating anogenital wart outcomes[14, 18, 32] and two of five evaluating cervical outcomes[22, 37] found that longer intervals increased effectiveness estimates. The findings of higher effectiveness with a longer interval between two doses in some observational studies could be due to the longer interval functioning as a buffer period and not related to the spacing between doses. The inconsistent findings by interval between doses across studies also could be due to differing importance of buffer periods for the endpoints and age groups evaluated.

The accuracy of vaccination history is important for vaccine effectiveness studies. Incomplete vaccination histories could lead to overestimating effectiveness of fewer than three doses. While many studies in this review were conducted in countries with high quality vaccination registries, underreporting of vaccinations to registries can occur.[20, 21] In countries without registries, use of claims or insurance data is preferable to use of self-reported vaccination, but these sources could be incomplete if persons moved or changed insurers during the vaccination series. Several studies limited evaluation to persons continuously enrolled in insurance plans or integrated health care systems, resulting in a much higher likelihood of complete vaccination data collection.[28, 32, 33]

In conclusion, most post-licensure observational studies report highest effectiveness with three doses; some, particularly those limited to persons who received vaccine at younger ages, those able to stratify by age at vaccination, or those using longer buffer periods, found smaller or no statistically significant differences by number of doses. There are several biases in currently available data that impact effectiveness estimates, with most biasing two- and one-dose results. Nevertheless, observational studies are increasingly showing effectiveness with fewer than three doses and some show similar effectiveness with three, two and one doses. Studies examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias are needed for more valid interpretation.

Clinical trials designed to examine single-dose vaccination as well as long term follow-up of post-hoc analyses from three-dose clinical trials, in which not all women completed the schedule, are now available; data show high efficacy with a single dose and suggest good duration of protection.[6, 9, 49] These and other trials have provided important data for policy considerations.[50] Disparate results from observational effectiveness studies using data from national programs should be interpreted with an understanding of the inherent biases discussed in this review.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

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Medline and Embase database search
3784 potentially eligible studies
with titles and abstracts scanned

3668 studies excluded

2777 No data on the population-level impact of vaccination for our outcomes
345 Not an epidemiological study
219 Mathematical modeling or cost-effectiveness study
27 Description of surveillance systems, no data
75 Pre-vaccination data only or data among unvaccinated women
81 No results according to the number of individual doses
144 Duplicate

116 full-text articles reviewed

95 studies excluded

51 No data on the population-level impact of vaccination for outcomes
43 No results according to the number of individual doses
1 Follow-up of a clinical trial

14 articles included from previous review

2 HPV infections
6 Anogenital warts
6 Cervical abnormalities

35 articles included

9 HPV infections
10 Anogenital warts
16 Cervical abnormalities

Figure 1.
Flow diagram of study selection

	Risk Ratio[a] (95% CI)
Quadrivalent	
Sonawane 2019	0.31 (NA-NA)
Widdice 2019	0.76 (NA-NA)
Markowitz 2020	0.25 (0.10-0.62)
Batmunkh 2020	0.08 (0.01-0.56)
Bivalent	
Kavanagh 2014	0.95 (0.51-1.76)
Cuschieri 2016	0.52 (0.31-0.83)
Kavanagh 2017	0.89 (0.63-1.25)
Quadrivalent	
Sonawane 2019	0.77 (NA-NA)
Widdice 2019	1.08 (NA-NA)
Markowitz 2020	0.15 (0.05-0.47)
Bivalent	
Kavanagh 2014	0.68 (0.42-1.12)
Cuschieri 2016	0.45 (0.29-0.69)
Kavanagh 2017	0.75 (0.57-0.99)
Hoes 2021	0.16 (0.03-0.73)
Quadrivalent	
Sonawane 2019	0.42 (NA-NA)
Widdice 2019	0.88 (NA-NA)
Markowitz 2020	0.17 (0.11-0.26)
Bivalent	
Kavanagh 2014	0.43 (0.34-0.55)
Cuschieri 2016	0.27 (0.20-0.36)
Kavanagh 2017	0.40 (0.33-0.48)
Quadrivalent	
Markowitz 2020	0.08 (0.01-0.54)
Batmunkh 2020	0.08 (0.01-0.56)
Bivalent	
Kavanagh 2014	0.65 (0.29-1.41)
Cuschieri 2016	0.52 (0.31-0.83)
Kavanagh 2017	0.89 (0.63-1.25)
Quadrivalent	
Markowitz 2020	0.07 (0.01-0.47)
Bivalent	
Kavanagh 2014	0.64 (0.37-1.14)
Cuschieri 2016	0.45 (0.29-0.69)
Kavanagh 2017	0.75 (0.57-0.99)
Hoes 2021	0.16 (0.03-0.73)
Quadrivalent	
Markowitz 2020	0.08 (0.04-0.15)
Bivalent	
Kavanagh 2014	0.34 (0.26-0.46)
Cuschieri 2016	0.27 (0.20-0.36)
Kavanagh 2017	0.40 (0.33-0.48)

All ages at vaccination

Age at vaccination ≤ 18 years[b]

Favors vaccination
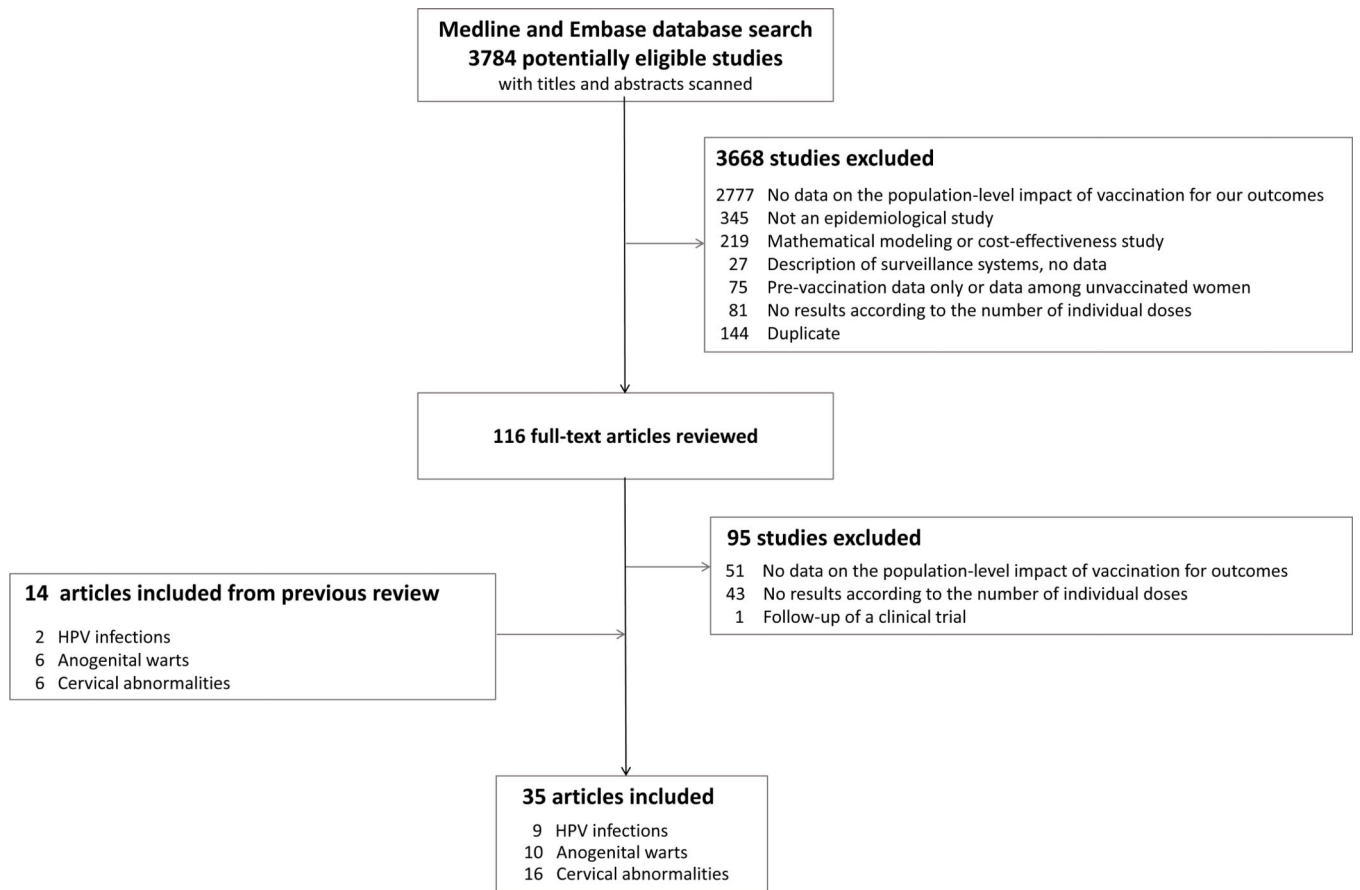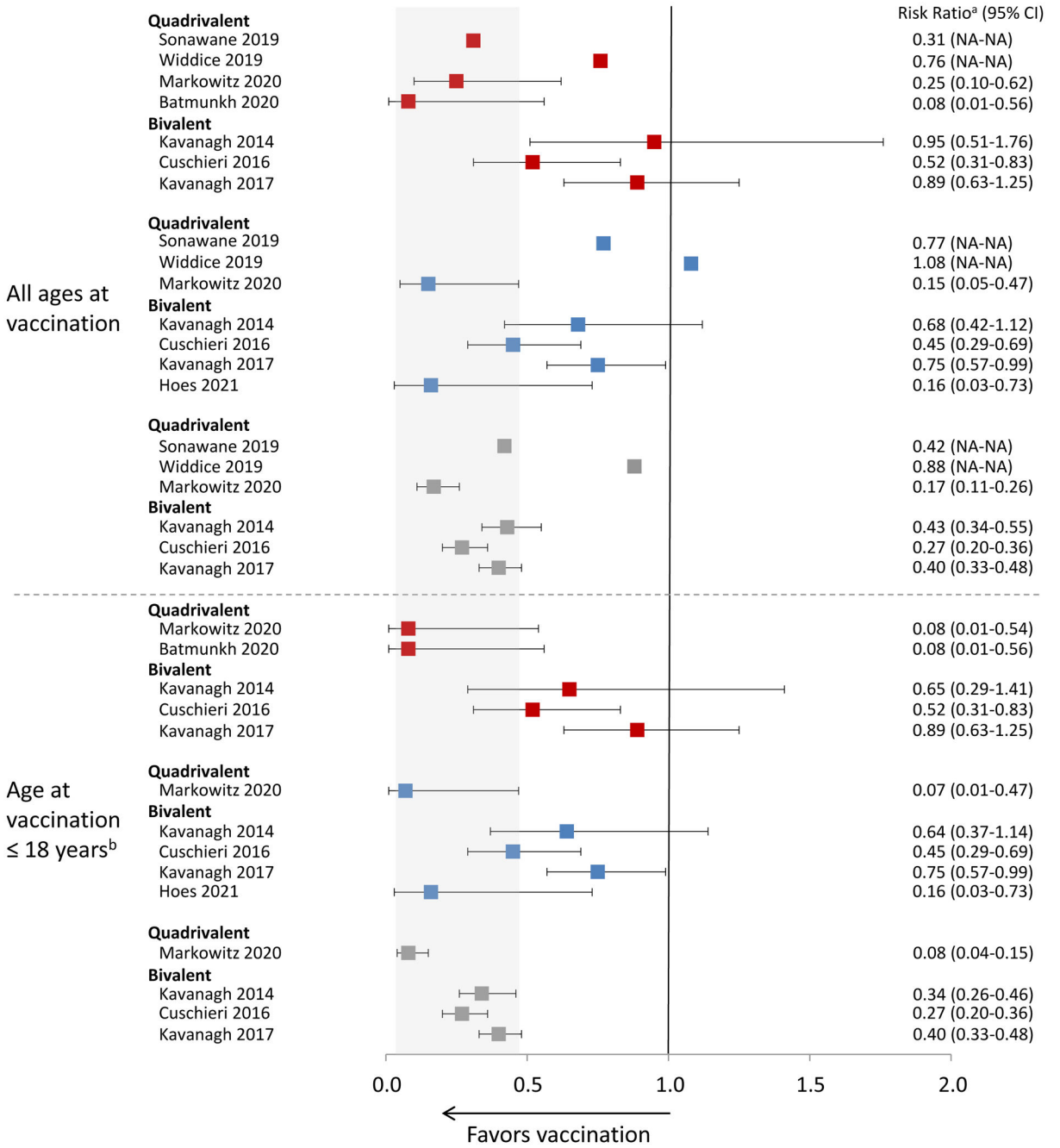
Figure 2.

Effectiveness of HPV vaccination against HPV infection by number of doses and age at vaccination

■ 1 dose vs 0 doses; ■ 2 doses vs 0 doses; ■ 3 doses vs 0 doses

Data included in this analysis were extracted from original published articles.

NA, not available

Gray area indicates the range of the CIs from the published studies for effectiveness of 3 doses among girls aged 18 or younger when vaccinated.

[a]Risk ratio includes different measures depending on study, including incidence rate ratio, prevalence ratio, risk ratio, odds ratio or hazard ratio; for Widdice 2019 and Sonawane 2019, risk ratio was estimated from the prevalence of HPV infection among the different dose groups presented in the article, but the authors did not formally assess the effectiveness of 1,2,3 doses compared to 0 dose.

[b]Age at vaccination 18 years of age varied by study; for Markowitz 2020, 18 years; for Batmunkh 2020, age 11–17 years; for Kavanagh 2014, estimates from an analysis adjusted for birth cohort and there were few individuals vaccinated at age >18 years; for Cushieri 2016, estimates from an analysis adjusted by birth cohort and there were few individuals vaccinated at age >18 years; for Kavanagh 2017 estimates from an analysis adjusted for birth cohort and there were few individuals vaccinated at age >18 years.

Risk Ratio[a] (95% CI)

	Risk Ratio[a] (95% CI)
No buffer	
Herweijer 2014	0.84 (0.70-1.01)
Navarro-Illana 2017	0.39 (0.13-0.80)
Willows 2018	0.60 (0.20-1.80)
Herweijer 2014	0.42 (0.34-0.51)
Navarro-Illana 2017	0.36 (0.14-0.68)
Willows 2018	1.40 (0.60-3.30)
Herweijer 2014	0.21 (0.18-0.24)
Navarro-Illana 2017	0.24 (0.15-0.34)
Perkins 2017	0.53 (0.46-0.60)
Willows 2018	0.40 (0.30-0.70)
1-month buffer	
Herweijer 2014	0.72 (0.59-0.88)
Blomberg 2015	0.51 (0.46-0.56)
Dominiak-Felden 2015	0.63 (0.35-1.16)
Baandrup 2021	0.29 (0.22-0.38)
Herweijer 2014	0.37 (0.30-0.46)
Dominiak-Felden 2015	0.34 (0.14-0.83)
Baandrup 2021	0.22 (0.18-0.26)
Herweijer 2014	0.21 (0.18-0.24)
Dominiak-Felden 2015	0.12 (0.07-0.21)
Baandrup 2021	0.16 (0.15-0.18)
3-month buffer	
Herweijer 2014	0.54 (0.43-0.68)
Zeybek 2018	0.65 (0.49-0.85)
Herweijer 2014	0.32 (0.26-0.40)
Zeybek 2018	0.67 (0.51-0.89)
Herweijer 2014	0.20 (0.17-0.23)
Zeybek 2018	0.58 (0.49-0.70)
6-month buffer	
Herweijer 2014	0.47 (0.37-0.60)
Hariri 2018	0.81 (0.60-1.08)
Herweijer 2014	0.25 (0.19-0.32)
Hariri 2018	0.32 (0.17-0.59)
Herweijer 2014	0.19 (0.16-0.23)
Hariri 2018	0.23 (0.17-0.31)
12-month buffer	
Herweijer 2014	0.33 (0.24-0.44)
Hariri 2018	0.32 (0.20-0.52)
Herweijer 2014	0.19 (0.14-0.26)
Hariri 2018	0.24 (0.13-0.44)
Herweijer 2014	0.19 (0.16-0.24)
Hariri 2018	0.20 (0.15-0.27)

0.0   0.5   1.0   1.5   2.0
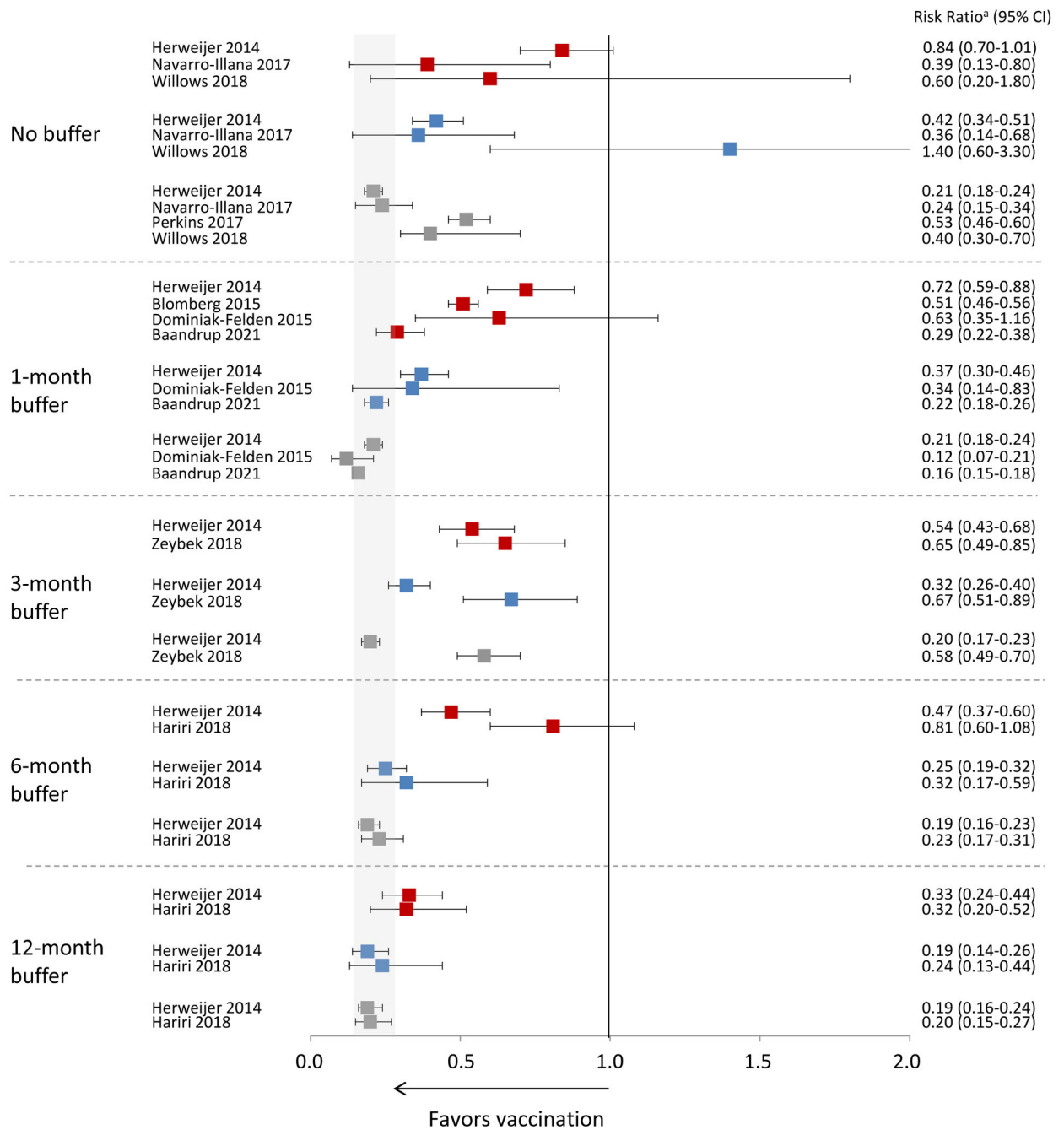
← Favors vaccination

Figure 3.
Effectiveness of HPV vaccination against anogenital warts by number of doses and duration of buffer period for studies using the quadrivalent vaccine

■ 1 dose vs 0 doses; ■ 2 doses vs 0 doses; ■ 3 doses vs 0 doses

Data included in this analysis were extracted from original published articles.

Gray area indicates the range of the CIs from the published studies for effectiveness of 3 doses using the longest buffer period.

Perkins reports using a buffer period but does not report results in the article.

[a] Risk ratio includes different measures depending on study, including incidence rate ratio, prevalence ratio, risk ratio, odds ratio or hazard ratio.
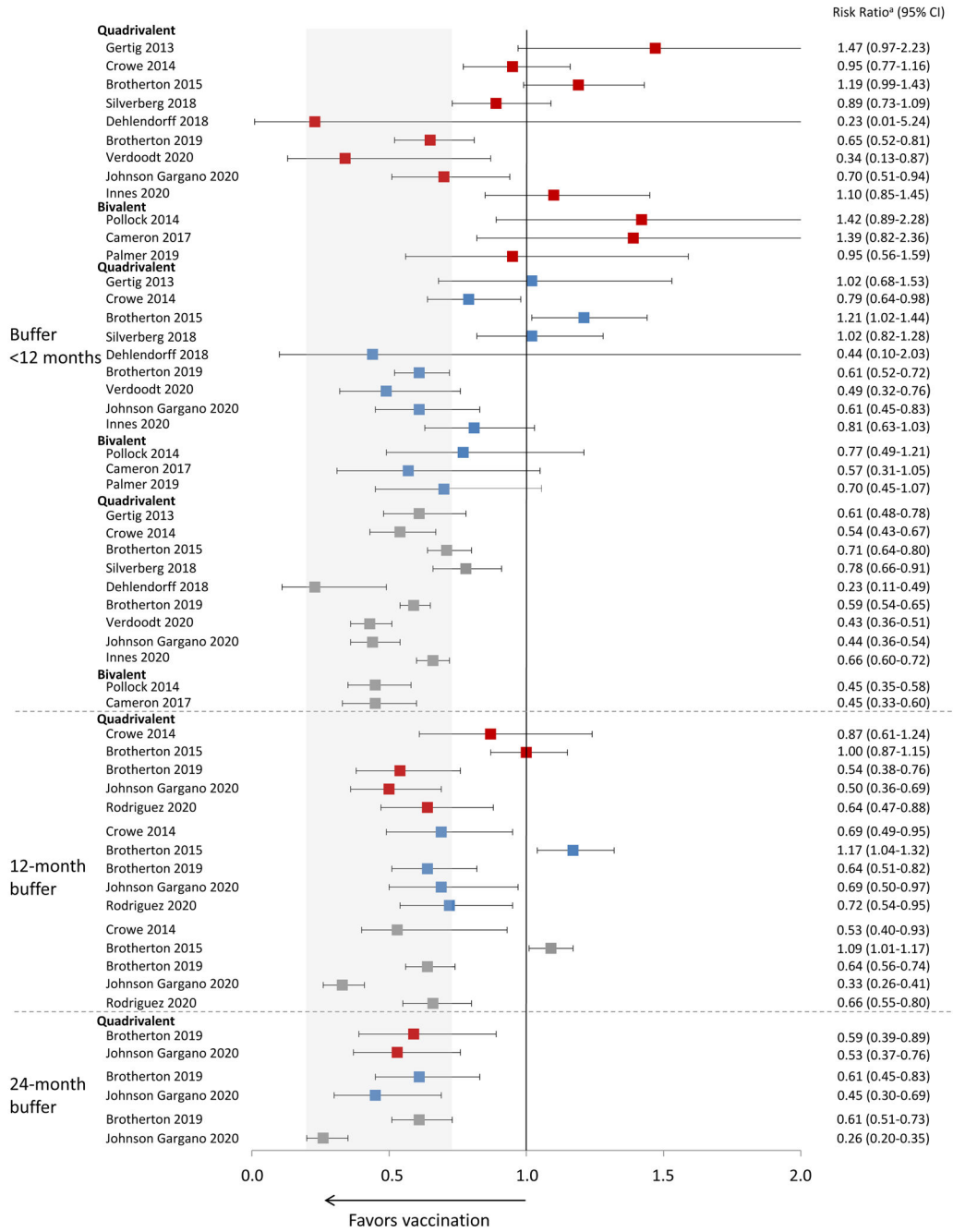
Figure 4.

Effectiveness of HPV vaccination against CIN2+ by number of doses and duration of buffer period

■ 1 dose vs 0 doses; ■ 2 doses vs 0 doses; ■ 3 doses vs 0 doses

Data included in this analysis were extracted from original published articles.

Gray area indicates the range of the CIs from the published studies for effectiveness of 3 doses using the longest buffer period.

CIN2+, cervical intraepithelial neoplasia grade 2, 3, or worse or adenocarcinoma in situ

[a] Risk ratio includes different measures depending on study, including incidence rate ratio, prevalence ratio, risk ratio, odds ratio, or hazard ratio.

Table 1.

Characteristics of studies that evaluated HPV vaccine effectiveness by number of doses

Endpoint/ vaccine/ authors	Country	Study design	Study population		Vaccination	Case definition	Statistical analyses			Overall risk of bias assessment [b]
			Age (years) at Vaccination Outcome	Age (years) at Vaccination	N by dose number		Assignment of dose number	Buffer periods [a] (months)	Adjustment or stratification	
Vaccine-type HPV infection										
Quadrivalent vaccine										
Chandler 2018	United States	Cross-sectional study using self-reported data - men	26 [c]	14–26	0: 82 1: NA 2: NA 3: NA	HPV 6,11,16, or 18 DNA positivity in self-collected penile and perianal/anal swabs [d]	Final status	0	None	Serious (2/3)
Widdice 2019	United States	Cross-sectional study using self-reported data - men	16.2 wave 1 (mean); 15.1 wave 2 (mean)	13–26	0: 471 1: 58 2: 37 3: 143	HPV 6,11,16, or 18 DNA positivity in genital and perianal/anal swabs [d]	Final status	0	Age at vaccination, sexual initiation before or after vaccination	Serious (1/3)
Sonawane 2019	United States	Cross-sectional study of a nationally representative sample	<26 [b]	18–26	0: 1,004 1: 106 2: 126 3: 384	HPV 6,11,16, or 18 DNA positivity in self-collected cervicovaginal samples [d]	Final status	0	Attained age, race/ ethnicity, age at sexual debut, lifetime number of male sexual partners	Serious (2/3)
Markowitz 2020	United States	Cross-sectional study of women enrolled in an integrated health-care delivery system	<29 [b]	20–29	0: 1,052 1: 303 2: 304 3: 2,610	HPV 6,11,16, or 18 DNA positivity in liquid-based cytology samples [d]	Final status	1	Age at vaccination, screening year, race/ ethnicity, attained age	Moderate (2/3)
Batmunkh 2020	Mongolia	Cross-sectional study of women	11–17	16–26	0: 357 1: 118	HPV 16 or 18 DNA positivity in self-collected swabs [e]	Final status	0	Attained age at assessment, sexual behavior, education, income, employment status, tobacco and alcohol use, pregnancy	Moderate (2/3)

Endpoint/ vaccine/ authors	Country	Study design	Study population — Age (years) at Vaccination / Outcome	Vaccination — N by dose number	Case definition	Statistical analyses — Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	Overall risk of bias assessment[b]
Bivalent vaccine									
Kavanagh 2014	Scotland	Cross-sectional study using screening registry data	15–17 / 20–21	0: 3,418 / 1: 55 / 2: 106 / 3: 1,100	HPV 16 or 18 DNA positivity in liquid-based cytology samples[f]	Final status	0	Birth year cohort, deprivation score	Serious (1/3)
Cuschieri 2016	Scotland	Cross-sectional study using screening registry data with additional sampling of those with <3 doses	15–>18 / 20–21	0: 3,619 / 1: 177 / 2: 300 / 3: 1,853	HPV 16 or 18 DNA positivity in liquid-based cytology samples[g]	Final status	0	Birth year cohort, deprivation score, age at first dose	Serious (1/3)
Kavanagh 2017	Scotland	Cross-sectional study using screening registry data	12–>18 / 20–21	0: 4,008 / 1: 223 / 2: 391 / 3: 3,962	HPV 16 or 18 DNA positivity in liquid-based cytology samples[g]	Final status	0	Age at vaccination, birth year cohort, deprivation score	Moderate (2/3)
Hoes 2021	Netherlands	Prospective cohort study	12–13 / 14–17	0: 929 / 2: 1098[h]	HPV 16 or 18 incident DNA positivity in self-collected vaginal swabs[i]	Final status	0	Attained age, ethnicity, ever had sex, ever used contraception	Moderate (1/3)
Anogenital warts									
Quadrivalent vaccine									
Herweijer 2014	Sweden	Retrospective cohort study using population-based health registries	10–19 / 10–24	0: 1,045,157 / 1: 115,197 / 2: 107,338 / 3: 89,836	First observed diagnosis: ICD-10 code A63.0 or podophyllotoxin / imiquimod prescription	Time-dependent Final status	0 to 12	Age at first vaccination, age at outcome, parental education	Serious (1/3)
Blomberg 2015	Denmark	Retrospective cohort study using population-based	12–27 / 12–27	0: 188,956 / 1: 55,666 / 2: 93,519 / 3: 212,549	First diagnosis: ICD-10 code A63.0 or podophyllotoxin prescription	Time-dependent	1	Attained age, age at vaccination, maternal education disposable income, calendar year	Serious (2/3)

Endpoint/ vaccine/ authors	Country	Study design	Study population Age (years) at Vaccination Outcome	Vaccination N by dose number	Case definition	Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	Overall risk of bias assessment[b]
		health national registries							
Dominiak-Felden 2015	Belgium	Retrospective cohort study using sick-fund/ insurance reimbursement database	10–21	16–23	0: 63,180 1: 4,020 2: 3,587 3: 35,792	First prescription of imiquimod and reimbursement	Time-dependent	1	Age at first dose	Serious (2/3)
Perkins 2017	United States	Retrospective cohort study using commercial claims database	9–25	9–25	0: 201,933 1: 30,438 2: 36,583 3: 118,962	ICD-9 and CPT codes and prescriptions[j]	Final status	0, 12	Age at start of exposure period, regions, SES indicators, calendar year, differential observation periods	Serious (1/3)
Navarro-Illana 2017	Spain	Retrospective cohort study using national registries	14	14–19	0: 607,006 1: 18,142 2: 31,420 3: 153,296 (person-yrs)	First diagnosis of ICD-9-CM code 078.11	Time-dependent	0	Attained age (time varying), calendar year, health department	Serious (1/3)
Lamb 2017	Sweden	Retrospective cohort study using national registries	10–19	10–27	2: 79,042 3: 185,456	First diagnosis of ICD-10 code A63.0 or podophyllotoxin / imiquimod prescription	Time-dependent	0	Attained age at outcome, age at vaccination time between doses	Serious (1/3)
Hariri 2018	United States	Retrospective cohort study in integrated health-care delivery systems	16–17 (mean)	11–28	0: 31,563 1: 5,864 2: 5,459 3: 21,631	ICD-9 code (078.10, 078.11, 078.19), specialty of diagnosing provider, and STI tests ordered	Final status	6 from last dose 12 from first dose	Race/ethnicity, health plan, age at enrollment in health plan, age at beginning of study period, evidence of sexual activity (as defined by composite measure), age at first evidence of sexual activity, age at first dose, continuous enrollment indicator, months enrolled in health plan, Medicaid enrollment	Moderate (3/3)
Zeybek 2018	United States	Matched retrospective cohort study using	9–26	10–31	0: 286,963 1: 54,280	ICD-9-CM or 10 code 078.11 or A63.0	Final status	3	Age group (based on age at last dose) sex, region	Serious (1/3)

Endpoint/ vaccine/ authors	Country	Study design	Study population — Age (years) at Vaccination / Outcome	Vaccination — N by dose number	Case definition	Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	Overall risk of bias assessment[b]
		health insurance claims databases (males and females)		2: 55,632 3: 177,051				of residence, history of STDs, enrollment history.	
Willows 2018	Canada	Matched retrospective cohort study using linked vaccine registry and claims and population-based databases	9–26	10–33	0: 94,327 1: 3,521 2: 6,666 3: 21,277	ICD-9-CM or 10 code 078.11 or A63.0 and related procedure code	Final status	0	Age at vaccination, place of residence, area-level income, birth date, previous hospitalizations and physician visits, history of chronic diseases, sexual activity (based on evidence using a composite measure)	Serious (2/3)
Baandrup, 2021	Denmark	Retrospective cohort study using population-based health national registries	12–30	12–30	0: 1,904,895 1: 235,653 2: 460,978 3: 1,934,589 (person-yrs)	First diagnosis: ICD-10 code A63.0 or podophyllotoxin prescription	Time-dependent	1	Attained age, age at vaccination, maternal education, calendar time	Serious (1/3)

Cervical abnormalities

Quadrivalent vaccine

Endpoint/ vaccine/ authors	Country	Study design	Study population — Age (years) at Vaccination / Outcome	Vaccination — N by dose number	Case definition	Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	Overall risk of bias assessment[b]
Gertig 2013	Australia	Retrospective cohort study using linked data from registries	12–19	12–21	0: 14,085 1: 1,422 2: 2,268 3: 21,151	Histology: CIN3/AIS, CIN2, CIN 1, any high grade Cytology: low grade and high grade	Time-dependent Final status	0	Age at first screen, remoteness area, SES	Serious (2/3)
Crowe 2014	Australia	Case control study using linked data from registries	12–26	11–31	0: 60,282 1: 10,879 2: 12,073 3: 25,119	Histology: CIN2+/AIS	Final status	0, 1, 6, 12	Year of birth, remoteness area, SES, follow-up time	Serious (2/3)
Brotherton 2015	Australia	Retrospective cohort study using linked regional data registries	12–26	12–30	0: 133,055 1: 20,659 2: 27,500 3: 108,264	Histology: CIN3/AIS, CIN2, any high grade Cytology: low grade and high grade	Final status	0, 1, 6, 12, 24	Age in 2007, remoteness, SES, screening start (before or after vaccination)	Serious (1/3)
Hofstetter 2016	United States	Retrospective cohort study using	11–20	11–27	0: 1,632 1: 695	Cytology: any abnormal and high grade[j]	Final status	1	Age at vaccination initiation or first missed opportunity	Serious (2/3)

Endpoint/ vaccine/ authors	Country	Study population		Vaccination	Case definition	Statistical analyses			Overall risk of bias assessment[b]
		Study design	Age (years) at Vaccination / Outcome	N by dose number		Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	
		medical center records		2: 604 3: 1,196				for vaccination for unvaccinated, insurance, language, clinic type, CT screening, and baseline cytology	
Kim 2016	Canada	Nested case-control study using linked data from registries	10–15 / 18–21	0: 5,712 1: 327 2: 490 3: 3,675	Cytology: low grade and high grade[k]	Final status	0	Attained age, urban/ rural, laboratory site, neighborhood income	Serious (2/3)
Silverberg 2018	United States	Nested case-control study of women enrolled in an integrated health-care delivery system	14–26 / 18–34	0: 23,293 1: 756 2: 554 3: 1,527	Histology: CIN2+/AIS	Final status	6	Smoking, parity, recent outpatient visits, race/ethnicity, STDs, hormonal contraceptives, immunosuppression	Serious (2/3)
Dehlendorff 2018	Denmark & Sweden	Retrospective cohort study using linked national registry data	13–29 / 13–30	0: 2,091,579 1: NA 2: NA 3: NA	Histology: CIN2+/AIS	Time-dependent	0	Attained age, age at vaccination, maternal education	Serious (1/3)
Brotherton 2019	Australia	Retrospective cohort study using linked regional data registries	13–22 / 15–22	0: 48,845 1: 8,618 2: 18,190 3: 174,995	Histology: CIN2+CIN3+	Final status (time-varying as a sensitivity analysis)	0, 12, 24	Birth cohort, age at study entry, area of residence, socioeconomic status, attained age (time varying)	Serious (1/3)
Verdoodt 2020	Denmark	Retrospective cohort study using linked national registry data	12–16 / 17–25	0: 374,327 1: 10,480 2: 30,259 3: 174,532	Histology: CIN2+CIN3+	Time-dependent (final status for the comparison between doses)	0 6 in secondary analysis	Attained age, maternal education	Serious (1/3)
Johnson Gargano 2020	United States	Case control study using medical records data from 5 US sites; test negative design	12–26 / 18–39	0: 2,731 1: 136 2: 108 3: 325	Histology: HPV type-specific CIN2+	Final status	1, 12, 24, 36	Birth cohort, geographic site, race/ethnicity, insurance status, age at vaccination	Moderate (3/3)

Endpoint/ vaccine/ authors	Country	Study design	Study population Age (years) at Vaccination	Outcome	Vaccination N by dose number	Case definition	Statistical analyses Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification	Overall risk of bias assessment[b]
Rodriguez 2020	United States	Retrospective matched cohort study using health insurance claims database	9–26	9–31	0: 66,541 1: 13,630 2: 14,088 3: 38,823	Histology: CIN2/3 Cytology: HSIL/ ASC-H	Final status	12	Age at vaccination, region, history of STDs and pregnancy, length of enrollment, history and results of pap test, US census region, age at beginning of follow-up	Serious (1/3)
Innes 2020	New Zealand	Retrospective cohort study using linked national registry data	14–21	20–24	0: 47,283 1 or 2: 8,317 3: 48,713	Histology: CIN1 CIN2+	Final status	0	Age at first dose, birth year cohort	Serious (1/3)
Bivalent vaccine										
Pollock 2014	Scotland	Retrospective cohort study using linked national registry data	15–>18	20–21	0: 76,114 1: 1,315 2: 2,725 3: 25,898	Histology: CIN1, CIN2, CIN3	Final status	0	Attained age, birth year cohort year, deprivation score	Serious (2/3)
Cameron 2017	Scotland	Retrospective cohort study using linked national registry data	14–>18	20–21	0: 75,683 1: 2,258 2: 4,462 3: 55,303	Histology: CIN1, CIN2, CIN3	Final status	0	Deprivation score, birth year cohort	Serious (2/3)
Palmer 2019	Scotland	Retrospective cohort study using linked national registry data	12–>18	20	0: 64,026 1: 2,051 2: 4,135 3: 68,480	Histology: CIN1, CIN2, CIN3 Cytology: Low grade, moderate grade, severe grade	Final status	0	Age at vaccination, deprivation score, rurality	Serious (2/3)
Acuti Martellucci 2021[l]	Italy	Retrospective cohort study using administrative data	14–>30	17–32	0: 7,394 1: 212 2: 83 3: 96	Cytology: Any abnormal cytology, low and high grade	Final status	1, 6, 12	Year of birth, residential area, country of birth, screening test kit, number of screens	Serious (2/3)

Abbreviations: CT, chlamydia trachomatis; SES, socioeconomic status; STD, sexually transmitted disease or infection; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade 2 or worse; AIS, adenocarcinoma in situ; ICD-9, International Classification of Disease, ninth revision; ICD-10, International Classification of Disease, tenth revision; NA, not available

Note: Crowe et al (2014) reported on an additional outcome defined using cytology and histology data for classification, results are not included in this paper

[a]Buffer period is the lag time between vaccination and counting of outcomes.

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[b] Overall risk of bias assessment considers 3 categories: selection, information bias and confounding (ratings are low, moderate, serious, critical) and is based on the worst rating. If different objectives have different overall assessments, this table includes the bias rating for 1 vs 0 doses when available. In parentheses is number of categories of bias (out of 3) with the worst rating. More information is provided in supplementary material.

[c] not explicitly stated in paper.

[d] By Roche Linear Array assay detecting 37 types.

[e] By Xpert HPV assay and Anypex II detecting 28 types.

[f] By multimetrix HPV assay detecting 24 types.

[g] By Optiplex HPV assay detecting 24 types.

[h] Numbers in first study year;

[i] By HPV-LIPA25 detecting 25 types.

[j] Three possible scenarios: a) 1 diagnosis of ICD-9 code 078.1; b) 1 diagnosis of ICD-9 code 078.1, 078.10, 078.19 plus destruction/excision procedure or ICD-9 code 211.4, 216.5, 221.8, 222.9; c) 1 prescription for anogenital warts plus destruction/excision procedure or ICD-9 code 211.4, 216.5, 221.8, 222.9.

[k] Low-grade cytology defined as atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. High-grade cytology defined as atypical squamous cells, cannot rule out a high-grade lesion, or high-grade squamous intraepithelial lesion.

[l] Either bivalent or quadrivalent HPV vaccine.

Table 2.

Studies that evaluated HPV vaccine effectiveness by number of doses: analyses and main findings

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome	Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated — Effect (95% CI)	Comparison with unvaccinated — Comments	Formal comparison between doses
Vaccine-type HPV infection						
Quadrivalent vaccine						
Chandler 2018	26[c]; 14–26	0	No/No/No	No significant effectiveness for 1 dose		1 vs 3 doses OR = 0.99 (0.33–2.96) 2 vs 3 doses OR = 0.60 (0.17–2.12)
Widdice 2019	16.2 wave 1 (mean); 15.1 wave 2 (mean); 13–26	0	Yes/No/No	No significant effectiveness for 1 dose	• Similar results for the analysis restricted to men vaccinated at 15 years and men vaccinated before sexual initiation, and men vaccinated after sexual initiation	Number of doses (0,1,2,3) not associated with 1 vaccine-type HPV or HPV16 and/or 18
Sonawane 2019	26[c]; 18–26	0	No/No/No	Difference in predicted probability 3: aPD = −4.3 (−4.6, −4.0) 2: aPD = −1.7 (−2.4, −0.1) 1: aPD = −5.0 (−5.6, −4.5)		1 vs 3 doses p-value = 0.70 2 vs 3 doses p-value = 0.40 1 vs 2 doses p-value = 0.12
Markowitz 2020	29[c]; 20–29	1	Yes/No/No	Overall results 3: aPR = 0.17 (0.11–0.26) 2: aPR = 0.15 (0.05–0.47) 1: aPR = 0.25 (0.10–0.62) Results for those with first dose at age 18 years 3: aPR = 0.08 (0.04–0.15) 2: aPR = 0.07 (0.01–0.47) 1: aPR = 0.08 (0.01–0.54)	• Similar results for unadjusted analyses and controlling for race/ ethnicity and age at screening	3 vs 1 dose PR = 1.06 (0.14–8.09) 3 vs 2 doses PR = 1.17 (0.15–8.96) 2 vs 1 dose PR = 0.90 (0.06–14.36)
Batmunkh 2020	11–17; 16–26	0	No/No/No	1: aPR = 0.08 (0.01–0.56)	• Adjusted for income and employment status	No

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
					Effect (95% CI)	Comments	
Bivalent vaccine							
Kavanagh 2014	15–17	20–21	0	Yes/No/No	3: aOR = 0.43 (0.34–0.55) 2: aOR = 0.68 (0.42–1.12) 1: aOR = 0.95 (0.51–1.76)	• Differences by number of doses still observed when stratified by age at vaccination	No
Cuschieri 2016	15–17	20–21	0	No/No/No	3: aOR = 0.27 (0.20–0.36) 2: aOR = 0.45 (0.29–0.69) 1: aOR = 0.52 (0.31–0.83)		No
Kavanagh 2017	12–>18	20–21	0	Yes/No/No	3: aOR = 0.40 (0.33–0.48) 2: aOR = 0.75 (0.57–0.99) 1: aOR = 0.89 (0.63–1.25)	• When stratified by age at first dose, 3-dose effectivness was highest in the youngest group and lower with age, but all were significant (range: 28.9%–89.1%)	No
Hoes 2021	12–13	14–17	0	No/No/No	2: aHR = 0.16 (0.035–0.73)	• Study conducted when routine 2-dose vaccination program recommended	No
Anogenital warts							
Quadrivalent vaccine							
Herweijer 2014	10–19	10–24	3	Yes/Yes/No	3: aIRR = 0.20 (0.17–0.23) 2: aIRR = 0.32 (0.26–0.40) 1: aIRR = 0.54 (0.43–0.68)	• Similar results for age groups 10–16 and 17–19 • Similar results for buffers of 0–12 months, except effectiveness for 1 dose was not significant among those vaccinated at 17–19 using buffers of 0 and 1 month(s)	3 vs 1 dose aIRR = 0.37 (0.28–0.48) 3 vs 2 doses aIRR = 0.63 (0.48–0.82) 2 vs 1 dose aIRR = 0.59 (0.43–0.81) • With buffer periods >4 months, no significant difference between 3 and 2 doses
Blomberg 2015	12–27	12–27	1	Yes/No/Yes	1: IRR = 0.51 (0.46–0.56)		3 vs 2 doses IRR = 0.46 (0.39–0.54) 2 vs 1 doses IRR = 0.44 (0.37–0.51) • With dose interval >4 months, no significant difference for 3 vs 2 doses • Similar results when stratified by age at vaccination

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
					Effect (95% CI)	Comments	
Dominiak-Felden 2015	10–21	16–23	1	Yes/No/No	3: aIRR = 0.12 (0.07– 0.21) 2: aIRR = 0.34 (0.14–0.83) 1: aIRR = 0.63 (0.35–1.16)	• 3 dose effectiveness estimates were higher for those vaccinated at age <15 and 15–17 years than 18 years • 3 dose effectiveness estimates higher with buffers >1 year	No
Perkins 2017	9–25	9–25	0	No/Yes/Yes	3: aIRR = 0.53 (0.46–0.60)		3 vs 1 doses aIRR = 0.82 (0.71–0.95) 3 vs 2 doses aIRR = 0.89 (0.78–1.03) • With 1 yr buffer period, no change in findings (data not shown) • Similar results with interval >5 months for 2 doses
Navarro-Illana 2017	14	14–19	0	No/No/No	3: aRR = 0.24 (0.15–0.34) 2: aRR = 0.36 (0.14–0.68) 1: aRR = 0.39 (0.13–0.80)		No
Lamb 2017	10–19	10–27	0	Yes/No/Yes	No analyses of 3, 2 or 1 doses compared to 0		• Higher effectiveness of 3 vs 2 doses, when 1st and 2nd doses administered 0–3 or >8 months apart but not 4–7 months • Similar results stratified by age at vaccination
Hariri 2018	16–17 (mean)	11–28	6 from last dose 12 from first dose	No/Yes/Yes	6 month buffer from last dose 3: aHR = 0.23 (0.17–0.31) 2^d: aHR = 0.32 (0.17–0.59) 1: aHR = 0.81 (0.60–1.08) 12 month buffer from first dose 3: aHR = 0.20 (0.15–0.27) 2^d: aHR = 0.24 (0.13– 0.44) 1: aHR = 0.32 (0.20–0.52)		6 month buffer from last dose 3 vs 1 dose aHR = 0.29 (0.20–0.42) 3 vs 2^d doses aHR = 0.74 (0.38–1.43) 2^d vs 1 dose aHR = 0.39 (0.20–0.76) 12 month buffer from first dose 3 vs 1 dose aHR = 0.63 (0.37–1.09) 2 vs 1 dose aHR = 0.74 (0.35–1.60)

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome	Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
				Effect (95% CI)	Comments	
Zeybek 2018	9–26	10–31	3 from last dose	Yes/No/Yes	Results for 15–19 yr-olds 3: aRR = 0.58 (0.49–0.70) 2: aRR = 0.67 (0.51–0.89) 1: aRR = 0.65 (0.49–0.85)	• No significant effect in older or younger age groups • Similar results with 2-dose interval <6 or 6 months	• No significant differences for 3 vs 1, 3 vs 2, or 2 vs 1 doses (only p-values reported)
Willows 2018	9–26	10–33	0	Yes/No/No	Results for those vaccinated at age 9–18 years 3: aHR = 0.4 (0.3–0.7) 2: aHR = 1.4 (0.6–3.3) 1: aHR = 0.6 (0.2–1.8)	• No significant effect in those vaccinated at older ages	No
Baandrup 2021	12–30	12–30	1	Yes/No/No	Results for first dose at age 12–14 years 3: aIRR = 0.16 (0.15–0.18) 2: aIRR = 0.22 (0.18–0.26) 1: aIRR = 0.29 (0.22–0.38)	• Results presented for 4 age at vaccination groups; in oldest age, 19 years, significant effect only with 3 doses • Significant but lower effectiveness for 3, 2 and 1 doses in 15–16 and 17–18 age groups than 12–14 years	Results for first dose at age 12–14 years 3 vs 1 dose: aIRR = 0.56 (0.43–0.73) 2 vs 1 dose: aIRR = 0.76 (0.56–1.03)

Cervical abnormalities [e]

Quadrivalent vaccine

| Gertig 2013 | 12–19 | 12–21 | 0 | No/No/No | Outcome summarized: CIN2+

3: aHR = 0.61 (0.48–0.78)
2: aHR = 1.02 (0.68–1.53)
1: aHR = 1.47 (0.97–2.23)

Outcome summarized: CIN3/AIS

3: aHR = 0.53 (0.36–0.77)
2: aHR = 0.87 (0.46–1.67)
1: aHR = 1.40 (0.75–2.61) | • Similar results for CIN2 as an outcome | No |

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
					Effect (95% CI)	**Comments**	
Crowe 2014	12–26	11–31	0	Yes/Yes/No	Outcome summarized: high grade histological lesions 3: aOR = 0.54 (0.43–0.67) 2: aOR = 0.79 (0.64–0.98) 1: aOR = 0.95 (0.77–1.16)	• Buffer periods from 1 to 12 months - no consistent impact on estimates • Similar results among those vaccinated at ages 15–18 and 19–22 years	No
Brotherton 2015	12–26	12–30	0	Yes/Yes/Yes	Results for those vaccinated prior to screening Outcome summarized: CIN2+ 3: aHR = 0.71 (0.64–0.80) 2: aHR = 1.21 (1.02–1.44) 1: aHR = 1.19 (0.99–1.43) Outcome summarized: CIN3/AIS 3: aHR = 0.69 (0.58– 0.81) 2: aHR = 1.17 (0.92–1.48) 1: aHR = 1.41 (1.12–1.77)	• Similar results for those vaccinated after screening, stratified by age at vaccination • With longer buffer periods, some effectiveness for 2 and 1 doses • No difference by interval between 2 doses	No
Hofstetter 2016	11–20	11–27	1	Yes/No/Yes	Outcome summarized: any abnormal cytology 3: aHR = 0.58 (0.48–0.69) 2: aHR = 0.81 (0.66–0.99) 1: aHR = 1.05 (0.88–1.26)	• Similar results when stratified by age at vaccination, although 2 doses not always significant • Highest effectiveness, although only significant for 3 doses, for those vaccinated at ages 11–14 years	No
Kim 2016	10–15	18–21	0	No/No/No	Outcome summarized: high grade cytology 3: aOR = 0.48 (0.28–0.81) 2: aOR = 0.17 (0.02–1.20) 1: aOR = 0.45 (0.11–1.83)		No
Silverberg 2018	14–26	18–34	6	Yes/No/No	Outcome summarized: CIN2+/AIS 3: aRR = 0.78 (0.66–0.91) 2: aRR = 1.02 (0.82–1.28) 1: aRR = 0.89 (0.73–1.09)	• Highest 3 dose effectiveness among those vaccinated at youngest ages	No

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
					Effect (95% CI)	Comments	
					Outcome summarized: CIN3+/AIS 3: aRR = 0.64 (0.48–0.84) 2: aRR = 0.97 (0.67–1.41) 1: aRR = 0.90 (0.65–1.24)		2 vs 3 doses aIRR = 1.60 (1.05–2.24)
Dehlendorff 2018	13–29	13–30	0	Yes/No/Yes	Outcome summarized: CIN2+/AIS (age 16 years) 3: aIRR = 0.23 (0.11–0.49) 2: aIRR = 0.44 (0.10–2.03) 1: aIRR = 0.23 (0.01–5.24)	• Similar results for age at vaccination 17–19 years	• No significant difference between 2 and 3 doses when interval between dose 1 and 2 >5 months and age at vaccination <20 years
Brotherton 2019	13–22	15–22	0	Yes/No/Yes	Outcome summarized: CIN2+ 3: aHR = 0.59 (0.54–0.65) 2: aHR = 0.61 (0.52–0.72) 1: aHR = 0.65 (0.52–0.81) Outcome summarized: CIN3+/AIS 3: aHR = 0.43 (0.35–0.53) 2: aHR = 0.42 (0.27–0.64) 1: aHR = 0.66 (0.41–1.06)	• Similar results for time-varying dose status, CIN3+, buffers of 0 and 12 months, and alternate status based on timing between 1 and 2 doses	Outcome summarized: CIN2+ 3 vs 1 doses aHR = 0.91 (0.74–1.13) 3 vs 2 doses aHR = 0.97 (0.83–1.14) 2 vs 1 doses aHR = 0.94 (0.73–1.21) Outcome summarized: CIN3+/AIS 3 vs 1 doses aHR = 0.66 (0.41–1.05) 3 vs 2 doses aHR = 1.04 (0.68–1.57) 2 vs 1 doses aHR = 0.64 (0.35–1.16)
Verdoodt 2020	12–16	17–25	0 (6 months for comparison between doses)	Yes/No/No	Outcome summarized: CIN2+/AIS 3: aIRR = 0.43 (0.36–0.51) 2: aIRR = 0.49 (0.32–0.76) 1: aIRR = 0.34 (0.13–0.87)	• Similar results by age at vaccination, but only significant for <23 year-olds	Outcome summarized: CIN2+/AIS 3 vs 1 dose aIRR = 0.99 (0.64–1.53) 2 vs 1 doses aIRR = 1.00 (0.61–1.64)

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated — Effect (95% CI)	Comments	Formal comparison between doses
					Outcome summarized: CIN3+/AIS 3: aIRR = 0.37 (0.30–0.45) 2: aIRR = 0.38 (0.22–0.66) 1: aIRR = 0.38 (0.14–0.98)		Outcome summarized: CIN3+/AIS 3 vs 1 dose aIRR = 0.95 (0.60–1.51) 2 vs 1 doses aIRR = 0.89 (0.53–1.52)
Johnson Gargano 2020	12–26	18–39	24	Yes/Yes/No	Outcome summarized: CIN2+/AIS 3: aOR = 0.26 (0.20–0.35) 2: aOR = 0.45 (0.30–0.69) 1: aOR = 0.53 (0.37–0.76)	• aORs were slightly higher using 1 and 12 month buffer periods and lower using a 36 month buffer period, but all showed significant effectiveness • Effectiveness was higher in earlier birth cohort and lower in later birth cohort	3 vs 1 dose aOR = 0.61 (0.38–0.99) 3 vs 2 dose: aOR = 0.64 (0.39–1.05) 2 vs 1 dose aOR = 0.96 (0.55–1.68)
Rodriguez 2020	9–26	9–31	12	Yes/No/Yes	Outcome summarized: CIN2/3 Age at first dose 15–19 years 3: aHR = 0.66 (0.55–0.80) 2: aHR = 0.72 (0.54–0.95) 1: aHR = 0.64 (0.47–0.88)	• Study underpowered for <15 year-olds • No vaccine effectiveness against high-grade cytology or against CIN2/3 for those who received first dose at age >20 years	No
Innes 2020	14–21	20–24	0	Yes/No/No	Outcome summarized: high-grade histology (1 dose <18 years) 3: IRR = 0.66 (0.60–0.72) 2: IRR = 0.81 (0.63–1.03) 1: IRR = 1.10 (0.85–1.45)	• No significant effectiveness against high-grade histology for 1 dose among women vaccinated at 18 years	No
Bivalent vaccine							
Pollock 2014	15–>18	20–21	0	No/No/No	Outcome summarized: CIN3 3: aOR = 0.45 (0.35–0.58) 2: aOR = 0.77 (0.49–1.21) 1: aOR = 1.42 (0.89–2.28)		No

Endpoint/ vaccine/ authors	Study population age (years) at vaccination and outcome		Buffer[a] (months)	Sensitivity analyses by age group/ buffer/ dose interval[b]	Comparison with unvaccinated		Formal comparison between doses
					Effect (95% CI)	Comments	
Cameron 2017	14–>18	20–21	0	No/No/No	Outcome summarized: CIN3 Significant effect only with 3 doses	• Vaccinated in each deprivation category, compared with unvaccinated in most deprived	No
Palmer 2019	12–>18	20	0	Yes/No/No	Outcome summarized: CIN3+ 2: aOR = 0.77 (0.48–1.24) 1: aOR = 1.19 (0.70–2.05)	• Effect of 3-dose vaccination larger with younger age at vaccination ranging from 0.14 to 0.85	No
Acuti Martellucci 2021[f]	14–>30	17–32	1,6,12	Yes/Yes/No	Outcome summarized: Any abnormal cytology, youngest birth cohort (1990–1993), 1-month buffer duration 3: aOR = 0.44 (0.14–1.43) 2: aOR = 0.65 (0.20–2.16) 1: aOR = 0.43 (0.17–1.05)	• Sensitivity analyses also for vaccine type (both bivalent and quadrivalent used), high and low grade cytology, and buffer duration	No

Abbreviations: IRR, incidence rate ratio; aIRR, adjusted incidence rate ratio; RR, relative risk; aRR, adjusted RR; aOR, adjusted odds ratio; HR, hazard ratio; CI, confidence intervals; CIN3, cervical intraepithelial neoplasia grade 3; CIN2+, CIN grade 2 or worse; AIS, adenocarcinoma in situ; Significant, 95% CI does not include 1.

[a]Buffer period is the lag time between vaccination and counting of outcomes. This column shows buffer period in main analysis.

[b]Interval between doses for 2-dose vaccine recipients.

[c]Not explicitly stated in paper.

[d]Data presented for 2 doses are those with an interval 6 months between doses.

[e]Some articles presented several outcomes for cervical cytological or histological abnormalities. In this table, we summarize results for the outcome most proximal to cervical cancer.

[f]Either bivalent or quadrivalent vaccine.