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Human papillomavirus vaccine effectiveness by number of doses: 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; a two-dose series is now recommended in some age groups and there is interest in possible one-dose vaccination.
Methods: We conducted a systematic literature review of HPV vaccine effectiveness by number of doses, including assessment of biases and impact of varying buffer periods (time between vaccination and outcome counting).
Results: Of 3787 articles identified, 26 full articles were assessed and 14 included in our review. All studies were conducted within the context of recommended three-dose schedules of bivalent (3) or quadrivalent HPV vaccine (11). Two evaluated effectiveness for prevention of HPV prevalence, six anogenital warts, and six abnormal cervical cytology or histology. Many studies found differences between three-, two- and one-dose vaccine recipients, indicating possible differences in HPV exposure prior to vaccination or in risk behavior. Adjusted or stratified analyses were conducted to control for potential confounding. All studies found significant vaccine effectiveness with three doses, 11 with two doses at various intervals, and six with one dose. Most studies showed a relationship (not always statistically significant) between effectiveness and number of doses, with greater decreases in HPV-related outcomes with three, followed by two and one dose(s). Few studies conducted formal comparisons of three vs fewer doses. Three of four studies that examined buffer periods found higher effectiveness and a smaller difference by number of doses with longer periods.
Conclusion: Most post-licensure studies report highest effectiveness with three doses; some found no statistically significant difference between two and three doses. Additionally, almost half found some effectiveness with one dose. Several biases impact estimates, with most biasing two- and one-dose results away from showing effectiveness. Future effectiveness studies, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias, can help inform vaccination policy.

1. Background

All three 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). However, interest in a reduced dose schedule arose soon after the first vaccines were licensed [1]. The high immunogenicity and efficacy observed in clinical trials with three doses and a post hoc analysis of one clinical trial stimulated interest in fewer doses [2]. Immunogenicity studies have been conducted with these available HPV vaccines and show non-inferior antibody response after two doses, administered 6–12 months apart, in young adolescents compared with three doses in women in the age group for which efficacy was demonstrated in clinical trials [3–5]. In 2014, the World Health Organization changed its guidance for number of doses

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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and recommended a two-dose HPV vaccination schedule for girls starting the series at age 9 through 14 years [6]. In 2016, the Advisory Committee on Immunization Practices recommended a two-dose schedule in the United States for this age group [7]. Many countries in Europe, the Americas, and countries funded by Gavi, the Vaccine Alliance, either changed from a three-dose to a two-dose schedule in this age group, or introduced HPV vaccination with a two-dose schedule [8].

While immunogenicity trials have demonstrated non-inferiority of two HPV vaccine doses in young adolescents and were accepted by regulatory agencies, many effectiveness studies conducted in real world programs have largely shown lower effectiveness with fewer than three doses. We conducted a systematic review of the literature to: (1) summarize evidence about effectiveness of HPV vaccination by the number of doses, as measured in post-licensure studies, and (2) explore and discuss the main limitations and challenges of these studies.

2. Methods

2.1. Study selection

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

We searched Medline and Embase databases from January 1, 2007 to June 15, 2017 using a combination of Medical Subject Headings (MeSH) terms, title or abstract words, without restriction on the 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 independently by MD and NP on title and abstract first, and secondly on the full-text article.

2.2. Data extraction

Two authors (NP and LM) independently extracted the main study characteristics and outcomes using standardized forms. Any discrepancy between the two independent extractions was resolved by MD. The main study characteristics included the country, study design, age of study population at vaccination and 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). Information on use of buffer periods (lag time between vaccination and counting of outcomes) was also collected. Buffer periods delay the case counting to attempt to exclude conditions caused by a prevalent infection at the time of vaccination.

Sources of bias in post-licensure studies examining the impact of HPV vaccination by number of doses include: (1) differences in the characteristics and age at vaccination between groups vaccinated with different number of doses; (2) likelihood of prevalent infection at vaccination; and (3) interval between the first and second dose of the HPV vaccine among two-dose vaccine recipients. Therefore, information on how authors dealt with these potential sources of bias was also extracted. Since one of the aims of this systematic review was to discuss the limitations of these studies, no studies were excluded on the basis of the methodological quality.

The main outcome was effectiveness of HPV vaccination comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different number of doses (three vs none, two vs none, one vs none, three vs two, three vs one, two vs one) of quadrivalent or bivalent vaccine. Results are presented as crude or adjusted risk ratios (RR) or odds ratios (OR). Of note, because eligible studies used different buffer periods or age groups at vaccination and at outcome assessment, it was not possible to pool results from the studies.

3. Results

The literature search identified 3787 articles, from which 26 full articles were assessed. After reading full texts, 12 articles were excluded, leaving 14 in our review (Fig. 1) [9–22]. These publications were from eight different countries, published from 2013 through 2017: Australia (three), Scotland (three), United States (two), Sweden (two), and one each from Belgium, Canada, Denmark, and Spain (Table 1). All evaluations were conducted within the context of a recommended three-dose schedule of either bivalent HPV vaccine (three) or quadrivalent HPV vaccine (eleven). Articles included analyses of effectiveness for prevention of HPV infection (two), anogenital warts (six), and cervical cytological or histological abnormalities (six) (Table 2 and Appendix).

Recognizing the potential for confounding, all investigators attempted to control for or stratified by potentially important variables, such as age at vaccination; however, limited other variables were available in most studies (Table 1). Four studies also evaluated the impact of different buffer periods and four evaluated different intervals between doses for two-dose vaccine recipients.

3.1. HPV prevalence

The two studies that reported vaccine effectiveness for reduction of prevalent vaccine type infection (HPV 16 or 18) were both from Scotland, conducted in the context of a three-dose bivalent HPV vaccination program that had achieved high coverage in the routine and catchup target age groups. The studies used residual cervical screening samples obtained at first screen of 20–21 year-olds and national vaccine registry data. Most two-dose vaccine recipients received doses at a one-month interval. Kavanagh et al. found statistically significant effectiveness for three doses, aOR = 0.43 (95% CI 0.34, 0.55); but not two doses, aOR = 0.68 (95% CI 0.42, 1.12); or one dose, aOR = 0.95 (95% CI 0.51, 1.76) [9]. There were few one- or two-dose vaccine recipients. In the second study, Cuschieri et al. over-selected women partially vaccinated [10]. Compared with three-dose vaccine recipients, partially vaccinated women were older than those fully vaccinated and differed by socioeconomic status. Statistically significant effectiveness was found for three doses, aOR = 0.27 (95% CI 0.20, 0.37); two doses, aOR = 0.45 (95% CI 0.29, 0.69); and one dose, aOR = 0.52 (95% CI 0.31, 0.83). Neither study performed a formal comparison of effectiveness of three doses vs fewer doses; confidence intervals for the effectiveness estimates of three, two and one dose(s) overlapped.

3.2. Anogenital warts

The six evaluations of anogenital wart outcomes were retrospective cohort studies from five different countries that had introduced quadrivalent HPV vaccination [11–16]. Only one study presented characteristics of women by number of doses [12]

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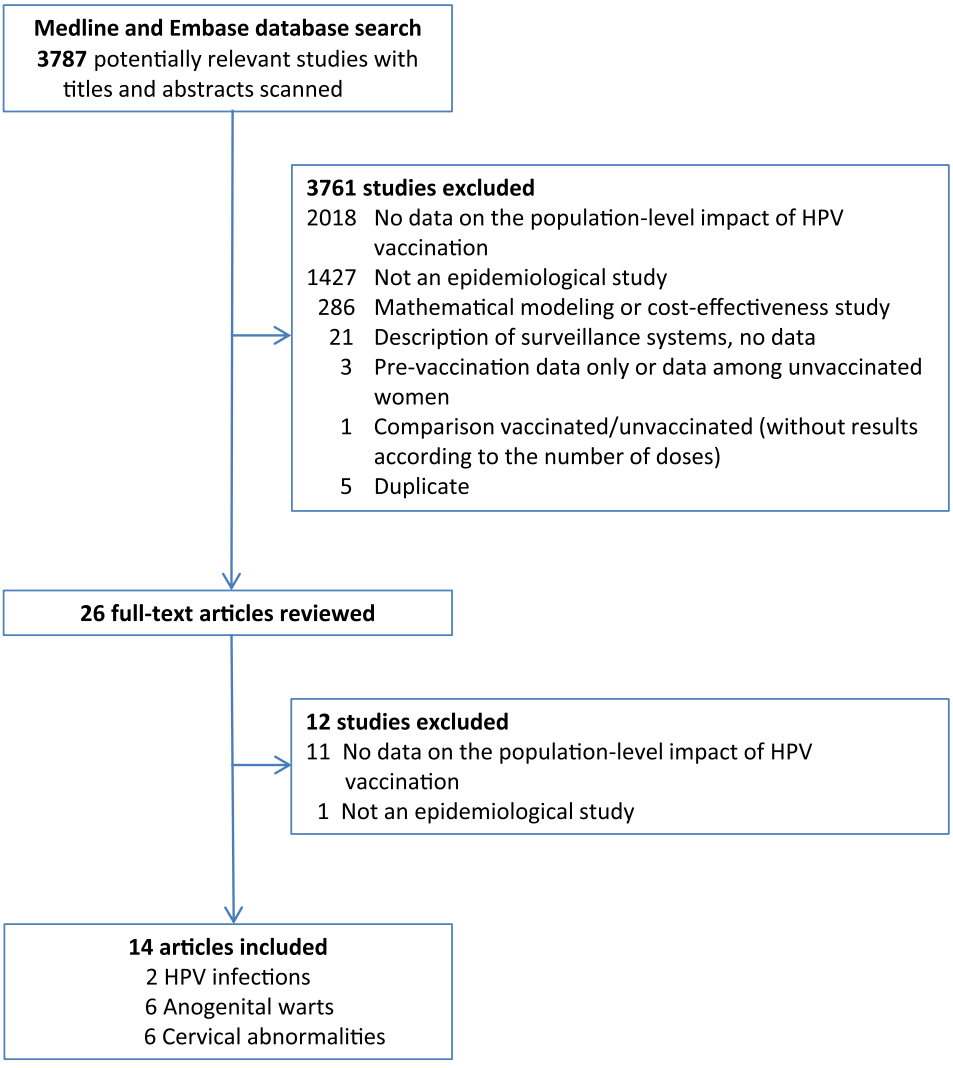

Fig. 1. Flow diagram of study selection process.

although all studies adjusted analyses for age at vaccination and some were able to adjust for educational level or markers of socioeconomic status (Table 1). Most two-dose vaccine recipients received doses separated by two months. Two studies also included assessment of different buffer periods [11,14] and three included assessment of different intervals between doses in two-dose vaccine recipients [12,14,16].

Herweijer et al. evaluated vaccine effectiveness in Sweden using data from national registries. The population evaluated included girls and women vaccinated during a time of opportunistic vaccination before HPV vaccination was incorporated into the routine school-based program [11]. In the primary analyses, a three-month buffer period was used before anogenital wart counting. The effect of different buffer periods was examined and analyses were stratified by age at vaccination (10–16 years and 17–19 years) and adjusted for attained age and parental education. There was statistically significant effectiveness for three doses, aRR = 0.20 (95% CI 0.17, 0.23); two doses, aRR = 0.32 (95% CI 0.26, 0.40); and one dose, aRR = 0.54 (95% CI 0.43, 0.68). Vaccine effectiveness was significantly higher for three compared with two or one dose(s). However, there was no statistically significant difference between two and three doses with a buffer period > four months, regardless of the age at vaccine initiation.

In a study conducted in Denmark using data from national registries, Blomberg et al. evaluated vaccine effectiveness among girls and women vaccinated as part of a routine and catchup program. Statistically significant effectiveness was found for one compared with no dose, RR = 0.51 (95% CI 0.46, 0.56). Data were not reported for effectiveness of three and two doses compared with no dose, but the investigators found that anogenital warts occurred significantly less frequently with each additional dose: two vs one, RR = 0.44 (95% CI 0.37, 0.51); three vs two, RR = 0.46 (95% CI 0.39, 0.54) [12]. After adjustment for age at vaccination, maternal educational level and income, and calendar time, effectiveness for three doses remained significantly higher than for two doses. However, there was no statistically significant difference between three and two doses with an interval > four months between doses; the RR was close to one with an interval of six months. This change in effectiveness for three compared with two doses, with increasing interval between doses, was observed for women who initiated vaccination at age <16 years and ≥16 years.

Somewhat similar findings related to the effect of interval between two doses were reported by Lamb et al. who examined effectiveness of three compared with two doses using data from Swedish national registries [16]. Higher effectiveness was observed for three compared with two doses, when two doses were admin-

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Table 1
Characteristics of studies that evaluated HPV vaccine effectiveness by number of doses.

Endpoint/vaccine/ reference	Country	Study design	Study population Age (years) at		Vaccination	Case definition	Statistical analyses		
			Vaccination	Outcome	N by dose number		Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification
HPV prevalence									
Bivalent vaccine									
Kavanagh et al. (2014) [9]	Scotland	Cross-sectional study using screening registry data	15–17	20–21	0: 3418 1: 55 2: 106 3: 1100	HPV 16 or 18 DNA positivity in liquid based cytology samples[b]	Final status	0	Birth year cohort, deprivation score
Cuschieri et al. (2016) [10]	Scotland	Cross-sectional study using screening registry data with additional sampling of women with < 3 doses	15–17	20–21	0: 3619 1: 177 2: 300 3: 1853	HPV 16 or 18 DNA positivity in liquid based cytology samples[c]	Final status	0	Birth year cohort, deprivation score, age at first dose
Anogenital warts									
Quadrivalent vaccine									
Herweijer et al. (2014) [11]	Sweden	Retrospective cohort study using population-based health registries	10–19	10–24	0: 926,119 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
Blomberg et al. (2015) [12]	Denmark	Retrospective cohort study using population-based health national registries	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	Age at vaccination, maternal education disposable income, calendar year
Dominiak-Felden et al. (2015) [13]	Belgium	Retrospective cohort study using sick-fund/ insurance data	10–23	16–23	0: 63,180 1: 4020 2: 3587 3: 35,792	First prescription of imiquimod and reimbursement	Time-dependent	1	Age at first dose
Perkins et al. (2017) [14]	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 codes[d]	Final status	0, 12	Age, regions, SES indicators, calendar year, differential observation periods
Navarro-Illana et al. (2017) [15]	Spain	Retrospective cohort study using national registries	14	14–19	0: NA[e] 1: NA 2: NA 3: NA	First diagnosis of ICD-9-CM code 078.11	Time-dependent	0	Age, calendar year, health department
Lamb et al. (2017) [16]	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	Age at outcome, time between doses
Cervical abnormalities									
Quadrivalent vaccine									
Gertig et al. (2013) [17]	Australia	Retrospective cohort study using linked data from registries	12–19	12–21	0: 14,085 1: 1422 2: 2268 3: 21,151	Histology: CIN3/AIS, CIN2, CIN1, any high grade Cytology: low grade and high grade	Time-dependent Final status	0	Age at first screen, remoteness area, SES
Crowe et al. (2014) [18]	Australia	Case control study using linked data from registries	12–26	11–31	0: 53,761 1: 9649 2: 10,950 3: 23,106	Histology: CIN2+/AIS	Final status	0, 1, 6, 12	Year of birth, remoteness area, SES, follow-up time

Table 1 (*continued*)

Endpoint/vaccine/ reference	Country	Study design	Study population Age (years) at		Vaccination	Case definition	Statistical analyses		
			Vaccination	Outcome	N by dose number		Assignment of dose number	Buffer periods[a] (months)	Adjustment or stratification
Brotherton et al. (2015) [19]	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, remoteness, SES, screening start (before or after vaccination)
Hofstetter et al. (2016) [20]	United States	Retrospective cohort study using medical center records	11–20	11–27	0: 1632 1: 695 2: 604 3: 1196	Cytology: low grade and high grade[f]	Final status	1	Age, insurance, language, clinic type, CT screening, and baseline cytology
Kim et al. (2016) [21]	Canada	Nested case-control study using linked data from registries	10–15	18–21	0: 5712 1: 327 2: 490 3: 3675	Cytology: low grade and high grade[g]	Final status	0	Age, urban/rural, neighborhood income
Bivalent vaccine									
Pollock et al. (2014) [22]	Scotland	Retrospective cohort study using linked national registry data	15–17	20–21	0: 75,113 1: 1315 2: 2725 3: 25,898	Histology: CIN1, CIN2, CIN3	Final status	0	Age, birth year cohort year, deprivation score

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

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

[b] By multimetrix HPV assay detecting 24 types including all established high risk types.

[c] By Optiplex HPV assay detecting 24 types including all established high risk types.

[d] 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.

[e] Presented as person-years in this article.

[f] 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.

[g] High-grade cytology defined as possible high-grade squamous intraepithelial lesion (HSIL), HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma. Low-grade cytology defined as possible low-grade squamous intraepithelial lesions (LSIL), LSIL and atypical endocervical cells of uncertain significance.

Table 2
Studies that evaluated HPV vaccine effectiveness by number of doses: analyses and main findings.

Endpoint/vaccine/ reference	Study population Age (years) at		Buffer[a] (months)	Sensitivity analyses by age group/buffer/dose interval[b]	Formal comparison of 3 vs 2 or 1 doses	Main findings
	Vaccination	Outcome				
HPV prevalence						
Bivalent vaccine						
Kavanagh et al. (2014) [9]	15–17	20–21	0	Yes/No/No	No	• Statistically significant effectiveness for 3, but not 2 or 1 doses compared to 0 3: aOR = .43 (CI .34, .55); 2: aOR = .68 (CI .42, 1.12); 1: aOR = .95 (CI .51, 1.76) • Effectiveness CI overlap for 3, 2 and 1 doses • Similar results when stratified by age at vaccination
Cuschieri et al. (2016) [10]	15–17	20–21	0	No/No/No	No	• Statistically significant effectiveness for 3, 2 and 1 doses compared to 0 3: aOR = .27 (CI .20, .37); 2: aOR = .45 (CI .29, .69), 1: aOR = .52 (CI .31, .83) • Effectiveness CI overlap for 3, 2 and 1 doses
Anogenital warts						
Quadrivalent vaccine						
Herweijer et al. (2014) [11]	10–19	10–24	3	Yes/Yes/No	Yes	• Statistically significant effectiveness for 3, 2 and 1 doses compared to 0 3: aRR = .20 (CI .17, .23), 2: aRR = .32 (CI .26, .40), 1: aRR = .54 (CI .43, .68) • Significantly higher effectiveness of 3 compared to 2 and 1 doses • With buffer periods > 4 months, no significant difference between 3 and 2 doses • Similar results for age groups 10–16 and 17–19, except effectiveness for 1 dose without buffer period statistically significant for 10–16 year-olds
Blomberg et al. (2015) [12]	12–27	12–27	1	Yes/No/Yes	Yes	• Statistically significant effectiveness for 1 compared to 0 dose, RR = .51 (CI .46, .56) • Effectiveness not reported for 3 and 2 doses compared to 0 • Effectiveness significantly increased with each dose: RR 2 vs 1 dose = .44 (CI .37, .51); RR 3 vs 2 doses = .46 (CI .39, .54) • With dose interval > 4 months, no significant difference between 3 and 2 doses • Similar results when stratified by age at vaccination
Dominiak-Felden et al. (2015) [13]	10–23	16–23	1	No/No/No	No	• Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 3: aRR = .12 (CI .07, .21); 2: aRR = .34 (CI .14, .83); 1: aRR = .63 (CI .35, 1.16) • Effectiveness CI overlap for 3 and 2 doses; no overlap for 3 and 1 doses
Perkins et al. (2017) [14]	9–25	9–25	0	No/Yes/Yes	Yes	• Statistically significant effectiveness for 3 doses compared to 0, aRR = .52 (CI .46, .60) • Effectiveness not reported for 2 and 1 doses compared to 0 • Higher effectiveness for 3 compared with 1 doses, aRR = .82 (CI .71, .95); but no significant difference between 3 and 2 doses, aRR = .89 (CI .78, 1.03) • With buffer period of 1 year, no change in findings (data not shown) • Similar results with dose interval > 5 months for 2 doses
Navarro-Illana et al. (2017) [15]	14	14–19	0	No/No/No	No	• Statistically significant effectiveness for 3, 2, and 1 doses compared to 0 3: aRR = .24 (CI .15, .34); 2: aRR = .36 (CI .14, .68); 1: aRR = .39 (CI .13, .80) • Effectiveness CI overlap for 3, 2 and 1 doses
Lamb et al. (2017) [16]	10–19	10–27	0	Yes/No/Yes	Yes	• Effectiveness not reported for 3, 2 and 1 doses compared to 0 • Higher effectiveness of 3 doses compared to 2 doses, when 2 doses administered either 0–3 months or $\geq$ 8 months apart; whereas no significant difference between 3 and 2 doses when the 2 doses administered within 4–7 months • Similar results when stratified by age at vaccination
Cervical abnormalities[c]						
Quadrivalent vaccine						
Gertig et al. (2013) [17]	12–19	12–21	0	No/No/No	No	Outcome summarized: CIN3/AIS • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 3: aRR = .53 (CI .36, .77); 2: aRR = .87 (CI .46, 1.67); 1: aRR = 1.40 (CI .75, 2.61) • Effectiveness CI overlap for 3, 2 and 1 doses

Table 2 (*continued*)

Endpoint/vaccine/ reference	Study population Age (years) at		Buffer[a] (months)	Sensitivity analyses by age group/buffer/dose interval[b]	Formal comparison of 3 vs 2 or 1 doses	Main findings
	Vaccination	Outcome				
Crowe et al. (2014) [18]	12–26	11–31	0	Yes/Yes/No	No	Outcome summarized: High grade histological lesions • Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 3: aOR = .54 (CI .43, .67); 2: aOR = .79 (CI .64, .98); 1: aOR = .95 (CI .77, 1.16) • Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses • Buffer periods from 1 to 12 months - no consistent impact on 3, 2 and 1 dose effectiveness estimates • Similar results when stratified by age at vaccination
Brotherton et al. (2015) [19]	12–26	12–30	0	Yes/Yes/Yes	No	Outcome summarized: CIN3/AIS • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 3: aRR = .69 (CI .58, .81); 2: aRR = 1.17 (CI .92, 1.48); 1: aRR = 1.41 (CI 1.12, 1.77) • Effectiveness CI for 3, 2 and 1 doses do not overlap • With increasing buffer periods, some effectiveness for 2 and 1 doses in several age groups • No difference in effectiveness by interval between 2 doses • Similar results when stratified by age at vaccination
Hofstetter et al. (2016) [20]	11–20	11–27	1	Yes/No/No	No	Outcome summarized: Any abnormal cytology • Statistically significant effectiveness for 3 and 2, but not 1 dose compared to 0 3: aRR = .58 (CI .48, .69); 2: aRR = .81 (CI .66, .99); 1: aRR = 1.05 (CI .88, 1.26) • Effectiveness CI overlap for 3, 2 and 1 doses • Similar results when stratified by age at vaccination, although effectiveness of 2 doses compared to 0 not always significant
Kim et al. (2016) [21]	10–15	18–21	0	No/No/No	No	Outcome summarized: High grade cytology • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 3: aOR = .48 (CI .28, .81); 2: aOR = .17 (CI .02, 1.20); 1: aOR = .45 (CI .11, 1.83) • Effectiveness CI overlap for 3, 2 and 1 doses
Bivalent vaccine						
Pollock et al. (2014) [22]	15–17	20–21	0	No/No/No	No	Outcome summarized: CIN3 • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 3: aRR = .45 (CI .35, .58); 2: aRR = .77 (CI .49, 1.21); 1: aRR = 1.42 (CI .89, 2.28) • Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses

Abbreviations: RR, relative risk; aRR, adjusted RR; aOR, adjusted odds ratio; CI, 95% confidence intervals; CIN3, cervical intraepithelial neoplasia grade 3; AIS, adenocarcinoma in situ

[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] Several outcomes were presented in some articles for cervical cytological or histological abnormalities. We summarized results for the outcome most proximal to cervical cancer.

istered 0–3 months apart, but not when the interval was 4–7 months. Effectiveness of three, two or one doses compared with no dose was not reported.

A study using a commercially available claims database in the United States determined vaccine effectiveness among girls continuously enrolled since January 2007 [14]. For three doses compared with no dose, the aRR was 0.52 (95% CI 0.46, 0.60). Data were not reported for one or two doses compared with no dose. While higher effectiveness was found for three doses compared with one dose, aRR = 0.82 (95% CI 0.71, 0.95), the difference between three and two doses, aRR = 0.89 (95% CI 0.78, 1.03), did not reach statistical significance. In the main analysis, exposure time was counted starting after the last dose; reported findings did not change when a one year buffer period was used. The study also examined interval between doses. Among two-dose vaccine recipients, there was no difference in incidence among those who received doses at an interval of <5 months or ≥5 months.

In a study from Belgium, using an insurance database, statistically significant effectiveness was found for three doses, aRR = 0.12 (95% CI 0.07, 0.21); and two doses, aRR = 0.34 (95% CI 0.14, 0.83); but not for one dose, aRR = 0.63 (95% CI 0.35, 1.16) [13]. There was no formal statistical comparison of three vs fewer doses; confidence intervals of three and two dose effectiveness overlapped.

In Spain, quadrivalent HPV vaccine was used for only two years, and in a narrowly focused target age group, before switching to bivalent HPV vaccine. In an effectiveness study, quadrivalent vaccine recipients had initiated vaccination at age 14 years [15]. Compared with no dose, statistically significant effectiveness was reported for three, aRR = 0.24 (95% CI 0.15, 0.34); two, aRR = 0.36 (95% CI 0.14, 0.68); and one dose, aRR = 0.39 (95% CI 0.13, 0.80). There was no formal statistical comparison of three vs fewer doses. The confidence intervals for three, two, and one dose effectiveness estimates overlapped. There were few anogenital wart diagnoses in one- and two-dose vaccine recipients, precluding evaluation of different buffer periods or varying time between two doses. However, while case counting started after the last dose, time between the last dose and first genital wart diagnosis was at least one year in all but one case.

In summary, among six studies evaluating quadrivalent HPV vaccine effectiveness for prevention of anogenital warts, four included a comparison of three, two and one doses with no dose; all found highest effectiveness with three doses, and lower but significant effectiveness with two doses. Three of the four studies found significant effectiveness with one dose [11,12,15]. Four studies also formally compared three and two doses, finding either no significant difference in the primary analysis or in analyses with different buffer periods or two-dose intervals [11,12,14,16]. Two studies examined different buffer periods; a longer buffer period decreased differences in effectiveness between three and two doses in one study [11]. In the three studies that explored intervals between doses in two-dose vaccine recipients [12,14,16] one found no difference between three doses and two doses with an interval longer than four months [12]. Another study found that effectiveness of two doses administered at a four to seven month interval was similar to the standard three-dose schedule [16].

Of note, two studies were able to examine impact of bivalent HPV vaccine, because both bivalent and quadrivalent HPV vaccines had been used in the countries (Spain and Belgium) [13,15]. No reduction in anogenital warts was observed after bivalent vaccination in either study.

3.3. Cervical cytological histological abnormalities

Six studies evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities, including five for quadrivalent vaccine and one for bivalent vaccine. Outcomes assessed were based on histology only (two), cytology only (two), and both cytology and histology (two). Histological abnormalities evaluated included cervical intraepithelial neoplasia (CIN) grade 1, 2 and 3 or CIN2+ (CIN grade 2 or worse or adenocarcinoma in situ [AIS]) and CIN3/AIS. All studies described characteristics of women by number of doses, with most reporting some differences, particularly for age at first vaccine dose; all adjusted analyses for age at vaccination as well as limited other characteristics (Table 1).

Three of the four studies evaluating abnormal histology were conducted in Australia, a country that had achieved high vaccination coverage in routine and catchup age groups [17–19]. Two studies included women vaccinated at a wide age range and stratified results by age at first vaccination [18,19]. In a retrospective cohort study, statistically significant effectiveness against CIN3/AIS was observed for three doses, aRR = 0.53 (95% CI 0.36, 0.77), but not for two doses, aRR = 0.87 (95% CI 0.46, 1.67), or one dose, aRR = 1.40 (95% CI 0.75, 2.61) [17]. There was no formal statistical comparison of three vs fewer doses. Results were similar for any high grade lesion. The second study was a nested case-control study [18]. Statistically significant effectiveness was reported for prevention of high grade histological lesions for three doses, aOR = 0.54 (95% CI 0.43, 0.67), and for two doses, aOR = 0.79 (95% CI 0.64, 0.98), but not for one dose, aOR = 0.95 (95% CI 0.77, 1.16). There was no formal statistical comparison of three vs fewer doses. The results were generally similar when stratified by age at vaccination. A buffer period of 1 to 12 months had little impact on three-dose vaccine effectiveness estimates but increased estimates in some age strata for one and two doses (Appendix).

In the third study from Australia, Brotherton et al. assessed effectiveness against cervical histological and cytological abnormalities, included varying buffer periods and also stratified by vaccination before or after the first cervical cancer screen [19]. Among women vaccinated before their first screen, there was statistically significant effectiveness against CIN3/AIS for three doses compared with no dose, aRR = 0.69 (95% CI 0.58, 0.81), but not for two doses, aRR = 1.17 (95% CI 0.92, 1.48), or one dose, aRR = 1.41 (1.12, 1.77). With increasing length of buffer period, some effectiveness for two and one doses in several age groups was observed (Appendix). There was no difference in effectiveness of two doses with an interval of >6 months vs <6 months, regardless of the buffer period.

The one study that evaluated histological abnormalities after bivalent vaccine was conducted in Scotland [22]. Three-dose bivalent vaccine recipients had a lower risk of CIN3 compared with those unvaccinated, aRR = 0.45 (95% CI 0.35, 0.58). There was no significant effectiveness after two doses, aRR = 0.77 (95% CI 0.49, 1.21) or 1 dose, aRR = 1.42 (95% CI 0.89, 2.28). There was no formal statistical comparison of three vs fewer doses.

Two studies exclusively evaluated cervical cytological outcomes. Hofstetter et al. evaluated reduction in any cervical cytological abnormality among women at U.S. community health clinics using data from medical systems registries [20]. For those vaccinated at age 11–20 years, statistically significant effectiveness was observed for three doses, aRR = 0.58 (95% CI 0.48, 0.69), and two doses, aRR = 0.81 (95% CI 0.66, 0.99), but not one dose, aRR = 1.05 (95% CI 0.88, 1.26). There was no formal statistical comparison of three vs fewer doses. Point estimates of effectiveness varied by age at vaccination but the findings by number of doses were generally similar. In a study from Canada, Kim et al. presented any, low grade, and high grade abnormal cytology results separately [21]. While point estimates varied by outcome, the results were similar in that statistically significant effectiveness was found only with three doses. For high grade cytological abnormalities results were: three doses, aOR = 0.48 (95% CI 0.28, 0.81); two doses, aOR = 0.17 (95% CI 0.02, 1.20); and one dose, aOR = 0.45 (95% CI

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0.11, 1.83). In contrast, the two studies from Australia that evaluated cytological results found three, two and one dose effectiveness against low grade[17,19] or high grade abnormalies[19] and a dose response was not observed.

In summary, among six studies evaluating vaccine effectiveness for prevention of cervical cytological (four) or histological abnormalities (four), all found effectiveness for three doses. Women who received less than three doses were different than three-dose vaccine recipients in many studies, and investigators conducted stratified and/or adjusted analysis to control for these differences. Four studies found some effectiveness for prevention of high grade histological abnormalities with two doses, and two studies found effectiveness with one dose, in some age groups, in analyses with longer buffer periods [18,19]. Most two-dose vaccine recipients received two doses at a one- or two-month interval. A longer interval between two doses had no impact on the effectiveness estimate in the one study that examined this [19].

4. Discussion

In this systematic review of HPV vaccine effectiveness by number of doses, most of the 14 studies found the highest point estimate of effectiveness with three doses, followed by two doses, and one dose. However, few studies directly compared three, two and one dose(s) and some effectiveness estimates had wide confidence intervals due to the small number of outcomes in one- and two-dose vaccine recipients. All found statistically significant effectiveness for three doses and 11 studies found effectiveness for two doses [10–20]. In six studies significant effectiveness was observed for one dose in some analyses [10–12,15,17,19].

Variation in effectiveness by number of doses was observed across all endpoints (prevalence, anogenital warts and cervical abnormalities). There were generally consistent findings regarding buffer periods in the studies that evaluated this, with three of four studies finding higher effectiveness estimates for one and two doses and a decrease in the differences by number of doses with longer buffer periods. Among studies presenting results stratified by age group, higher effectiveness estimates were generally found with younger age at vaccination, although the differences were not formally tested. There were differences in the impact of varying time interval between two doses. Two studies of anogenital warts found higher two-dose effectiveness with increasing interval through six or seven months [11,16]. The one study of cervical abnormalities that evaluated interval between two doses did not find a difference [19].

Findings in these studies are, in large part, different from what might be expected based on immunogenicity trials which showed non-inferiority of two compared with three doses, and other studies which suggest efficacy with a single dose. However, there are several important caveats that need to be considered when interpreting the findings. Firstly, the post-licensure studies were all conducted in settings of a national three-dose recommendation and girls who received one or two doses differed from those completing the recommended schedule. Most of the studies included girls who were vaccinated beyond the routine target age group, in the early years of the vaccination programs when catch-up programs had been implemented. In several studies, fewer than three-dose vaccine recipients were older than three-dose vaccine recipients at the time of vaccination, had lower socio-economic status, and/or had indicators of earlier sexual exposure (e.g., younger cervical screening, vaccination at a family planning clinic, screening for a sexually transmitted infection). Thus, girls who received fewer doses were at higher risk of HPV infection, which biases results towards a greater effectiveness of three doses compared to one or two doses. Although most studies adjusted analyses for some risk factors, it is likely that residual confounding remained.

Secondly, in retrospective studies it is impossible to identify individuals who were already infected with HPV at the time of vaccination. The proportion of individuals already infected increases with older age at vaccination. Since girls vaccinated with one or two doses in the studies were often older when vaccinated and had indicators of earlier sexual exposure, prevalent infections at the time of vaccination would bias towards lower vaccine effectiveness of one and two doses (compared with three doses). To overcome the problem of prevalent infections, some researchers introduced buffer periods in their analyses, which delay case counting to exclude conditions caused by a prevalent infection. In Herweijer et al. the effectiveness of one dose compared to no vaccination increased with increasing buffer period and the difference between the effectiveness of three and two doses decreased [11]. With a buffer period of one month, the effectiveness of one dose compared to no vaccination increased to 28%, and to >50% with buffer periods > four months. Brotherton et al. also evaluated different buffer periods in a study of effectiveness for cervical lesions, showing that effectiveness increased with longer buffer periods [19]. One study of genital warts reported no effect of buffer periods, although data were not shown [14].

Longer buffer periods might be more helpful for evaluation of vaccine effectiveness against cervical high grade histological abnormalities than anogenital warts, since the former take more time to develop after infection [23]. In addition, buffer periods could be of greater importance based on age at vaccination. Therefore, the impact of buffer periods could vary across studies. While ideally buffer periods should be explored for effectiveness studies, they reduce the number of person-years with one or two doses, which is generally small in post-licensure studies; this results in low statistical power (i.e., insufficient power to detect statistically significant differences in effectiveness between one, two and three doses).

Thirdly, since all post-licensure studies published to date were conducted in settings of a national three-dose recommendation, most individuals vaccinated with two doses had received doses at a 0–1 month or 0–2 month interval, as recommended with a three-dose schedule. However, immunogenicity studies have found non-inferior results with two doses compared to three doses when the two doses were separated by about six months [3–5]. The longer interval is thought to allow maturation of B cells and the second vaccination to act as a booster dose. Results of the immunogenicity studies led to the recommendation for a two-dose schedule (administered at 0, 6–12 months) for females aged 9 through 14 years old at the time of their first dose [6,7]. Although the number of girls vaccinated with two doses separated by at least six months was small in the post-licensure studies identified, four studies evaluated interval between doses [12,14,16,19]. Blomberg et al. found that as the time between dose one and two increased from two to six months, the difference in effectiveness between two and three doses decreased; with an interval of >four months there was no difference [12]. However, two studies in this review did not find that varying intervals between two doses had that same effect [14,19]. It is possible that the finding of higher effectiveness with a longer interval between two doses in these observational studies is the result of the longer interval acting as a buffer period and is not related to the spacing between doses. If so, the inconsistent findings by interval between doses could be due to differing importance of buffer periods for the endpoints and age groups evaluated.

Finally, as in all vaccine effectiveness studies, the accuracy of vaccine history is important. Assessment of vaccination status can be more challenging for HPV than for other vaccine preventable diseases, as the outcomes generally occurs years after

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vaccination and because vaccine registries in some countries do not include adolescent vaccinations. Most studies included in this review were conducted in countries with national vaccine registries. However, underreporting of vaccinations to registries can still occur [18,19]. In studies using claims or insurance data, particularly in the United States, vaccination history could be incomplete if girls moved or changed insurers during the vaccination series. Incomplete vaccination histories could lead to overestimating effectiveness of fewer than three doses.

In conclusion, most post-licensure studies examining HPV vaccine effectiveness by number of doses report highest effectiveness with three doses, but some found no statistically significant difference between two and three doses. Additionally, almost half of the studies found some effectiveness for one dose. Several biases in currently available data impact estimates, with most biasing two- and one-dose results away from showing effectiveness. Future studies of real-world HPV vaccination effectiveness, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias, can help inform vaccine policy.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.01.057.

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