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Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study

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Summary

Background The population effectiveness of human papillomavirus (HPV) catch-up vaccination, defined in the USA as first vaccination at ages 13–26 years, has not been studied extensively. We aimed to assess the risk of cervical intraepithelial neoplasia (CIN) 2, CIN3, adenocarcinoma in situ, or cancer (CIN2+ and CIN3+) by prior HPV vaccination status, age at first dose, and number of doses in women participating in a screening programme within a large integrated health-care system.

Methods We performed a nested case-control study of women enrolled in Kaiser Permanente Northern California (an integrated health-care delivery system in California, USA). Cases were women with CIN2+ or CIN3+ confirmed by histology between Jan 1, 1995, and June 30, 2014, and incidence density-selected controls were age-matched women without CIN2+ or CIN3+ at the time each case occurred. For each case, we randomly selected five controls. Cases and controls were aged 26 years or younger when the HPV quadrivalent vaccine became available in 2006. Rate ratios (RRs) from conditional logistic regression were estimated by age at time of first HPV quadrivalent vaccine dose (14–17 years, 18–20 years, and ≥21 years), and number of doses (one, two, and three or more doses) compared with no prior vaccination, with adjustment for smoking, hormonal contraceptive prescription, race or ethnicity, sexually transmitted infections, immunosuppression, parity, and number of outpatient visits.

Findings 4357 incident CIN2+ cases and 21 773 matched controls were included in the study. Of these, 1849 were incident CIN3+ cases with 9242 matched controls. The youngest age at time of first vaccination was 14 years. One or more HPV vaccine doses conferred protection against CIN2+ (RR 0·82, 95% CI 0·73–0·93) and CIN3+ (0·77, 0·64–0·94). We found the strongest protection against CIN2+ in women who had received at least three vaccine doses and had received their first dose aged 14–17 years (0·52, 0·36–0·74) or aged 18–20 years (0·65, 0·49–0·88). No significant protection was found in women aged 21 years or older at time of first dose (0·94, 0·81–1·09). Inferences were similar for CIN3+, but with stronger effects for women who received at least three vaccine doses and had received their first dose aged 14–17 years (0·27, 0·13–0·56) or aged 18–20 years (0·59, 0·36–0·97).

Interpretation Catch-up quadrivalent HPV vaccination with three doses was effective against CIN2+ and CIN3+ in girls and women aged 14–20 years at time of first vaccine dose but not for women aged 21 years and older at first dose.

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Introduction

In the USA, human papillomavirus (HPV) vaccination is recommended for girls aged 11–12 years, with catch-up vaccination for girls and women aged 13–26 years. Although originally approved as a three-dose series, recommendations from the US Centers for Disease Control and Prevention in 2016 allow for a two-dose series for girls who initiate the vaccine series aged 9–14 years.[1] The potential protection against cervical neoplasia afforded by the available HPV vaccines is substantial, but the actual vaccine effect has yet to be fully observed because girls vaccinated in early adolescence have only recently reached the recommended age for cervical cancer screening. However, vaccine effectiveness can be evaluated in girls and women who initiated the vaccine series at older ages.

Evidence suggests vaccination has population effectiveness, which includes reduced prevalence of abnormal cervical cytology or HPV vaccine-type specific infections.[2–9] Data from a randomised clinical trial[10] of the quadrivalent HPV vaccine in India suggested that catch-up vaccination with fewer than three doses was both immunogenic and protective against HPV. Evidence in support of a vaccine effect on high-grade precancerous lesions, including cervical intraepithelial neoplasia (CIN) grades 2, 2/3, 3, adenocarcinoma in situ, or cancer (CIN2+ or CIN3+), is limited and consists mainly of study findings showing ecological decreases in CIN2+ incidence over time,[11–18] with most

Research in context

Evidence before this study

In the USA, human papillomavirus (HPV) vaccination is recommended for girls aged 11–12 years, with catch-up vaccination for girls and women aged 13–26 years who have not started the vaccine series. We searched PubMed, without language restrictions, for studies of cervical intraepithelial neoplasia (CIN) 2, CIN3, adenocarcinoma in situ, or cancer (CIN2+ and CIN3+) in HPV-vaccinated and unvaccinated women with a combination of the terms "papillomavirus vaccine", "papillomavirus vaccination", "HPV vaccine", "HPV vaccination", "effectiveness", "papillomavirus infection", "cervical intraepithelial neoplasia", "cervical dysplasia", "cervical neoplasm", "HPV related diseases", "histology", "biopsy", and "colposcopy". The search was limited to articles published before March 21, 2018. We found few epidemiological studies in which the effectiveness of HPV vaccination in reducing the risk of CIN2+ or CIN3+ had been assessed, especially in girls and women vaccinated at older ages.

Added value of this study

In a large sample of women with uniform access to comprehensive care and who were engaged in a robust cervical cancer screening programme, we found that catch-up HPV vaccination with three doses was effective against CIN2+ and CIN3+ in women aged 14–20 years at time of first dose. However, we found no significant effectiveness in women who initiated vaccination aged 21–26 years or in women who received fewer than the full three doses.

Implications of all the available evidence

These results support existing guidelines recommending the full three-dose HPV vaccination series for girls and women who start the series after their 15th birthday. Additional research is needed to confirm the limited effectiveness of catch-up vaccination for women aged 21–26 years.

data showing no change for older women.[11,13,14,16,17] In randomised clinical trials the quadrivalent HPV vaccine has been found to decrease the risk of CIN2+ in women who initiated vaccination aged 15–26 years,[19] but in another trial[20] with women initiating vaccination aged 24–45 years, the quadrivalent HPV vaccine had no effect on CIN2+ incidence. Vaccine effectiveness against CIN2+ was shown in studies in Australia and Scotland,[21–24] where vaccination coverage in school programmes reached 70–90%, although few studies[23,24] included women who initiated vaccination aged 17 years or older.

In this study, we aimed to estimate the effectiveness of catch-up quadrivalent HPV vaccination to prevent CIN2+ and CIN3+, by age at first dose and by number of doses.

Methods

Study design and data source

This nested case-control study included women enrolled in Kaiser Permanente Northern California (KPNC), a large integrated health-care system in California, USA, providing comprehensive care for more than 3·9 million members in the greater San Francisco Bay Area, which represent 28% of insured Californians in the same region.[25] The institutional review board at KPNC approved this study with a waiver of written informed consent.

The study population was a subset of participants in a previous nested case-control study[26] in which cases were women with a new diagnosis of CIN2+ or CIN3+ and incidence density-selected controls were women without CIN2+ or CIN3+ at the time each case occurred. The source population for the parent case-control study[26] included more than 2 million women who had cytology between Jan 1, 1995, and June 30, 2014. We focused on women targeted for screening by excluding girls younger than 18 years, women older than 70 years, and all women with prior hysterectomy. For each case, we randomly selected five controls who met these same eligibility criteria and matched them by age (within 1 year), time since first cytology in the health system (within 1 year), and years of continuous prior health plan membership (within 1 year). The 5:1 sampling scheme provided adequate power for rare exposures, as described previously.[26] The index date for cases was the diagnosis date, and controls were assigned the same index date as the case to which they were matched. Cases and controls were also required to have a cytology test within 12 months before their assigned index date. The study was limited to women eligible for the HPV vaccine since its introduction in 2006, and who were old enough to participate in the cervical cancer screening programme, corresponding to women aged 18–26 years between 2006 and 2014.

Although a cohort study design was a viable alternative approach, we used the nested case-control design to enhance computational efficiency because a cohort study would have involved a multivariable analysis of more than 2 million women and relies on covariate adjustment, instead of precise matching of risk factors between cases and controls.

Electronic medical records were used as the primary data source, including vaccination data. Histopathology results of cervical biopsies were ascertained by Systematized Nomenclature of Medicine topology and morphology codes. Text-based natural language processing of the corresponding pathology reports was used to more accurately assign the diagnosis (eg, CIN2, CIN3). KPNC has offered the quadrivalent HPV vaccine since 2006; the nonavalent HPV vaccine was introduced in August, 2015, after the end of the study period. Other clinical risk factors ascertained included recent (within

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18 months) history of smoking and high parity (defined as three or more livebirths). We also identified factors potentially associated with increased screening frequency, including number of recent outpatient visits (within the previous 18 months) and race or ethnicity. Finally, factors (within the previous 18 months) that were both clinical risk factors and associated with screening frequency included documented sexually transmitted infections (herpes, gonorrhoea, syphilis, and chlamydia), prescription of hormonal contraceptives, and immunosuppression (HIV infection, previous solid organ transplantation, and prescription of immunosuppressive medication), defined in detail previously.[26]

Statistical analysis

HPV vaccination history before the index date was obtained for all women. We only ascertained vaccine doses received at least 6 months before index because more proximal vaccine doses are not likely to have an effect on disease risk. The following comparisons by vaccination status were made: first, prior HPV vaccination (ie, at least one HPV vaccine doses) versus no prior HPV vaccination; second, age at first dose (14–17 years, 18–20 years, and ≥21 years) versus no prior HPV vaccination; third, number of doses received (one, two, and three or more doses) versus no prior HPV vaccination; and fourth, various combinations of age at first dose and number of doses received, including six categories for three age strata (ie, 14–17 years, 18–20 years, and ≥21 years) and two dose strata (ie, at least three doses and fewer than three doses), each compared with women with no prior HPV vaccination. Conditional logistic regression was used to estimate odds ratios, which represent unbiased estimates of rate ratios (RRs) in a nested case-control study with incidence density sampling.[27]

Adjusted models included covariates representing recent smoking (yes or no), recent hormonal contraceptive use (yes or no), race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other, unknown), recent sexually transmitted infections (yes or no), three or more livebirths (yes or no), prior outpatient visits (continuous), and immunosuppression status (yes or no). For the model including the combined variable of age at first dose and number of doses, a custom contrast tested the interaction of whether the effects of age at first dose (14–17 years, 18–20 years, and ≥21 years, each compared with no prior HPV vaccination) significantly differed by number of doses (fewer than three doses *vs* three or more doses).

We performed several sensitivity analyses: first, we limited to cases and controls with continuous health plan membership since 2006, to minimise misclassification of HPV vaccine history. In the second analysis, we excluded controls with abnormal cytology from recent cytology to minimise misclassification of outcome status (ie, misclassification might have occurred if controls with abnormal cytology had not yet been followed up with colposcopy to identify CIN2+). Finally, we replaced all versions of covariates categorised as recent with versions categorised as ever (ie, any time in the past as a proxy for lifetime exposure) to minimise potential for residual confounding.

We used the LOGISTIC procedure in SAS, version 9.3, for all statistical analyses.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

	CIN2+			CIN3+		
	Cases (N=4357)	Matched controls (N=21 773)	p value*	Cases (n=1849)	Matched controls (n=9242)	p value*
Age at index, years	26·3 (3·7)	26·3 (3·7)	Matching	26·4 (3·7)	26·4 (3·7)	Matching
Years with health plan membership before index	7·4 (5·2)	7·5 (5·3)	Matching	7·2 (5·1)	7·3 (5·2)	Matching
Index year						
2006–08	1189 (27%)	5945 (27%)	Matching	556 (30%)	2780 (30%)	Matching
2009–11	1420 (33%)	7099 (33%)	Matching	614 (33%)	3070 (33%)	Matching
2012–14	1748 (40%)	8729 (40%)	Matching	679 (37%)	3392 (37%)	Matching
Outpatient visits per year	7·5 (5·9)	6·9 (5·3)	<0·0001	7·5 (6·0)	7·0 (5·3)	<0·0001
Race or ethnicity						
Non-Hispanic white	2155 (49%)	9611 (44%)	<0·0001	987 (53%)	4070 (44%)	<0·0001
Non-Hispanic black	459 (11%)	2107 (10%)	<0·0001	163 (9%)	890 (10%)	<0·0001
Hispanic	946 (22%)	5035 (23%)	<0·0001	397 (21%)	2113 (23%)	<0·0001
Other	660 (15%)	4153 (19%)	<0·0001	259 (14%)	1780 (19%)	<0·0001
Unknown	137 (3%)	867 (4%)	<0·0001	43 (2%)	389 (4%)	<0·0001
Smoking						
Recent†	1044 (24%)	3725 (17%)	<0·0001	441 (24%)	1596 (17%)	<0·0001
Ever	1730 (40%)	7051 (32%)	<0·0001	724 (39%)	2968 (32%)	<0·0001
Hormonal contraceptive use						
Recent†	2880 (66%)	12 696 (58%)	<0·0001	1243 (67%)	5403 (58%)	<0·0001
Ever	3730 (86%)	17 969 (83%)	<0·0001	1584 (86%)	7606 (82%)	0·0001
Sexually transmitted infection‡						
Recent†	314 (7%)	953 (4%)	<0·0001	106 (6%)	392 (4%)	0·004
Ever	996 (23%)	3272 (15%)	<0·0001	383 (21%)	1366 (15%)	<0·0001
Three or more livebirths	212 (5%)	1207 (6%)	0·065	106 (6%)	507 (5%)	0·67
Immunosuppressed§	506 (12%)	2672 (12%)	0·219	215 (12%)	1142 (12%)	0·37

Data are mean (SD) or n (%). The full study population is represented by the CIN2+ cases and matched controls. The subset of CIN3+ cases and matched controls are also reported separately. CIN=cervical intraepithelial neoplasia. *p value based on bivariate conditional logistic regression models; not computed for matching variables. †Within 18 months prior to index. ‡Herpes, gonorrhoea, syphilis, chlamydia. §HIV-infected, solid organ transplant, or immunosuppressive therapy in preceding 18 months.

Table 1: **Baseline characteristics of CIN cases (CIN2+ and CIN3+) and matched controls, Kaiser Permanente, 2006–14**

	CIN2+ cases (N=4357)	Matched controls (N=21 773)	Unadjusted rate ratio (95% CI)*
HPV vaccine history			
Prior vaccination	429 (10%)	2408 (11%)	0·86 (0·76–0·96)
No prior vaccination	3928 (90%)	19 365 (89%)	1 (ref)
HPV vaccine history, age at first dose			
Prior vaccination, 14–17 years	77 (2%)	516 (2%)	0·62 (0·46–0·83)
Prior vaccination, 18–20 years	113 (3%)	686 (3%)	0·76 (0·61–0·94)
Prior vaccination, ≥21 years	239 (5%)	1206 (6%)	0·98 (0·84–1·13)
No prior vaccination	3928 (90%)	9365 (89%)	1 (ref)
HPV vaccine history			
Prior vaccination, three doses or more†	214 (5%)	1313 (6%)	0·78 (0·66–0·91)
Prior vaccination, two doses	97 (2%)	457 (2%)	1·02 (0·82–1·28)
Prior vaccination, one dose	118 (3%)	638 (3%)	0·89 (0·73–1·09)
No prior vaccination	3928 (90%)	19 365 (89%)	1 (ref)
HPV vaccine history, age at first dose, number of doses			
Prior vaccination, 14–17 years, three doses or more	42 (1%)	333 (2%)	0·52 (0·36–0·74)
Prior vaccination, 18–20 years, three doses or more	56 (1%)	379 (2%)	0·68 (0·50–0·91)
Prior vaccination, ≥21 years, three doses or more	116 (3%)	601 (3%)	0·95 (0·78–1·17)
Prior vaccination, 14–17 years, fewer than three doses	35 (1%)	183 (1%)	0·80 (0·54–1·19)
Prior vaccination, 18–20 years, fewer than three doses	57 (1%)	307 (1%)	0·86 (0·64–1·15)
Prior vaccination, ≥21 years, fewer than three doses	123 (3%)	605 (3%)	1·00 (0·82–1·22)
No prior vaccination	3928 (90%)	19 365 (89%)	1 (ref)

Data are n (%) unless indicated otherwise. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. *Based on bivariate conditional logistic regression models. †Only four cases and 16 controls had four or more vaccine doses.

Table 2: **HPV vaccine history and unadjusted rate ratios in CIN grade 2 or worse cases and matched controls, Kaiser Permanente, 1996–2014**

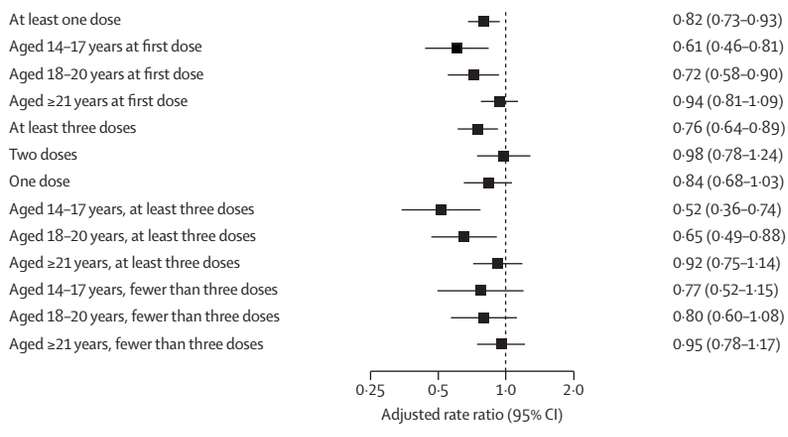

Figure 1: **Adjusted rate ratios and 95% CI for cervical intraepithelial neoplasia grade 2 or worse by HPV vaccination history**
HPV=human papillomavirus.

Results

The study population included 4357 CIN2+ cases and 21773 matched controls, including a subset of 1849 CIN3+ cases with 9242 matched controls. 4348 of 4357 CIN2+ cases had five matched women in the control group, eight women in the case group had four matched women in the control group, and one woman in the case group had one matched woman in the control group. 1599 women in the control group matched to more than one woman in the case group, and 211 women in the control group became cases at a later date. Cases and controls were similar with respect to matching parameters of age, index year, and mean number of years with health plan membership (table 1). Compared with controls, cases (both CIN2+ and CIN3+) were more likely to be non-Hispanic white, had a higher mean number of outpatient visits per year, and were more likely to have a history of smoking, recent hormonal contraceptive use, and recent sexually transmitted infections. Of 4357 CIN2+ cases, 874 (20%) were CIN2, 1634 (38%) were CIN2/3, 1744 (40%) were CIN3, 82 (2%) were adenocarcinoma in situ, and 23 (<1%) were cancer (nine adenocarcinoma, 13 squamous cell carcinoma, and one other cancer).

429 (10%) of 4357 CIN2+ cases and 2408 (11%) of 21773 controls had any prior HPV vaccination (table 2). Women aged 14–17 years and 18–20 years at time of first vaccination had protection against CIN2+ compared with women with no prior vaccination, whereas women aged 21 years or older at time of first vaccination were not protected (table 2). Receipt of at least three HPV vaccine was associated with CIN2+ protection, whereas receipt of one or two doses was not. For analyses that considered the combined association of age at first dose and number of doses, CIN2+ protection was only seen in women with at least three HPV vaccine doses and who were aged 14–17 years or 18–20 years at time of first dose (table 2).

After adjustment for covariates, women with at least one HPV vaccine dose were at an overall decreased risk for CIN2+ compared with women with no prior vaccination (figure 1). A significantly reduced CIN2+ risk was also found for women who received their first HPV vaccine dose at ages 14–17 years and 18–20 years, but not in women who received their first HPV vaccine dose aged 21 years or older. A significantly reduced CIN2+ risk was found for women who received at least three HPV vaccine doses but not in women who received one or two doses. In adjusted models that considered the combined association of age at first dose and number of doses, we only found protection against CIN2+ in women who received at least three HPV vaccine doses and were aged either 14–17 years or 18–20 years at time of first dose, compared with no prior vaccination (figure 1). No statistically significant protection against CIN2+ was found in women who received fewer than three vaccine doses, although point estimates were

protective for those aged 14–17 years and 18–20 years at time of first dose. Finally, although the associations of age at first dose with CIN2+ appeared stronger for women who received at least three HPV vaccine doses, the test for interaction between age at first dose and number of doses in vaccinated women was not statistically significant (p=0·41).

154 (8%) of 1849 CIN3+ cases and 893 (10%) of 9242 controls had prior HPV vaccination (table 3). Receipt of a first dose when aged 14–17 years conferred protection against CIN3+ compared with no prior vaccination, whereas women who received their first dose aged 18–20 years or 21 years or older had no protection. Receipt of at least three HPV vaccine doses was associated with CIN3+ protection, whereas receipt of one or two doses was not. For analyses that considered the combined association of age at first dose and number of doses, CIN3+ protection was only found for women who received at least three HPV vaccine doses and received their first dose aged 14–17 years. Of the 23 CIN3+ cases with cancers, only three had prior HPV vaccination; all three women had received at least three doses, and all were 21 years or older at time of first dose.

After adjustment for covariates, women with at least one HPV vaccine dose were at an overall decreased risk for CIN3+ compared with women with no prior vaccination (figure 2). Protection against CIN3+ was also found in women who received their first HPV vaccine dose aged 14–17 years but not in women who received their first dose aged 18–20 years or 21 years or older. Significant protection against CIN3+ was found in women with at least three HPV vaccine doses but not in women who received one or two doses. In adjusted models that considered the combined association of age at first dose and number of doses, we found protection against CIN3+ in women with at least three HPV vaccine doses and who received their first dose aged 14–17 years and, by contrast with unadjusted results, in women with at least three HPV vaccine doses and who received their first dose aged 18–20 years (figure 2). No statistically significant protection against CIN3+ was found within any of the age strata for women who received fewer than three vaccine doses, although point estimates were protective for those aged 14–17 years at time of first dose. Finally, although the associations of age at first dose with CIN3+ appeared stronger for women with at least three HPV vaccine doses, the test for interaction between age at first dose and number of doses in vaccinated women was not statistically significant (p=0·13).

Sensitivity analyses limiting to cases and controls with continuous health plan membership since 2006 did not change inferences for association with at least one HPV vaccine dose, although the association strengthened for CIN2+ (RR 0·69, 95% CI 0·59–0·81) and CIN3+ (0·70, 0·54–0·90). Other sensitivity analyses had negligible changes in inferences (data not shown).

	CIN3+ cases (N=1849)*	Matched controls (N=9242)*	Rate ratio (95% CI)†
HPV vaccine history			
Prior vaccination	154 (8%)	893 (10%)	0·82 (0·68–1·00)
No prior vaccination	1695 (92%)	8349 (90%)	1 (ref)
HPV vaccine history, age at first dose			
Prior vaccination, 14–17 years	22 (1%)	188 (2%)	0·45 (0·27–0·76)
Prior vaccination, 18–20 years	56 (3%)	312 (3%)	0·84 (0·59–1·21)
Prior vaccination, ≥21 years	76 (4%)	393 (4%)	0·92 (0·73–1·17)
No prior vaccination	1695 (92%)	8349 (90%)	1 (ref)
HPV vaccine history, number of doses			
Prior vaccination, three doses or more‡	71 (4%)	486 (5%)	0·68 (0·52–0·90)
Prior vaccination, two doses	36 (2%)	168 (2%)	1·02 (0·71–1·48)
Prior vaccination, one dose	47 (3%)	239 (3%)	0·94 (0·68–1·30)
No prior vaccination	1695 (92%)	8349 (90%)	1 (ref)
HPV vaccine history, age at first dose, number of doses			
Prior vaccination, 14–17 years, three doses or more	10 (1%)	126 (1%)	0·29 (0·14–0·60)
Prior vaccination, 18–20 years, three doses or more	20 (1%)	132 (1%)	0·67 (0·41–1·10)
Prior vaccination, ≥21 years, three doses or more	41 (2%)	228 (2%)	0·88 (0·62–1·25)
Prior vaccination, 14–17 years, fewer than three doses	12 (1%)	62 (1%)	0·77 (0·40–1·49)
Prior vaccination, 18–20 years, fewer than three doses	22 (1%)	93 (1%)	1·08 (0·66–1·75)
Prior vaccination, ≥21 years, fewer than three doses	49 (3%)	252 (3%)	0·95 (0·70–1·30)
No prior vaccination	1695 (92%)	8349 (90%)	1 (ref)

Data are n (%) unless indicated otherwise. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus. *CIN3+ cases and matched controls are a subset of CIN2+ cases and matched controls. †Based on bivariate conditional logistic regression models. ‡No CIN3+ cases and four controls had four or more vaccine doses.

Table 3: **HPV vaccine history and unadjusted rate ratios among CIN grade 3 or worse cases and matched controls, Kaiser Permanente, 1996–2014**

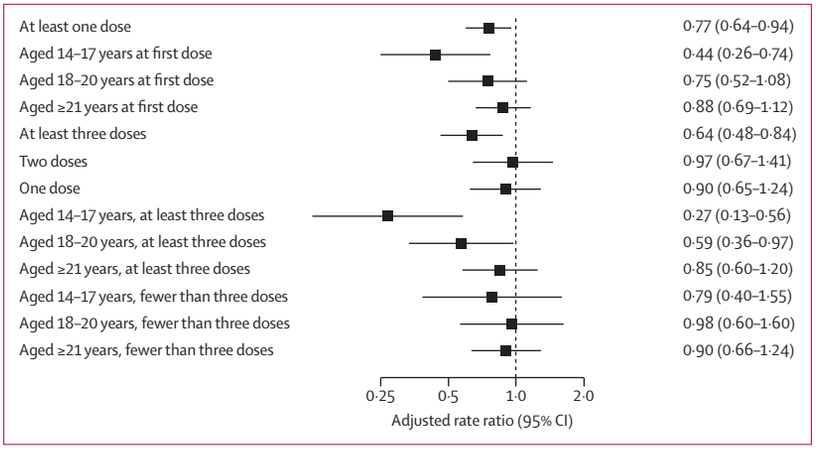

Figure 2: **Adjusted rate ratios and 95% CI for cervical intraepithelial neoplasia grade 3 or worse by HPV vaccination history**
HPV=human papillomavirus.

Discussion

In this large population-based case-control study in an integrated health-care system, catch-up HPV vaccination with three doses was effective against CIN2+ and CIN3+ in women younger than 21 years at time of first dose. We found no significant effectiveness, however, in women who initiated vaccination aged 21–26 years or in women who received fewer than the full three doses in the series. These results support existing guidelines recommending the full three-dose series for girls and women who start the series after their 15th birthday. The finding that catch-up vaccination had limited effectiveness in women aged 21–26 years should be confirmed in other settings.

The 18% reduction (1·00–0·82 RR) in CIN2+ incidence in women who received at least one dose of the vaccine is similar to findings from randomised clinical trials of the quadrivalent vaccine[19] showing a 19% reduction in the intention-to-treat analysis for CIN2+ in girls and women aged 15–26 years who received at least one vaccine dose. In a trial[20] with women aged 24–45 years who were randomised to the quadrivalent vaccine or placebo, the quadrivalent vaccine had 89% efficacy against the combined outcome of persistent infection, CIN, and external genital lesions related to HPV vaccine types; although not powered for CIN2+, the trial investigators also noted no decrease in CIN2+ incidence. The 23% reduction we noted in CIN3+ incidence is similar to the 18% reduction for CIN3 or adenocarcinoma in situ reported in these trials.

Few epidemiological studies have been done to evaluate the population effectiveness of HPV vaccination for CIN2+.[21–24,28] The effectiveness of the bivalent HPV vaccine was assessed in a large study in Scotland,[22] where vaccination of girls aged 13–17 years with three doses was associated with a 50% reduction in CIN2 incidence and a 55% reduction in CIN3 incidence compared with girls who were not vaccinated; these effects attenuated with increasing age. In an Australian study with girls aged 12–17 years (mean age 16 years),[21] vaccination with at least one dose was associated with a 28% reduction in CIN2+ and 36% reduction in CIN3 or adenocarcinoma in situ incidence, which is stronger in magnitude than our findings, whereas girls vaccinated at older ages had reduced protection. Protection was only found in girls who were fully vaccinated. In a follow-up Australian case-control study[23] with girls and women aged 11–27 years at first dose who were just entering the cervical cancer screening programme, effectiveness against CIN2+ was 46% with three vaccine doses and 21% with two doses. CIN3+ was not evaluated. The investigators also reported 26% effectiveness for at least one vaccine dose compared with those receiving no vaccine, but no evidence was found of any vaccine effectiveness in women aged 23–27 years. Vaccine effectiveness for CIN2+ (but again not for CIN3+) by age and number of doses was compared before and after cervical cancer screening initiation in another Australian study with girls and women aged 11–27 years.[24] Vaccination was associated with a 29% effectiveness against CIN2+ for girls and women fully vaccinated before screening initiation and a 13% effectiveness for girls and women fully vaccinated after screening initiation, but those receiving fewer than three doses had no protection. Results were similar for the outcome of CIN3/adenomacarcinoma in situ. Effectiveness was reduced but remained significant for women aged 20–23 years and 24–26 years but only for those who were vaccinated after screening initiation.

The study has several key strengths. First, we are among the first to evaluate vaccine effectiveness in a large sample in the USA where HPV vaccine uptake has been lower than in other countries. This study is one of few to evaluate effectiveness in women vaccinated after age 17 years and is one of the largest to do so; compared with a study in Australia,[23] our study had four times the number of cases overall (n=4357 *vs* n=1062), enhancing our ability to detect small differences between cases and controls. In the randomised trial[20] in which vaccine efficacy was assessed in women initiating vaccination at ages 24–45 years, only 62 CIN2+ cases were identified in the vaccinated group and 51 CIN2+ cases were identified in the placebo group. We also adjusted for clinical risk factors such as smoking, hormonal contraceptive use, and sexually transmitted infections, which was not done in previous studies.[21–24] An additional strength was the comprehensive database allowing for complete ascertainment of clinical data and the ability to precisely match controls on factors associated with engagement with the health-care system.

Some study limitations should be acknowledged. First, clinically ascertained study measurements such as smoking might have been subject to misclassification. Other measurements based on pharmacy or laboratory data (ie, hormonal contraceptive use, sexually transmitted infections) were more accurately ascertained. Replacing recent exposure to covariates with ever exposure (with potentially more complete data) in the sensitivity analyses had no effect on results. Second, results of the sensitivity analysis was limited to women with continuous membership since the introduction of the vaccine showed moderately stronger results, suggesting there might have been some misclassification of vaccination status. Third, residual confounding related to screening vigilance might have affected the results. Cases and controls, however, were carefully matched to reflect similar engagement in the health plan. Fourth, although the case-control design offered advantages with respect to analytical efficiency and careful adjustment for confounders, the design precluded the calculation of absolute rates. Fifth, the increased HPV type vaccine coverage of the recently introduced nonavalent HPV vaccine is anticipated to prevent more CIN2+ cases than the quadrivalent HPV vaccine is, thus requiring future investigation. Sixth, despite the large sample size, the low uptake of catch-up vaccination resulted in limited statistical power and wide CIs for some comparisons (eg, fewer than three doses). Seventh, given the observational design, vaccinated and unvaccinated women might have differed in ways that we could not fully measure. Finally, the results

might have limited generalisability given the single health-care setting. However, the results are generalisable to other integrated health-care settings and insured women in the San Francisco Bay Area, given the current membership of more than 2 million members, representing a quarter of all insured women in the region.[25]

In summary, our findings support existing US guidelines recommending three HPV vaccine doses for girls and women initiating vaccination at ages 15–20 years. Consistent with some,[20,23] but not all studies,[24] our findings do not support catch-up vaccination of women aged 21–26 years. Because this finding conflicts with recent calls to extend HPV vaccination to women of older ages,[29] our results should be confirmed in other settings, especially those that have adopted the nonavalent HPV vaccine.

Contributors

All study authors contributed to study design; data interpretation; and preparation, critical revision, and approval of the manuscript. WAL also contributed to data collection and data analysis. SEG and SK also contributed to biostatistical consultation. MJS and GFS created figures. MJS, GFS, and JOL contributed to literature searches. MJS, SEG, SK, MK, KKS-M, and GFS also contributed to obtaining funding.

Declaration of interests

We declare no competing interests.

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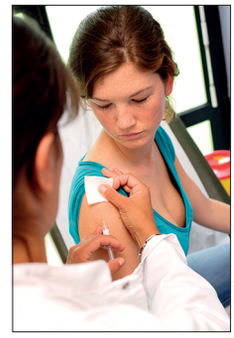
Catch-up human papillomavirus vaccination: don't throw the baby out with the bathwater

The human papillomavirus (HPV) vaccine provides an extraordinary opportunity to mitigate the burden of HPV-related diseases, including cervical intraepithelial neoplasia (CIN) and cancer. However, the ideal vaccine schedule to maximise cervical cancer prevention continues to be debated and refined. In the USA, the nonavalent HPV vaccine is approved for females and males between the ages of 9 and 26 years. The US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all adolescents at age 11 or 12 years, with catch-up dosing up to age 26 years when appropriate.[1] These recommendations are based on data showing equivalent immunogenicity with two versus three doses of the vaccine in adolescents.[2] Age at vaccination and time since first sexual activity are important factors that contribute to the effectiveness of the HPV vaccine.[3] However, data have shown that vaccination is still effective at preventing CIN2+ in women who have been exposed to HPV.[4] Rates of adolescent HPV vaccination are low in the USA, with only 43% of children aged 13–17 years up to date with the HPV vaccine series.[5] The USA lags behind other high-income countries, such as Australia, which has achieved vaccination completion rates of greater than 70% and seen reductions in incidence of cervical dysplasia and anogenital warts.[6]

In *The Lancet Child & Adolescent Health,* Michael Silverberg and colleagues[7] describe a nested case-control study comparing more than 4000 patients with CIN2+ to more than 21 000 matched controls without CIN2+ on the basis of age and HPV vaccination status, including a subset of 1800 CIN3+ cases with 9000 matched controls. In their study, 10% of patients with CIN2+ and 11% of controls had received prior HPV vaccination. The strongest associations between HPV vaccination and reduced risk of CIN were in models for CIN3+ that were adjusted for age, smoking, race or ethnicity, hormonal contraceptive use, sexually transmitted infections, parity, outpatient visits, and immunosuppression. The authors found a decreased risk for CIN3+ in girls who received their first HPV vaccine dose between the ages of 14 and 17 years (adjusted rate ratio [RR] 0·44, 95% CI 0·26–0·74), regardless of number of doses received. They did not observe protection against CIN3+ in any age group who received fewer than three doses, but there was a decreased risk in girls aged 14–17 years (0·27, 0·13–0·56) and a decreased risk in women aged 18–20 years (0·59, 0·36–0·97) who received three or more doses. In models evaluating risk of CIN2+, the authors showed a decreased risk in women of any age who received at least one dose of HPV vaccine (0·82, 0·73–0·93). Adjusted rate ratios were less robust than in the CIN3+ analysis, but similarly showed that women younger than 21 years (14–17 years [0·61, 0·46–0·81]; 18–20 years [0·72, 0·58–0·90]) and those who received three doses of the vaccine (0·76, 0·64–0·89) had a significantly decreased risk of CIN2+. Neither analysis showed a statistically significant decrease in risk of CIN in participants older than 21 years who had received the vaccine when stratified by age.

This study[7] examined a population enrolled in Kaiser Permanente Northern California, which provided a large and thorough database; however, this population of insured women is not representative of the USA as a whole, and certainly not representative of the most at risk populations, specifically women who are uninsured or underinsured with poor access to routine health care. The authors note that patients in this study primarily received a quadrivalent vaccine, which does not confer the same protection as the newer nonavalent vaccine.[7] Although the authors examined the association between HPV vaccination and risk of CIN in detail, they did not actually examine the effectiveness of the HPV vaccine on prevention of cervical cancer. Only 23 women were diagnosed with cervical cancer in the study,[7] and although only three (13%) of those women had received the HPV vaccine, the natural history of HPV infection and cervical cancer limits any researcher's ability to quantify the effect of the HPV vaccine on cervical cancer incidence. Furthermore, the authors did not examine the effect of the HPV vaccine on low-grade dysplasia, persistent HPV infection, or genital warts, all of which are clinically important outcomes.[7]

Other studies have shown a benefit of HPV vaccination in older teenagers and young women. Munoz and



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colleagues[8] evaluated women aged 15–26 years and showed a 19% reduction in high-grade cervical lesions, as well as a 62% reduction in genital warts. However, this population was not further stratified by age group as in the current study. Castellsagué and colleagues[9] found a decreased risk of CIN, external genital lesions, and persistent HPV infection in women aged 24–45 years, even those with previous exposure to HPV.[9] Notably, in the context of improved outcomes in women, outside US Food and Drug Administration (FDA) approval, Merck has been granted priority review by the FDA for a supplemental license application for the nonavalent HPV vaccine in women and men aged 27–45 years for the prevention of HPV-related cancers and diseases.[10]

Silverberg and colleagues[7] present compelling data to support catch-up HPV vaccination in older adolescence. They found an impressive reduction in CIN3+ in girls who received all three doses as adolescents between the ages of 14 and 17 years (adjusted RR 0·44, 95% CI 0·26–0·74). These data support the updated ACIP HPV vaccination schedule, which recommends administration of three doses to any women who start the vaccine series after age 14 years.[1] The results of this study[7] confirm existing research, which showed that the HPV vaccine is most effective when given to females at younger ages, but no benefit was found in patients older than 21 years. Efforts towards increasing HPV vaccine uptake should be focused on younger adolescents—with a priority on vaccinating children aged 11–12 years—and providing catch-up dosing for older adolescents. However, in the setting of low rates of HPV vaccination in the USA, the importance of catch-up dosing in young women should not be ignored. Given that prospective efficacy studies have shown benefits for catch-up vaccination up to at least age 26 years, more data is needed before abandoning this practice.

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