

## Original Investigation

# Incidence of Sexually Transmitted Infections After Human Papillomavirus Vaccination Among Adolescent Females

Anupam B. Jena, MD, PhD; Dana P. Goldman, PhD; Seth A. Seabury, PhD

**IMPORTANCE** Human papillomavirus (HPV) vaccination rates among US females remain low, in part because of concerns that HPV vaccination may promote unsafe sexual activity by lowering perceived risks of acquiring a sexually transmitted infection (STI).

**OBJECTIVE** To study whether HPV vaccination of females is associated with increases in STI rates.


**DESIGN, SETTING, AND PARTICIPANTS** Using a large, longitudinal insurance database of females aged 12 to 18 years insured from January 1, 2005, through December 31, 2010, in the United States, we examined whether HPV vaccination was associated with an increase in incident STIs among females who were vaccinated compared with those who were not. We defined STIs as one or more medical claims for any of the following infections in a given quarter: chlamydia, gonorrhea, herpes, human immunodeficiency virus or AIDS, or syphilis. We used difference-in-difference analysis to compare changes in STI rates among HPV-vaccinated females before and after vaccination (index quarter) to changes among age-matched nonvaccinated females before and after the index quarter. We analyzed whether effects varied according to age and prior contraceptive medication use.


**MAIN OUTCOMES AND MEASURES** Rates of STIs.

**RESULTS** The rates of STIs in the year before vaccination were higher among HPV-vaccinated females (94 of 21 610, 4.3 per 1000) compared with age-matched nonvaccinated females (522 of 186 501, 2.8 per 1000) (adjusted odds ratio, 1.37; 95% CI, 1.09-1.71;  $P = .007$ ). The rates of STIs increased for the vaccinated (147 of 21 610, 6.8 per 1000) and nonvaccinated (781 of 186 501, 4.2 per 1000) groups in the year after vaccination (adjusted odds ratio, 1.50; 95% CI, 1.25-1.79;  $P < .001$ ). The difference-in-difference odds ratio was 1.05 (95% CI, 0.80-1.38;  $P = .74$ ), implying that HPV vaccination was not associated with an increase in STIs relative to growth among nonvaccinated females. Similar associations held among subgroups aged 12 through 14 years and aged 15 through 18 years and among females with contraceptive use in the index quarter.

**CONCLUSIONS AND RELEVANCE** Human papillomavirus vaccination was not associated with increases in STIs in a large cohort of females, suggesting that vaccination is unlikely to promote unsafe sexual activity.

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Nearly one-quarter of US women aged 14 through 19 years and 45% of women aged 20 through 24 years are affected by human papillomavirus (HPV).<sup>1</sup> The annual incidence of cervical cancer, the leading public health concern of HPV, is approximately 12 000 in the United States and more than 500 000 worldwide.<sup>2,3</sup> In 2006, the Food and Drug Administration approved the first quadrivalent HPV vaccine indicated for use in women aged 9 through 26 years for the prevention of cervical, vulvar, and vaginal cancers caused by HPV-16 and HPV-18 and genital warts caused by HPV-6 and HPV-11.<sup>4</sup> In 2009, approval for the quadrivalent vaccine was expanded to males aged 9 through 26 years, and a new bivalent vaccine was also approved for the prevention of cancers associated with HPV-16 and HPV-18 in women alone.<sup>5</sup> The most recent recommendations of the Advisory Committee on Immunization Practices advocate for females a 3-dose series of either vaccine at 11 or 12 years of age and through 26 years of age if not vaccinated previously. For males, a 3-dose vaccination is recommended at 11 or 12 years of age and through 21 years of age if not vaccinated previously.<sup>6</sup>

Despite the widespread prevalence of HPV in the United States, vaccination among females remains low. In 2008, 37% of females aged 13 through 17 years received at least 1 dose of the vaccine series, whereas 18% received all 3 recommended doses.<sup>7</sup> By 2013, only 57% of females aged 13 through 17 years received at least 1 dose, whereas 38% received all 3 doses.<sup>7</sup>

Although several factors have been proposed to explain why HPV vaccination rates in the United States are so low,<sup>8-14</sup> few barriers have received as much attention as the concern that vaccination against HPV, a sexually transmitted infection (STI), could promote unsafe sexual activity among females by lowering perceived risks of acquiring an STI (ie, behavioral disinhibition or risk compensation) or implicitly endorsing sexual activity by recognizing the need for HPV vaccination.<sup>14-21</sup> These concerns spurred immediate legislative efforts to prohibit HPV vaccination mandates in several states.<sup>15</sup>

Several surveys of females or their parents have suggested that HPV vaccination is unlikely to lead to unsafe sexual activity among adolescents.<sup>16,20,22-26</sup> Although rich in their assessment of knowledge and attitudes about vaccination and sexual activity, these studies rely on self-reported outcomes, do not follow up adolescents longitudinally, and, with the exception of 2 studies,<sup>24,25</sup> are small and not nationally representative. In addition to these studies, an important retrospective cohort study<sup>27</sup> of girls aged 11 through 12 years enrolled in a managed care organization found no difference in a composite measure of sexual activity-related outcomes between 493 girls who received HPV vaccination and 905 girls who did not. Despite the strengths of directly measuring sex-related outcomes and having a 3-year follow-up, the study was conducted in one metropolitan area, had limited sample size, and did not study changes in outcomes before and after vaccination.

Using a large longitudinal database of insurance claims from January 1, 2005, through December 31, 2010, we examined whether HPV vaccination was associated with an increase in STIs among females who were vaccinated com-

pared with those who were not. We used a difference-in-difference analysis comparing changes in STI incidence among HPV-vaccinated females before and after vaccination to changes in incidence over time among matched females who were not vaccinated. Large data are required to examine STIs given their low incidence in the population (eg, annual chlamydia and gonorrhea rates among US females aged 15-19 years are approximately 3% and 0.5%, respectively).<sup>28,29</sup> We analyzed whether effects of HPV vaccination varied according to age and use of contraceptive medications before vaccination.

## Methods

### Data Sources

We used compiled data on all pharmacy and medical claims from January 1, 2005, through December 31, 2010, from 41 large employers across the United States. Each employer offered one or more health plans to its current or retired employees and their dependents. These data have been used to study STIs among adults,<sup>28</sup> the effect of pharmacy benefit design on medication use,<sup>30,31</sup> and use of medications by the chronically ill.<sup>32</sup> The study was exempt from human subjects review by the institutional review board of the University of Southern California; therefore, no informed consent was required.

### Study Sample

All females in our study were dependents of primary insured adults. We identified all females who were 12 through 18 years of age at any point during the study period and who received at least one dose of the HPV vaccine based on the presence of *Common Procedural Terminology* (CPT) codes for quadrivalent HPV-6, -11, -16, and -18 recombinant vaccine (Gardasil; Merck & Co; CPT code 90649 or 90649-SL) in the medical claims or appropriate national drug codes in the pharmacy claims. Vaccinations that were financed by the state or a free vaccine program, rather than paid for by the insurer, were identified by the suffix -SL in the CPT codes. The HPV bivalent vaccine (Cervarix; GlaxoSmithKline) users were excluded from the analysis because the vaccine was approved in the United States late in our study period (October 2009).<sup>5</sup> We did not have additional information from Immunization Information Systems to assign HPV vaccinations to females.

For each vaccinated female, we identified the first calendar quarter in which the vaccine was administered and the female's age in years, zip code of residence, and health plan (based on employer) during that quarter. We then matched vaccinated females to nonvaccinated females according to age, zip code of residence, and health plan in the first quarter of HPV vaccine use. The quarter of match was defined as the index quarter for each matched cohort, and we tracked outcomes on a quarterly basis for 1 year before and after the index quarter. We sampled with replacement, meaning the same nonvaccinated female could match to more than one vaccinated female if she met the same matching criteria. We required all vaccinated and nonvaccinated females in the sample to have at least 2 years of continuous enrollment before and after HPV vaccination (ie, 9 quarters total). This approach allowed us to

estimate rates of STIs before and after a common index date among females who received the vaccine and a matched group of nonvaccinated females. For each vaccinated female, we allowed multiple nonvaccinated female matches, rather than 1:1 matching, to improve the precision of our STI estimates.

### Outcome Measure

Our primary outcome was an indicator variable for whether a female had at least one medical claim for any of the following STIs in a given quarter: chlamydia, gonorrhea, herpes, human immunodeficiency virus or AIDS, or syphilis. Outcomes were measured at the person-quarter level. The STIs were identified in medical claims according to *International Classification of Diseases, Ninth Revision* diagnoses.

### Statistical Analysis

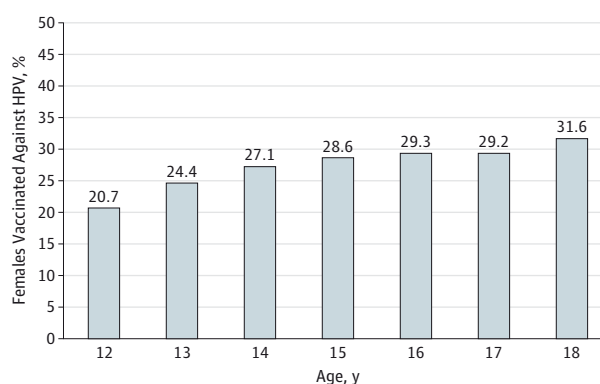
A simple comparison of STI rates between vaccinated and nonvaccinated females could be confounded by selection bias. That is, females receiving HPV vaccination may have unobserved characteristics that are associated with higher rates of STIs compared with nonvaccinated females (eg, females who are sexually active may have higher demand for the vaccine because they know they are at higher risk of acquiring HPV). Moreover, females receiving the HPV vaccine may be expected to have higher rates of STIs after vaccination simply because rates of STIs increase with age<sup>28</sup>; this expectation would preclude an analysis that studies the effect of HPV vaccination on STI incidence by only analyzing females who are vaccinated. We addressed these issues through a difference-in-difference approach that estimated changes in STI rates before and after HPV vaccination (among females who were vaccinated) and compared this difference to changes in STI rates among age-matched females who were not vaccinated. This approach eliminates time-invariant differences in unobserved characteristics of vaccinated and nonvaccinated females that are correlated with HPV vaccine receipt and STI incidence.

We compared STI rates among females who were vaccinated against HPV with those of the matched females who were never vaccinated for 1 year before and after vaccination using a logistic regression model of the form:

$$\text{Logit}(\text{STI}) = b_0 + b_1 \times \text{HPV\_vac} + b_2 \times \text{Post} + b_3 \times \text{HPV\_vac} \times \text{Post} + b_4 \times \text{Age} + b_5 \times \text{Covariates}$$

in which *STI* was a binary indicator for an STI in the year, *HPV\_vac* was an indicator for whether a female had ever been vaccinated against HPV, *Post* was an indicator for the year (4-quarter period) after vaccination, *Age* included binary indicator variables for the female's age at the start of the index quarter, and *Covariates* included indicator variables for year and census region. To control for potential differences in sexual activity before baseline, we also included an indicator for any pharmacy claim for a contraceptive medication in the year before the index quarter. The model selection followed past work and included factors available in the claims data that were hypothesized to be associated with sexual activity and STI rates and that might be confounded with HPV vaccination. We used the Hosmer-Lemeshow goodness-of-fit tests with 10 groups to assess model fit.<sup>33</sup>

**Figure 1. Vaccination Against Human Papillomavirus (HPV) According to Age of Female, 2010**



The difference-in-difference odds ratio (OR), which can be thought of as a ratio of ORs, derived from coefficient  $b_3$  would be greater than 1 if, relative to nonvaccinated females, those vaccinated against HPV had greater increases in STIs in the year after the index quarter compared with the year before. We estimated the logistic model for all ages combined (adjusting for age at baseline) and separately for subgroups aged 12 through 14 years and aged 15 through 18 years. We also analyzed whether the association between HPV vaccination and STI was modified by the level of sexual activity before vaccination as measured by a pharmacy claim for a contraceptive medication in the index quarter. Specifically, we estimated the difference-in-difference model among the subgroup of females who had a contraceptive medication claim in the index quarter. These females were more likely to have been sexually active with or without vaccination, so any association between STI incidence and vaccine use in this population would more likely reflect a change in the riskiness of sexual activity (as opposed to the overall analysis, which reflected changes in any sexual activity and changes in the riskiness of the sexual activity). Model SEs allowed for correlation (or clustering) within each match cohort.

## Results

### Characteristics of Study Population

The HPV vaccine uptake increased during the study period, with 2.5% of females aged 12 through 18 years in the fourth quarter of 2006 receiving the vaccine compared with 27.3% by the fourth quarter of 2010. Vaccination increased with age (Figure 1). For example, in the fourth quarter of 2010 among 12 862 females aged 12 years, 2675 (20.8%) received the HPV vaccine, increasing to 3740 (27.1%) of 13 809 by the age of 14 years and 3894 (31.6%) of 12 311 by the age of 18 years.

Table 1 presents the characteristics of 21 610 females who were vaccinated against HPV and 186 501 matched nonvaccinated females. The mean age among vaccinated females was 15.0 years compared with 14.9 years among matched nonvaccinated females. Geographic differences were found in HPV vaccination rates, with females living in the southern United

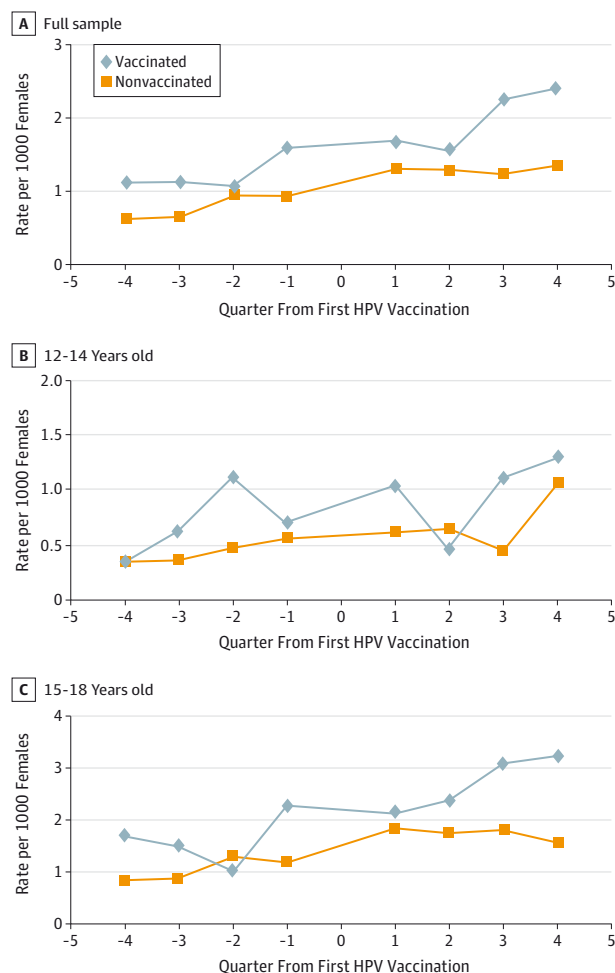
Table 1. Characteristics of Females Vaccinated Against HPV and Matched Nonvaccinated Females<sup>a</sup>

Characteristic	All Females			Females Aged 12-14 Years			Females Aged 15-18 Years		
	Full Sample (n = 208 111)	HPV Vaccinated (n = 21 610)	Nonvaccinated (n = 186 501)	Full Sample (n = 90 821)	HPV Vaccinated (n = 9024)	Nonvaccinated (n = 81 797)	Full Sample (n = 117 290)	HPV Vaccinated (n = 12 586)	Nonvaccinated (n = 104 704)
Mean age, y	14.9	15.0	14.9	13.0	13.1	13.0	16.3	16.3	16.3
Geographic region, %									
South	39.4	29.1	40.6	38.9	29.8	40.0	39.7	28.7	41.0
Northeast	26.2	31.5	25.6	26.8	31.1	26.3	25.8	31.7	25.2
Midwest	17.4	22.1	16.8	17.0	20.9	16.5	17.7	22.9	17.0
West	17.0	17.3	17.0	17.3	18.2	17.2	16.8	16.7	16.8
Any STI in previous year, No. per 1000 females	3.0	4.4	2.8	1.7	2.7	1.5	4.0	5.6	3.8
Oral contraceptive use in previous year, %	10.1	17.9	9.2	2.0	4.2	1.7	16.4	27.7	15.1

Abbreviations: HPV, human papillomavirus; STI, sexually transmitted infection.

<sup>a</sup> Females who were vaccinated were matched with replacement to nonvaccinated females according to age at first vaccination, employer providing insurance, and 3-digit zip code. The STI rates were computed in the year before HPV vaccination among vaccinated females and in the year before matched age among nonvaccinated females. All differences were statistically significant at  $P < .05$ .

Figure 2. Unadjusted Quarterly Rates of Sexually Transmitted Infection Among Human Papillomavirus (HPV)-Vaccinated and Nonvaccinated Females



A, Full sample; B, females aged 12 through 14 years; and C, females aged 15 through 18 years.

States less likely to be vaccinated. For example, among females vaccinated against HPV, 29.1% lived in the south compared with 39.4% in the overall sample and 40.6% among females who were not vaccinated ( $P = .006$ ). Females vaccinated against HPV were more likely to be sexually active in the year before vaccination compared with matched nonvaccinated females. For instance, the STI rate was 4.3 per 1000 females in the year before vaccination among vaccinated females compared with 2.8 per 1000 females among matched nonvaccinated females ( $P = .007$ ). Similarly, contraceptive medication use in the year before vaccination was higher among vaccinated females. Comparable patterns were noted for females aged 12 through 14 years and aged 15 through 18 years.

#### Unadjusted Trends in STIs Between HPV-Vaccinated and Nonvaccinated Females

Vaccinated females had higher rates of STIs before and after vaccination compared with matched nonvaccinated females (Figure 2). In the full sample, those who were vaccinated had 1.6 STIs per 1000 females in the quarter before vaccination compared with 0.9 STIs per 1000 among nonvaccinated females in the quarter before the index quarter. By the fourth quarter after vaccination, STI rates increased to 2.4 and 1.4 per 1000 vaccinated and matched nonvaccinated females, respectively. Similar patterns were noted for females aged 12 through 14 years and aged 15 through 18 years, with STI rates less variable in the older group given the higher incidence of STIs.

#### Difference-in-Difference Results

Higher prevaccination rates of STIs among females who received the HPV vaccine highlight the importance of accounting for these differences when estimating the effect of HPV vaccination on STIs. Table 2 gives the estimates of this association using a difference-in-difference approach that analyzed the difference in STI trajectories between HPV-vaccinated females (before and after vaccination) and matched nonvaccinated females (before and after the index quarter). In the full sample, the adjusted OR of STIs in the year before vaccination was 1.37 (95% CI, 1.09-1.71) in vac-

Table 2. Change in STI Rates After HPV Vaccination in Vaccinated Females vs Matched Nonvaccinated Females

Vaccination Status	Total No. of Females	Year Before HPV Vaccination			Year After HPV Vaccination			
		Unadjusted STI Rate, No. (Rate per 1000)	OR (95% CI) [P Value]		Unadjusted STI Rate, No. (Rate per 1000)	OR (95% CI) [P Value]		Difference-in-Difference
			Unadjusted	Adjusted		Unadjusted	Adjusted	
Full Sample								
Vaccinated	21 610	94 (4.3)	1.56 (1.25-1.90)	1.37 (1.09-1.71)	147 (6.8)	1.63 (1.37-1.94)	1.50 (1.25-1.79)	1.05 (0.80-1.38)
Nonvaccinated	186 501	522 (2.8)	[<.001]	[.007]	781 (4.2)	[<.001]	[<.001]	[.74]
Females Aged 12-14 Years								
Vaccinated	9024	24 (2.7)	1.73 (1.12-2.68)	1.75 (1.12-2.73)	33 (3.7)	1.63 (1.12-2.36)	1.53 (1.05-2.22)	0.94 (0.54-1.65)
Nonvaccinated	81 797	126 (1.5)	[.01]	[.01]	184 (2.2)	[.01]	[.03]	[.83]
Females Aged 15-18 Years								
Vaccinated	12 586	70 (5.6)	1.44 (1.14-1.90)	1.26 (0.97-1.64)	114 (9.1)	1.59 (1.30-1.95)	1.49 (1.21-1.83)	1.08 (0.79-1.49)
Nonvaccinated	104 704	396 (3.8)	[.003]	[.08]	597 (5.7)	[<.001]	[<.001]	[.62]

Abbreviations: HPV, human papillomavirus; OR, odds ratio; STI, sexually transmitted infection.

Table 3. Change in STI Rates After HPV Vaccination in Vaccinated Females vs Matched Nonvaccinated Females With Contraceptive Medication Use in Index Quarter

Vaccination Status	Total No. of Females	Year Before HPV Vaccination			Year After HPV Vaccination			
		Unadjusted STI Rate, No. (Rate per 1000)	OR (95% CI) [P Value]		Unadjusted STI Rate, No. (Rate per 1000)	OR (95% CI) [P Value]		Difference-in-Difference
			Unadjusted	Adjusted		Unadjusted	Adjusted	
Full Sample								
Vaccinated	3865	33 (8.5)	1.16 (0.79-1.72) [.45]	1.21 (0.81-1.80) [.36]	51 (13.2)	1.29 (0.94-1.78) [.11]	1.36 (0.99-1.89) [.06]	1.11 (0.68-1.81) [.70]
Nonvaccinated	14 567	107 (7.3)			149 (10.2)			
Females Aged 15-18 Years								
Vaccinated	3490	31 (8.9)	1.20 (0.80-1.80) [.37]	1.24 (0.82-1.87) [.31]	47 (13.5)	1.25 (0.90-1.75) [.18]	1.33 (0.95-1.86) [.10]	1.04 (0.63-1.73) [.27]
Nonvaccinated	13 374	99 (7.4)			144 (10.8)			

Abbreviations: HPV, human papillomavirus; OR, odds ratio; STI, sexually transmitted infection.

nated (94 of 21 610, 4.3 per 1000) and nonvaccinated (522 per 186 501, 2.8 per 1000) females. The STI rates increased in the year after vaccination for the vaccinated (147 of 21 610, 6.8 per 1000) and nonvaccinated (781 of 186 501, 4.2 per 1000) females. However, the adjusted OR in the year after vaccination was 1.50 (95% CI, 1.25-1.79), implying a difference-in-difference OR of 1.05 (95% CI, 0.80-1.38;  $P = .74$ ). Among females aged 12 through 14 years and aged 15 through 18 years, the difference-in-difference ORs were 0.94 (95% CI, 0.54-1.65;  $P = .83$ ) and 1.08 (95% CI, 0.79-1.49;  $P = .62$ ), respectively. The Hosmer-Lemeshow test failed to reject the fit of our model at the  $P = .05$  level of significance.

A similar association was found among females who were more likely to have been sexually active before HPV vaccination as proxied by contraceptive use. Table 3 reports the results of difference-in-difference analysis for females with contraceptive medication use in the index quarter, all females, and females aged 15 through 18 years (we excluded a separate analysis of females aged 12-14 years because of small sample sizes from comparatively infrequent contraceptive medication use). In the full sample, the adjusted OR was 1.21 (95% CI, 0.81-1.80;  $P = .36$ ) before vaccination and 1.36 (95% CI, 0.99-1.89;  $P = .06$ ) after vaccination. The difference-in-difference estimate provided no evidence of increased risky sexual activity, with an OR of 1.11 (95% CI,

0.68-1.81;  $P = .70$ ). Among females aged 15 through 18 years in the index quarter, the difference-in-difference OR was 1.04 (95% CI, 0.63-1.73;  $P = .27$ ).

## Discussion

Using longitudinal insurance data on adolescent females aged 12 through 18 years across the United States, we examined whether HPV vaccination was associated with an increase in unsafe sexual behavior. We found that, although vaccinated females had higher STI rates after vaccination compared with matched controls, these differences existed before vaccination as well. Our difference-in-difference analysis that compared changes in STI rates over time between vaccinated and nonvaccinated females found no evidence of an association between HPV vaccination and higher STI rates. Even among females who were more likely to be sexually active before HPV vaccination as measured by contraceptive medication use, there was no evidence of increased unsafe sexual behavior.

Despite the widespread prevalence of HPV in the United States, approximately half of all US adolescent females have never been vaccinated, and only one-third have received the recommended 3-dose vaccination.<sup>34</sup> In contrast, approximately 80% of females aged 14 through 19 years in Australia,



which in 2007 became one of the first countries to implement a school-based free HPV vaccination program, received at least one dose of the HPV vaccine in 2012, and 70% completed the full series.<sup>35,36</sup> Although high rates of vaccination in Australia have been attributed to the program's increased accessibility to vaccines through school-based administration, mandated vaccine use, and elimination of costs, it is unknown which of these factors has been most important in increasing high rates of vaccination.

Although low rates of HPV vaccination in the United States have been attributed to several factors, including difficulty adhering to a multiple-dose regimen, high out-of-pocket costs for some patients, infrequent state vaccine mandates, patient and physician concerns about vaccine safety, and physician concerns about insurance reimbursement,<sup>8-14</sup> among the most widely discussed concerns about the HPV vaccine is that it could promote unsafe sexual activity through behavioral disinhibition or by simply advancing discussions about sexual activity with adolescents before parents and health care professionals would otherwise do so.<sup>14-21</sup> In a national survey of pediatricians, for example, 60% of those surveyed thought parents would be concerned that HPV vaccination would promote unsafe sexual behavior, and 11% of pediatricians themselves reported this concern.<sup>37</sup> In a more recent physician survey, factors associated with not strongly recommending HPV vaccination to females aged 11 through 12 years included a perceived need to first discuss sexual activity before recommending the vaccine and a reported higher rate of vaccination refusals among parents of younger vs older children.<sup>38</sup> Similar concerns about the timing of vaccination compared with onset of sexual activity were noted in a small but qualitative survey of pediatric health care professionals.<sup>39</sup>

We found no evidence that HPV vaccination leads to unsafe sexual activity as measured by STI rates reflected in insurance claims data. Our findings are consistent with surveys of adolescents and their parents in which HPV vaccination is reported as being unlikely to promote unsafe sexual activity,<sup>16,20,22-25</sup> as well as a retrospective study<sup>27</sup> of adolescent females insured by a large managed care organization in Atlanta, Georgia, in which a combined end point of sexual activity was similar between vaccinated and nonvaccinated females. Our study adds to these findings by measuring STI rates among more than 20 000 vaccinated females across the United States and analyzing changes in STI rates before and after vaccination.

Although HPV vaccination does not appear to lead to higher rates of STIs, females who receive the vaccine have mean higher rates of STIs before vaccination compared with age-matched females during the same period. This finding has at least 2 implications. First, because females with a history of STI are at higher risk of subsequent HPV exposure, early vaccination against HPV is particularly important among these females and in some instances may have been directly prompted by a pre-

ceding non-HPV STI diagnosis. Second, our finding that HPV-vaccinated females have higher STI rates before vaccination suggests that, until HPV vaccination becomes widespread, females who elect to receive the vaccine may benefit from screening questions and counseling about safe sexual practices.

Our study had several limitations. First, the decision to vaccinate against HPV may be correlated with unobserved characteristics that are also associated with STI risk, which would confound our estimates. For example, females who expect to become sexually active may be more likely to become vaccinated, which could spuriously suggest that HPV vaccination leads to greater sexual activity. Our difference-in-difference approach accounted for preexisting differences in STI rates between vaccinated and nonvaccinated females and found no effect of HPV vaccination on STI rates. It is possible, however, that HPV vaccination is more likely in households that are wealthier and more educated, which, if unaccounted for, could bias toward zero any deleterious effect of HPV vaccination on STI rates. Although we did not have data on family income or educational level, HPV vaccination was not associated with family socioeconomic status in several prior surveys.<sup>14,40,41</sup> Second, we identified STIs from insurance claims, which may miss visits to anonymous clinics and may also include episodes of STI testing rather than confirmed infection. We similarly identified HPV vaccinations from insurance claims, which may miss instances in which females were vaccinated in clinics that did not bill an individual's insurance. Third, STIs are but one measure of unsafe sexual activity, which could alternatively be assessed through questionnaires about condom use and number of sexual partners. Fourth, we focused on the privately insured for whom effects of HPV vaccination may differ from those with public insurance or without insurance. Fifth, our analysis was not powered to analyze specific STIs. Sixth, parents of adolescent females would in most instances be aware if their daughter had an insurance claim filed by the health care professional for diagnosis and/or treatment of an STI, in contrast to free testing in a clinic that did not file an insurance claim. It is possible that sexual activity may be influenced by parents' potential awareness of an STI diagnosis, which we could not account for. Finally, we conducted a subgroup analysis of females with a contraceptive claim in the index quarter to identify females who were likely to already be sexually active. This approach misses other females who may be sexually active and using barrier contraception methods.

## Conclusions

We found no evidence that HPV vaccination leads to higher rates of STIs. Given low rates of HPV vaccination among adolescent females in the United States, our findings should be reassuring to physicians, parents, and policy makers that HPV vaccination is unlikely to promote unsafe sexual activity.

### ARTICLE INFORMATION

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*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Jena, Seabury.

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