


Prevalence of Oral Human Papillomavirus Infection by Number of Vaccine Doses Among US Adults

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Abstract

The human papillomavirus (HPV) vaccine is effective at reducing the incidence of cervical cancer caused by HPV. Studies have shown that 1 dose of the HPV vaccine offers comparable protection against genital HPV infection as additional doses; however, it is unknown whether oral HPV prevalence also differs by number of vaccine doses. We examined differences in prevalence of oral HPV by number of doses using the National Health and Nutrition Examination Survey from 2009 to 2016. The prevalence of HPV 6, 11, 16, and 18 infections was statistically significantly lower in individuals who received 1 dose (0.3%, 95% confidence interval [CI] = 0.0% to 0.9%) or 2-3 doses (0.4%, 95% CI = 0.0% to 1.2%) compared with unvaccinated individuals (1.2%, 95% CI = 0.9% to 1.6%). Smokers, individuals who initiated oral sex at age 17 years or younger, and those with more than 2 oral sexual partners had higher rates of oral HPV infection. Ongoing prospective studies are essential to further evaluate the efficacy of a single-dose regimen for prevention of oral HPV.

The human papillomavirus (HPV) vaccine is an effective prevention strategy against cervical cancer, and the US Food and Drug Administration recently expanded the indication of the vaccine to include the prevention of HPV-associated oropharyngeal cancers in June 2020 (1,2). However, vaccination rates remain suboptimal, with only 51.1% of US adolescents receiving the recommended vaccine doses in 2018 (3). To simplify recommendations and improve vaccination coverage and compliance, trials are evaluating the efficacy of a single-dose regimen. Studies have shown that 1 dose of the HPV vaccine may offer similar protection against genital HPV infection as additional doses (4,5). However, it is currently unclear whether the prevalence of oral HPV infection similarly differs by number of HPV vaccine doses.

To assess this question, we performed a cross-sectional study that used the 2009-2016 National Health and Nutritional Examination Survey (NHANES), which collects self-reported sociodemographic and health behavior information, immunization history, and laboratory specimens on a nationally representative sample of US adults aged 18 years or older.

Interview questionnaires were administered in-home by trained interviewers, and physical examinations were performed at mobile examination centers (6). All participants provided written informed consent. For the purposes of this study, we restricted age to 18-36 years, with 36 years chosen as the upper limit because these individuals were 26 years old, the maximum recommended age for HPV vaccination, when the vaccine was first administered in 2006. This study used de-identified data and was exempt from institutional review board approval.

Participants were asked whether they had received the quadrivalent HPV vaccine and, if they had, the number of doses that were administered. We excluded participants with missing vaccination information. Participants were also asked questions regarding sexual behavior, including whether they have had sex, age at first oral sexual encounter, and number of oral sexual partners. Age at first sexual encounter and number of sexual partners were dichotomized using their median values. Substance use, including tobacco and alcohol use, was also evaluated.

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Table 1. Prevalence of oral HPV infections among US adults by HPV vaccination status, NHANES 2009-2016

HPV types	Vaccinated		Unvaccinated (n = 4801)
	1 dose (n = 198)	2-3 doses (n = 799)	
HPV 6, 11, 16, 18 (4-valent vaccine serotypes)			
No. of participants with infection	1	2	59
Weighted ^a Prevalence, % (95% CI)	0.3 (0.0 to 0.9)	0.4 (0.0 to 1.2)	1.2 (0.9 to 1.6)
No. with infection/total No.	5184/1 825 495	36 773/8 484 653	614 210/49 282 243
P ^b (vs 2-3 doses)	.75		
P ^b (vs unvaccinated)	.01	.05	
HPV 31, 33, 45, 52, 58 (additional 9-valent vaccine serotypes)			
No. of participants with infection	1	6	27
Weighted ^a Prevalence, % (95% CI)	0.3 (0.0 to 0.8)	0.6 (0.1 to 1.1)	0.3 (0.2 to 0.8)
No. with infection/total No.	5028/1 825 495	48 956/8 484 653	256 071/49 282 243
P ^b (vs 2-3 doses)	.44		
P ^b (vs unvaccinated)	.44	.85	
HPV 35, 39, 51, 56, 59, 68 (other high-risk types)			
No. of participants with infection	2	12	74
Weighted ^a Prevalence, % (95% CI)	0.7 (0.0 to 1.8)	1.0 (0.4 to 1.5)	1.5 (1.0 to 2.0)
No. with infection/total No.	13 322/1 825 495	71 625/8 484 653	759 073/49 282 243
P ^b (vs 2-3 doses)	.65		
P ^b (vs unvaccinated)	.17	.06	

^aWeighted frequency based on National Health and Nutrition Examination Survey (NHANES) Mobile Examination Centers sampling weights. CI = confidence interval; HPV = human papillomavirus.

^bP values for survey weight-adjusted Wald F test. All tests were 2-sided.

Oral rinse samples for HPV detection were also collected at mobile examination centers. Subjects were asked to rinse and gargle for 30 seconds with mouthwash or saline. Purified DNA was analyzed for 37 types of HPV using a multiplex polymerase chain reaction assay targeted to the L1 region of the viral genome using PGYM09/11 primer pools and primers for β -globin. Details regarding sampling and processing are described elsewhere (7,8).

We used survey weight-adjusted Wald F tests to evaluate differences in the prevalence of oral HPV infection, divided into serotypes covered by the quadrivalent vaccine (6, 11, 16, 18), additional serotypes covered by the 9-valent vaccine (31, 33, 45, 52, 58), and other high-risk serotypes (35, 39, 51, 56, 59, 68) by the number of doses received. The differences in predicted probability for oral HPV 6, 11, 16, and 18 by number of vaccine doses were estimated using multivariable logistic regression, with 1 dose as the reference group to assess differences in oral HPV infection by number of vaccine doses. We adjusted for age as a linear term, sex, race and ethnicity, smoking status, age at oral sexual debut, and lifetime number of oral sexual partners, similar to prior literature (4). All tests were 2-sided, and a P value less than or equal to .05 was considered statistically significant. Analyses were performed using SAS Enterprise Guide 7.1 (Cary, North Carolina) and adjusted for strata, cluster, and weights using SAS PROC SURVEY procedures to account for oversampling in the complex survey design and to ensure generalizability to the US population.

A total of 8037 individuals aged 18-36 years were included in the NHANES cohort, and 7294 (90.8%) received oral rinse sampling that was evaluated for HPV testing. After excluding individuals who had missing information about the HPV vaccine (n = 1400) or the number of doses of HPV vaccine received (n = 96), our final cohort consisted of 5798 participants (mean [SD] age = 22 [5.7] years; 58.6% were women; 57.5% were White). The median age at oral sexual debut was 17 years, and the median number of oral sexual partners was 2. Of these participants, 4801 were unvaccinated, 198 received 1 dose, and 799

received 2-3 doses of the HPV vaccine. The weighted prevalence of HPV 6, 11, 16, and 18 infections was statistically significantly lower in individuals who received 1 dose (0.3%, 95% confidence interval [CI] = 0.0% to 0.9%; $P = .01$) or 2-3 doses (0.4%, 95% CI = 0.0% to 1.2%; $P = .05$) compared with unvaccinated individuals (1.2%, 95% CI = 0.9% to 1.6%) (Table 1). There was no statistically significant difference in prevalence of HPV 6, 11, 16, and 18 for 1 dose vs 2-3 doses. Additionally, there were no statistically significant differences in prevalence of cross-protection and other high-risk serotypes by number of administered vaccine doses.

In the adjusted analysis, the predicted probability of infection with HPV 6, 11, 16, and 18 was lower in individuals who received 1 dose (0.4%, 95% CI = 0.3% to 0.4%) or 2-3 doses (0.6%, 95% CI = 0.5% to 0.7%) compared with unvaccinated individuals (1.4%, 95% CI = 1.4% to 1.5%) (Table 2). Current smokers had a greater predicted probability of infection (3.3%, 95% CI = 3.1% to 3.5%) vs nonsmokers (0.7%, 95% CI = 0.6% to 0.7%) or former smokers (0.7%, 95% CI = 0.7% to 0.8%), as did individuals who initiated oral sex at ages 17 years or younger (2.0%, 95% CI = 1.8% to 2.1%) vs those aged older than 17 years (0.7%, 95% CI = 0.6% to 0.7%) and those with more than 2 (1.8%, 95% CI = 1.7% to 1.9%) vs 2 or less oral sexual partners (0.6%, 95% CI = 0.6% to 0.6%).

To our knowledge, our study is one of the first to suggest that individuals who receive 1 dose of the HPV vaccine may show similar prevalence of oral HPV 6, 11, 16, and 18 infections as those who receive additional doses. Although prior studies have demonstrated lower oral HPV infections among vaccinated individuals, these studies do not evaluate how prevalence differs by vaccine doses (9,10). Our findings also suggest that tobacco use, increased number of oral sexual partners, and earlier oral sexual debut are associated with higher risk of oral HPV infection, which is consistent with prior literature (11,12).

A strength of our study is the use of a large national, highly representative sample of the population in the United States. However, despite our novel findings, there are a number of

Table 2. Predicted probability of oral HPV type 6, 11, 16, and 18 infection by risk factors, NHANES 2009-2016

Factors	Predicted probability of infections, % (95% CI) ^a	Differences in predicted probability, % (95% CI) ^{a,b}
HPV vaccine dose		
1	0.4 (0.3 to 0.4)	Referent
0	1.4 (1.4 to 1.5)	1.1 (1.0 to 1.2)
2-3	0.6 (0.5 to 0.7)	0.2 (0.1 to 0.3)
Sex		
Female	0.7 (0.61 to 0.7)	Referent
Male	2.2 (2.0 to 2.3)	1.5 (1.4 to 1.7)
Race and ethnicity		
Black	2.0 (1.7 to 2.2)	0.5 (0.3 to 0.7)
Mexican American	0.4 (0.4 to 0.5)	-1.0 (-1.1 to -0.9)
Other Hispanic	0.6 (0.5 to 0.7)	-0.9 (-1.0 to -0.7)
White	1.5 (1.4 to 1.6)	Referent
Other ^c	0.7 (0.6 to 0.8)	-0.8 (-0.9 to -0.6)
Smoking status		
Nonsmoker	0.7 (0.6 to 0.7)	Referent
Former smoker	0.7 (0.7 to 0.8)	0.1 (0.0 to 0.2)
Current smoker	3.3 (3.1 to 3.5)	2.6 (2.4 to 2.8)
Age at first oral sex ^d		
≤17 y	2.0 (1.8 to 2.1)	Referent
>17 y	0.7 (0.6 to 0.7)	-1.3 (-1.4 to -1.2)
No. of lifetime oral sexual partners ^d		
≤2	0.6 (0.6 to 0.6)	Referent
>2	1.8 (1.7 to 1.9)	1.2 (1.1 to 1.3)

^aThe multivariable model was adjusted for HPV dose, age, sex, race and ethnicity, smoking, age at first oral sex, and number of lifetime oral sexual partners. The model included all individuals with complete information on all variables (n = 4127). CI = confidence interval; HPV = human papillomavirus; NHANES = National Health and Nutrition Examination Survey.

^bRisk of HPV infections in comparison to the indicated reference group adjusting for all variables in the model.

^cOther race includes Asians, multiracial, and other race.

^dMedian value was used as the cutoff.

limitations, including its retrospective nature and small sample size. Because self-reported immunization is prone to recall and misclassification bias, conclusions about the efficacy of a single-dose regimen are limited. Other limitations include lack of data regarding age at vaccination and assessment of the duration of immunity against HPV; as such, we cannot make conclusions regarding the temporal relationship between vaccination and oral HPV infection. Moreover, it is important to note that our findings do not imply that 1 dose of the HPV vaccine is sufficient for protection against oral HPV. Prospective studies are ongoing and may shed light on the efficacy of a single-dose regimen for sustained protection against oral HPV.

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Data Availability

The data underlying this article were provided by the National Health and Nutritional Examination Survey (NHANES). Data will be shared on request to the corresponding author with permission from NHANES.

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