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Effect of vaccination against oral HPV-16 infection in high school students in the city of Cali, Colombia

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ABSTRACT

Introduction: In recent years, an association between HPV-16 and oropharyngeal cancers has been reported. Therefore, it is necessary to evaluate whether vaccination decreases the exposure of HPV-16 in the oral cavity.
Objective: To evaluate the effect of vaccination on oral HPV-16 infection in high school students in the city of Cali, Colombia.
Methods: In this cross-sectional study, HPV-16 DNA was detected in samples from the oral cavity and throat of 1,784 high school students of both genders, aged 14–17 years old, in 21 schools in the city of Cali, Colombia. The number in vaccinated girls were 944 vs., 95 unvaccinated girls and 745 unvaccinated boys.
Results: The HPV exposure percentages were: 0.7% in vaccinated girls, 3.2% in unvaccinated girls and 2.3% in unvaccinated boys. The odds ratio (OR) of detection of HPV-16 in vaccinated versus unvaccinated students was 0.28 (95% CI: 0.07–0.88), representing a 72% reduction in HPV-16 detection in students immunized with two doses. The odds of detection of HPV-16 in unvaccinated male students were 3.6 times those of vaccinated girls (OR = 3.6, 95% CI: 1.21–12.81) and increased to almost eight-fold in boys who had initiated sexual activity (OR = 7.74, 95% CI: 1.53–75.09).
Conclusions: HPV vaccination was associated with the reduction of HPV-16 exposure percentages in the oral and oropharyngeal cavity.

1. Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus with more than 150 genotypes [1]. Approximately 40 of them are transmissible through direct contact during vaginal, anal and oral sex. More than half of the sexually active population is infected with one or several HPV genotypes at an early age, but the infection resolves spontaneously in most individuals. HPV is a necessary but not enough causative agent for the development of cervical cancer, with the HPV-16 and HPV-18 genotypes accounting for almost 70% of all cases [2,3]. HPV can also cause anal cancer; 85% of anal cancer cases are caused by HPV-16. This virus also causes vaginal, vulvar and penile cancer; almost half of the cases of these cancers are associated with HPV-16 and HPV-18 [4].

In recent years, the association of HPV-16 with oropharyngeal cancers of the soft palate, base of the tongue and tonsils has been reported [5,6]. Although most cancers of the oropharynx have traditionally been associated with the use of tobacco and alcohol, 30% of these types of tumors are now considered to be related to oral HPV-16 infection, which is transmitted mainly through oral sex, based on existing data [7,8]. However, studies have shown that the geographical area is also a risk factor in the prevalence of oropharyngeal cancer positive for HPV: geographic location seems to have a strong association with HPV positivity in carcinoma of the oropharynx, independently of smoking [9]. Worldwide, the incidence of oropharyngeal cancer associated with HPV-16 has increased over the past 20 years, especially in men. It has been estimated that by 2020, HPV will cause more oropharyngeal cancers than cervical cancers in higher-resource countries

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such as the United States [10].

In 2018 for Colombia, the estimated age-standardized incidence rates (ASR) in cancers of the oral cavity and oropharynx were 1.5 and 0.82 per 100,000, respectively, both sexes, all ages [11]. Compared with Brazil, the most populous South American country and the first regional power, both the ASR of cancers of the oral cavity and oropharynx, as well as, cigarette smoking is lower in Colombia [12]. Therefore, it is essential to evaluate HPV exposure percentages in the oral cavity and oropharynx in the context of Colombian population epidemiological profiles. For example, in Colombia, the city of Cali, HPV was found in 67% of oral cavity cancer [13] and the city of Medellin, HPV was found in 23.9%, and 13.3% of oral cavity, and oropharynx cancer cases respectively [14]. These studies suggest that the prophylactic HPV vaccines may have a potential to reduce the number of oral cavity and oropharynx cancers cases in Colombia, and therefore, it is essential to do studies to evaluate the efficacy of these vaccines in the prevention of HPV oral infection.

The recognition of HPV as the principal causative agent of cervical cancer and its precursor lesions led to the development of prophylactic vaccines, with the primary objective of preventing HPV infection [15,16]. The HPV vaccine could provide additional benefits in the prevention of other types of cancers associated with the virus. Currently, three commercial vaccines against HPV have been approved by the FDA: Gardasil, Gardasil 9 and Cervarix [17,18]. All these vaccines protect against the HPV-16 and HPV-18 genotypes. The Gardasil vaccine also protects against genotypes HPV-6 and HPV-11, which cause 90% of genital warts [18]. The Gardasil 9 vaccine helps prevent infection by the four previously mentioned HPV genotypes plus another five high-risk HPV genotypes: HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, which are responsible for an additional 20% of cervical cancers [19]. It is estimated that the Gardasil 9 vaccine could prevent 90% of cervical cancers.

Since 2012, the Ministry of Health and the National Institute of Health of Colombia, through their Immunization Program (PAI, initials in Spanish) have implemented free vaccination against HPV with the Gardasil 4 vaccine only in school-aged girls from 9 to 17 years old. The program features a three-dose vaccination schedule (at 0, 2 and six months) and has achieved coverage levels of 98%, 96.6% and 89.2% for the first, second and third dose, respectively [20]. In 2018, the vaccination schedule was changed to two doses (at 0 and six months) to only girls and woman from 9 to 18 years old [21]. However, although the HPV vaccine is safe and effective [22], the vaccination coverage has decreased in Colombia in recent years, due to a massive psychogenic reaction in a small village of the Caribbean region in 2014, where 15 adolescent girls were admitted to the local hospital with bizarre symptoms months after receiving the vaccine. Unfortunately, some parents and anti-vaccine groups attribute the HPV vaccine for what happened until now [23]. To figure out what was happening, The Ministry of Health of Colombia send their medical teams, and a thorough study was carried out that showed that no infectious nor post-vaccine adverse event was to be pointed as the cause of the symptoms [24]. Therefore, the decrease in the number of women vaccinated against HPV in recent years in Colombia requires conducting scientific studies and massive educational and awareness campaigns to explain the benefits of vaccination against HPV infection to parents, educators, health personnel and society in general, so that soon the risk of developing the cancers associated with HPV can be reduced.

The main objective of this study was to determine the effect of HPV vaccination on the HPV-16 exposure percentages in the oral cavity and oropharynx of high school students aged 14–17 years old in the city of Cali, Colombia.

2. Materials and methods

2.1. Study population

The participants were students in public or private high schools registered with the Municipal secretary of Education of Cali, aged between 14 and 17 years, both sexes, complied with the informed consent process and agreed to participate in the study by reading and signing an informed consent form. Consent was provided by the students and their legal representatives. The high schools were selected by convenience using the PAI immunization program databases of the Health municipal secretary of Cali, which lists the educational institutions where girls' students received at least two doses of the HPV vaccine.

For the exclusion criteria, we assigned students' vaccination status based on the number of visits made by the PAI to the school; additionally, DNA samples with poor integrity as determined by PCR amplification of a 110-bp fragment of the human beta-globin gene were excluded from analysis.

2.2. Questionnaire and biological sample collection

Before biological sample collection, each participant completed an anonymous self-assessment questionnaire, with information on sociodemographic characteristics, sexual behavior and HPV vaccination status. Each student's inquiry and biological samples were labeled with the same code, guaranteeing the anonymity of each participant.

Biological sample collection consisted of mouth rinsing for 15 s and gargling for 15 s with 15 mL of pathogenic bacteria-free commercial water. This method was done to collect oral cells from the oral and oropharyngeal cavity. Subsequently, the sample was placed in a 50-mL sterile Falcon test tube. The test tubes with the samples were maintained at 4 °C during transportation to the Molecular Pathology Laboratory of the School of Medicine at Universidad del Valle for processing. The period between the acquisition of the samples and processing was immediately, and after that, the DNA samples were stored - 20C.

For the DNA amplification procedures, the laboratory personnel did not know the identity or vaccination status of the participant from whom the DNA sample came, to guarantee the veracity of the test results. For both detection procedures, HPV-18 DNA obtained from HeLa cells was used as a positive control, and a preparation that did not include a biological sample or viral DNA was used as a negative control.

2.3. DNA extraction

DNA extraction was performed with the PrepMan® Ultra Sample Preparation Reagent commercial extraction kit, following the manufacturer's protocol. Then, using a Nanodrop 2000 spectrophotometer, the concentration and purity of the DNA samples were determined based on the 260/280 absorbance ratio. The degree of DNA integrity was assessed by conventional PCR amplification of a 110-bp fragment of the human beta-globin gene. For the PCR, the PCO3 (ACA CAA CTG TGT TCA CTA GC) and PCO4 (CAA CTT CAT CCA CGT TCA CC) primers were used. Amplification was performed in 35 cycles at 95 °C for 20 s, 55 °C for 45 s and 75 °C for 45 s. The amplified products were visualized by electrophoresis in 1% agarose gel with ethidium bromide staining [13].

2.4. HPV detection

HPV-16 detection was performed by real-time PCR using specific primers for this viral genotype in a CFX96™ Touch Real-Time PCR thermal cycler (Bio-Rad). The primers used were as follows: HPV16_E6F 5′-GAG CAA TGC GTT AAT TCA GGA CC-3'; y HPV16_E6R 5′-TGT TGT AGT TTG ATA CAG CTC TGT GC-3'. The reaction mix included 20 µL of 2x QuantiTect SYBR Green PCR kit (Qiagen, Helden, Germany) and

0.3 μM of primers. Reaction conditions were as follows: incubation for 10 min at 95 °C, followed by 40 cycles of amplification at 95 °C for 15 s and 60 °C for 1 min each [13]. Next, the samples negative for HPV-16 were screened using conventional PCR and GP5+/GP6+ generic primers that amplify a 150-bp fragment of the viral L1 gene [25]. The positive samples were subsequently identified by direct sequencing using the Sanger method. The viral nucleic acid sequences were genotyped by analysis of percent identity in sequence alignment using the BLASTn-NIH algorithm (https://blast.ncbi.nlm.nih.gov/). The reference sequences for the HPV genotypes were obtained from the GenBank-NCBI-NIH repository (https://www.ncbi.nlm.nih.gov/taxonomy/?term=HPV).

2.5. Data analysis

HPV-16 detection (yes/no) was defined outcome variable. Also, participants were classified into one of three groups according to their HPV vaccination status and gender: vaccinated girls; unvaccinated girls; and unvaccinated boys. The vaccinated boys not were included in the analysis due to that the PAI immunization program only had records of free doses received in vaccinated girls.

To assess the association between HPV-16 detection by independent variables, such as gender, age, grade level, and sexual behavior in all students; and by the number of doses received among vaccinated girls, bivariate analyses were done. Furthermore, a logistic regression model, adjusted by covariates significantly associated in the bivariate analysis was used. Variables that were significant ($p < 0.05$) in the bivariate analyses to the outcome variable for each case and those considered relevant based on the previous literature, such as sexual activity status and gender, were adjusted in the logistic regression models to estimate the adjusted odds ratio (OR). The statistical package Stata (Version 13.0, College Station, TX, USA) was used to perform data management and all statistical analyses.

2.6. Ethical considerations

The present study was approved by the Ethics Committee on Human Research of Universidad del Valle under number 011–014 of 2014.

3. Results

Of the 1,900 students, 116 were excluded from the study because 110 did not meet the inclusion criteria for DNA integrity based on amplification of the beta-globin gene. An additional six students were excluded because they reported receiving the HPV vaccine but, the information they provided did not match the number of visits made to the school by the PAI HPV vaccination program.

Of the 1,784 students included in the study, 72% were 15 years or older, and 51% were in the tenth and eleventh grades. In the group of 745 unvaccinated boys, 42% reported having had sex; this percentage was higher than those found by the groups of vaccinated and unvaccinated girls, which were 36.6% and 36.8% respectively (Table 1).

The percentage of HPV detection were: 0.7% in vaccinated girls, 3.2% in unvaccinated girls and 2.3% in unvaccinated boys. The detection rate was higher in the unvaccinated groups ($p = 0.01$).

Regarding the HPV genotypes, HPV-16 was identified in 0.53% of vaccinated girls, whereas in unvaccinated girls and unvaccinated boys the detection rates were 2.1% and 1.9%, respectively. Prevalence was higher in the unvaccinated groups ($p = 0.02$). Other identified HPV genotypes were HPV-6 and HPV-32, each of which was detected in 0.06% of samples, and HPV-66, which was discovered in 0.22% of samples.

Table 2 shows the OR for detection of HPV-16 according to the number of vaccine doses received age, grade level, and sexually active status. The OR for HPV-16 exposure in students who had received two doses of the vaccine compared to the unvaccinated students was 0.28 (95% CI: 0.07–0.88). There was a 72% reduction in HPV-16 infections in students who received two doses of the vaccine. The data also suggest an increased risk of infection with HPV-16 in the older students, in the more advanced grades and in those who reported being sexually active, but these findings were not statistically significant.

Table 3 shows the OR for HPV-16 detection according to gender, vaccination status, and sexually active status. The percentages of HPV 16 detection were higher in boys compared to girls, with an OR of 2.82 (95% CI: 1.06–8.30). When comparing the prevalence of HPV-16 in the group of unvaccinated boys with vaccinated girls as a reference, an OR of 3.6 (95% CI: 1.21–12.81) was observed. Thus, the odds of detecting HPV-16 in high school students were 3.6 times higher in unvaccinated boys than in vaccinated girls. Additionally, the odds of HPV-16 detection increased to 7.74 (95% CI: 1.53–75.09) when the analysis was adjusted for gender.

4. Discussion

In 2007, the IARC declared that HPV-16 is the necessary, but not enough, the causative agent for the development of a subset of cancers of the head and neck, specifically in some instances of oropharyngeal cancer that mainly affect males [26]. However, in most countries, including Colombia, free HPV vaccination campaigns target girls only. This strategic is because, in developing countries, cervical cancer is the first or second most common cancer, which is why the World Health Organization (WHO) recommended priority vaccination only in girls. Just a few countries such as the United States, Canada, Australia, and some European countries and Argentina have begun to provide the HPV vaccine free of charge for both girls and boys. And then, to decrease infection in other parts of the body, such as the oral cavity, throat and anogenital region in both genders, to possibly increase the protective effect of immunization against cancers associated with HPV [27].

In the present study, HPV was detected more frequently in unvaccinated students compared to the group of vaccinated female students (Table 1). As this is a pioneering study in the region due to the type of sample and the age of the population studied, it was not possible to make comparisons across Latin America. However, studies conducted in Poland reported HPV detection in the oral and oropharyngeal cavity in 1.1% of a sample of 4,150 students aged 10–18 years old (1.08% in boys and 1.13% in girls) [28]. A study conducted in Sweden with high school students detected HPV in the oral cavity in 3.1% of girls and 0.6% of boys [29]. The HPV detection rates found in the present study are equivalent to those reported by these two studies, and it is important to note that the genotype identified was HPV-16, which is responsible for the development of 50% of cases of cervical cancer in females and identified in almost 90% of cases of oral and oropharyngeal cancers positive for HPV [30].

In the United States, the detection rates of HPV in the oral and oropharyngeal cavity in adolescents were 1.5% in participants 12–15 years old and 3.3% in the 16–20 age group [31]. These findings suggest that oral HPV infection increases with age. This pattern was also observed in our study. When comparing the rate of HPV-16 detection by age group, a rate of 1.25% was found in participants who were 15 years or older, which was higher than the rate seen in those who were less than 15 years old (0.99%) (Table 2). A similar difference was observed when comparing the HPV-16 detection rate by grade level and in students who reported being sexually active, the main risk factor for HPV-16 transmission.

Studies in various parts of the world have suggested that adolescents are at similar stages of sexual development at this stage of life, characterized by physical, sexual, psychological and cognitive changes. However, in specific populations, these changes can be very complex due to cultural and social factors [32]. For example, in Latin American countries, a trend toward initiation of sexual activity at increasingly younger ages [33–37] has been reported; this may result in an increased risk of transmission of pathogenic viruses and sexually transmitted

Table 1
Participant variables by sex and vaccination status.

Variable	Vaccinated Girls	Unvaccinated Girls	Unvaccinated Boys	Total
	(n = 944)	(n = 95)	(n = 745)	(n = 1,784)
		N (%)		
Age (years)				
< 15	273 (28.92)	26 (27.37)	205 (27.52)	504 (28.25)
≥ 15	671 (71.08)	69 (72.63)	540 (72.48)	1,280 (71.75)
Grade level *				
6-9	444 (47.03)	49 (51.58)	390 (52.35)	883 (49.50)
10-11	500 (52.97)	46 (48.42)	355 (47.65)	901 (50.50)
Sexually active †				
No	598 (63.35)	60 (63.16)	429 (57.58)	1,087 (60.93)
Yes	346 (36.65)	35 (36.84)	316 (42.42)	697 (39.07)
HPV detection ‡				
Negative	937 (99.26)	92 (96.84)	728 (97.72)	1,757 (98.49)
Positive	7 (0.74)	3 (3.16)	17 (2.28)	27 (1.51)
Genotypes				
HPV-6	-	-	1 (0.13)	1 (0.06)
HPV-16	5 (0.53)	2 (2.11)	14 (1.88)	21 (1.18)
HPV-33	1 (0.11)	-	-	1 (0.06)
HPV-66	1 (0.11)	1 (1.05)	2 (0.27)	4 (0.22)

*Vaccinated girls vs., unvaccinated boys by HPV detection, *chi-square P = 0.008*.
†Vaccinated girls vs., unvaccinated boys by grade level, *chi-square P = 0.030*.
‡Vaccinated girls vs., unvaccinated boys by sexually activity, *chi-square P = 0.016*.
Vaccinated girls vs., unvaccinated girls by HPV detection, *chi-square P = 0.021*.

Table 2
The odds ratio of HPV-16 detection according to the number of HPV vaccine doses received age, grade level and sexual activity in high school students.

Variable	HPV-16		OR (95% CI)
	Positive	Negative	
	(n = 21)	(n = 1,763)	
	N (%)		
Vaccine doses received			
None	16 (1.90)	824 (98.10)	1
One dose	1 (0.47)	210 (99.53)	0.24 (0.01–1.60)
Two doses	4 (0.55)	729 (99.45)	0.28 (0.07–0.88)*
Age (years)			
< 15	5 (0.99)	499 (99.01)	1
≥ 15	16 (1.25)	1,264 (98.75)	1.26 (0.44–4.43)
Grade level			
6-9	6 (0.68)	877 (99.32)	1
10-11	15 (1.66)	886 (98.34)	2.47 (0.90–7.82)
Sexually active			
No	9 (0.83)	1,078 (99.17)	1
Yes	12 (1.72)	685 (98.28)	2.10 (0.80–5.67)

*Statistically significant, *p = 0.01*.

Table 3
The odds ratio for HPV-16 detection according to gender and adjusted by vaccination and sexual activity status, in high school students aged 14–17 years old.

Variable	HPV-16		OR (95% CI)
	Positive	Negative	
	(n = 21)	(n = 1,763)	
	N (%)		
Gender			
Girl	7 (0.67)	1,032 (99.33)	1
Boy	14 (1.88)	731 (98.12)	2.82 (1.06–8.30)*
Gender + Vaccination status			
Vaccinated girls	5 (0.53)	939 (99.47)	1
Unvaccinated girls	2 (2.11)	93 (97.89)	4.04 (0.38–25.03)
Unvaccinated boys	14 (1.88)	731 (98.12)	3.60 (1.21–12.81)†
Gender + Vaccination status + Sexually active (SA) status			
Vaccinated girls	2 (0.33)	596 (99.67)	1
Vaccinated girls + SA	3 (0.87)	343 (99.13)	2.06 (0.30–31.31)
Unvaccinated girls	1 (1.67)	59 (98.33)	5.05 (0.08–97.92)
Unvaccinated girls + SA	1 (2.86)	34 (97.14)	8.70 (0.14–170.8)
Unvaccinated boys	6 (1.40)	423 (98.6)	4.22 (0.75–42.95)
Unvaccinated boys + SA	8 (2.53)	308 (97.47)	7.74 (1.53–75.09)‡

*Statistically significant, $p = 0.02$.
†Statistically significant, $p = 0.01$.
‡Statistically significant, $p = 0.01$.
Note: the adjustment was made using Fisher's exact test.

infections in younger age groups. According to the results of the National Demographic and Health Survey (Encuesta Nacional de Demografía y Salud - ENDS) conducted in Colombia in 2015, the median age at first sexual intercourse for girls was 17.7 years among women aged 25–49 years, whereas in men, sexual intercourse starts approximately 1.5 years earlier than in women [38]. Also, the same study indicated that 16.3% of females and 33% of males between 15 and 24 years had their first sexual intercourse before age 15. When analyzing the change in the median age of first sexual intercourse in recent decades, there is a trend toward initiating sexual activity at increasingly younger generations.

In our study, the percentage of male students between 14 and 17 years who have had intercourse was 42.4% (Table 1). This percentage was significantly higher than that reported by girls, suggesting that unvaccinated males have a higher risk of becoming infected with sexually transmitted viruses such as HPV-16 at an early age. In the statistical analysis, unvaccinated male students had 3.6-fold higher odds of testing positive for HPV-16 in the oral cavity and oropharynx compared to the vaccinated female students. Also, when this result was adjusted for sexually active status, the odds ratio increased to 7.7 (Table 3). The percentage of HPV-16 detection rate was higher in girls who were not treated compared to those who were vaccinated.

To quantify the effect of vaccination against HPV in students, the HPV-16 detections were compared between the unvaccinated students

and vaccinated students, stratified by the number of vaccine doses received (Table 2). The results showed a 72% reduction in HPV-16 detection in the oral and oropharyngeal cavity in students who had received two doses of the vaccine compared to the reference group. Likewise, many unvaccinated boys who tested positive for HPV were sexually active, unlike vaccinated girls, which suggests also that girls are protected because fewer are sexually active or because the infection is transmitted less commonly from males to females than from females to men, and not from having received the vaccine.

The HPV-16 detection was higher in this group compared to vaccinated girls (2.1% vs. 0.5%, respectively), but this difference was not significant concerning protection from the vaccine (Table 3). Our results support the findings from the Guanacaste cohort in Costa Rica in 2013, which showed that the HPV vaccine provides reliable protection against oral HPV-16 infection in vaccinated young women [39].

The study shown limitation in the number of unvaccinated girls as well as vaccinated boys in recruiting due to vaccination policies in Colombia as above was mentioned. For these reasons, in order to control for the effect of the sampling design on the prevalence estimation, first we proposed only to do the association analysis between vaccinated students (nearly all of them girls) vs., unvaccinated students (almost all of them boys), however, the oral HPV infection prevalence greatly varies by gender, and, in addition, we found sexual activity differences between gender as well (Table 1). So, we decided to adjust the logistic model by gender and sexual activity, and we found that not only the HPV vaccine but not having sexual activity, reduce the risk of HPV exposure in the oral cavity (Table 3).

5. Conclusions

The results of the present study are substantial to discuss the strategy of vaccinating in Colombia that only included girls, and that is necessary the vaccination in boys as well, because they have more risk on HPV infection due to early sexual activity debut. Besides, our results suggest that the treatment in boys will reduce the risk of HPV-positive males sexually transmitting the virus to their partners unknowingly in earlies ages. Although studies have shown that vaccinating only females against HPV can have a protective effect on their partners, this is possible just if vaccination coverage is above 90%. HPV vaccination programs such as the one implemented by the Australian government have shown that vaccinating males, and female free of charge decreased the HPV rate in females aged 18–24 from 22.7% to 1.1% between 2005 and 2015 [40]. Thus, HPV vaccination was associated with the reduction of HPV-16 exposure percentages in the oral and oropharyngeal cavity.

Conflicts of interest

None.

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