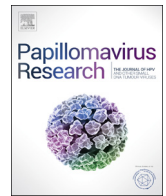




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## Seroprevalence of HPV 6, 11, 16 and 18 and correlates of exposure in unvaccinated women aged 16–64 years in Puerto Rico

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### ABSTRACT

**Background:** To understand risk factors for HPV exposure in Puerto Rican women, we evaluated HPV 6, 11, 16, and 18 serology in women aged living in the San Juan metropolitan area.

**Methods:** As part of a cross-sectional study, a population-based sample of 524 HPV unvaccinated Hispanic women ages 16–64 years completed face-to-face and computer assisted interviews and provided blood and self-collected anal and cervical specimens. Serology used multiplex virus-like particle based-IgG ELISA and HPV DNA was detected with L1-consensus PCR.

**Results:** 32% and 47% were seropositive to HPV types included in the bivalent (16/18) and quadrivalent (6/11/16/18) vaccines, respectively. Type-specific seroprevalence was HPV6 – 29%, HPV11 – 18%, HPV16 – 23%, and HPV18 – 17%; seroprevalence was high in the youngest age-group (16–19: 26–37%). HPV seropositivity was associated with having  $\geq 3$  lifetime sexual partners (OR = 2.5, 95% CI = 1.7–3.9) and detection of anogenital HPV DNA (OR = 1.8, 95% CI = 1.2–2.6).

**Conclusions:** The high cumulative exposure of HPV vaccine types 6/11/16/18 in this Hispanic population was influenced by factors related to HPV exposure through sexual behavior. High seroprevalence in the youngest age-group indicates early age of exposure to HPV in Puerto Rico, highlighting the need for HPV vaccination starting prior to age 16.

### 1. Introduction

Over 190 types of Human papillomavirus (HPV) have been identified, of which 14 types are classified as high-risk types [1]. In women, infection with high risk HPV types has been associated with cancers of the cervix, vulva, vagina, anus, and oropharynx [2]. HPV 16 and 18 are responsible for about 70% of cervical cancer cases worldwide [3], whereas two other types (6 and 11) have been linked to 90% of genital warts [4]. It is estimated that 66% of cervical cancers and 80% of anal cancers in women in the United States (US) are attributed to HPV 16 and 18, whereas 15% of cervical cancers and 11% of anal cancers are attributed to other high risk-HPV types 31/33/45/52/58 [5]. HPV-related cancers continue to be a burden world-wide [6]. In the US the incidence of HPV-related cancers in women is estimated to be 13.5 per 100,000 compared with corresponding incidence estimates in Puerto

Rico of 16.5 per 100,000 [7]. Puerto Rico also had the highest rate of cervical cancer incidence (11.7 per 100,000) for all US states and territories from 2008 to 2012 [7]. Currently, there are three available prophylactic HPV vaccines that provide type-specific protection against anogenital neoplasia in individuals previously naïve to the vaccine type: bivalent (2vHPV) vaccine (HPV 16/18), quadrivalent (4vHPV) vaccine (HPV 6/11/16/18), and nonavalent (9vHPV) vaccine (HPV 6/11/16/18/31/33/45/52/58).

In an unvaccinated population HPV serology is used to estimate cumulative exposure despite the recognition that this would be an underestimate because of the low seroconversion rate; only about 34–63% of women with detectable HPV DNA seroconvert [8,9]. National Health and Nutritional Examination Survey (NHANES) data from prevaccine era (2003–2006) indicates seropositivity to any of the four HPV quadrivalent vaccine types was 31.8% among US women aged

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14–59 years [10] and was lowest in the youngest age group (14–19 years). Data for the 9vHPV types (NHANES 2005–2006) indicate about 40% of females were exposed to at least one of the 9 types and provide some evidence of variation by race/ethnicity [11]. Puerto Rico is not sampled as part of NHANES, and data on HPV in this Hispanic population is limited. In a subsample of a population-based household survey conducted in 2007–2008 among individuals aged 21–64 years, 15.8% of women were seropositive to HPV 16 [12]. This study determines 2010–2013 seroprevalence to HPV 6, 11, 16 and 18 among a population-based sample of Hispanic women aged 16–64 years living in the San Juan metropolitan area (SJMA) of Puerto Rico and describes epidemiologic correlates of seropositivity.

## 2. Materials and methods

### 2.1. Study population

The surveillance study design and methodology has been described elsewhere [13]. In brief, the population-based sample was selected following a cluster probability sampling design with unequal selection probability of households in the SJMA and proportional allocation by age. From each selected household, only one eligible female was invited to participate. Inclusion criteria included sexually active women, aged 16–64 years, not pregnant, residing in the selected households, and with no history of HIV diagnosis. A total of 566 women aged 16–64 years living in the SJMA were recruited between 2010 and 2013. As there is no clear demarcation of race in Puerto Rico, this variable was not assessed. Nonetheless, all study participants were of Hispanic origin. Data collection consisted on a home based face-to-face personal interview and an Audio Computer Assisted Self-Interview (ACASI) system. The personal interview included socio-demographic, lifestyles and reproductive characteristics, as well as history of HPV vaccination. The ACASI collected information on sexual behavior and lifetime drugs use. Participants provided cervical and anal self-collected samples for HPV DNA testing and blood samples for HPV serology. Among recruited women, 94% (530/566) provided blood samples. Of these 530, an additional 6 women with history of HPV vaccination reported in the study questionnaire were excluded, resulting in a study sample of 524 women for this analysis. The study protocol was approved by the University of Puerto Rico-Medical Sciences Campus (UPR-MSC) Institutional Review Board (IRB).

### 2.2. Analysis of biological specimens

Antibodies to the 4vHPV vaccine types HPV 6, 11, 16, and 18 were measured using a multiplex L1-virus-like particle (VLP) based IgG enzyme-linked immunosorbent assay (M4ELISA) at the Centers for Disease Control and Prevention (CDC) in Atlanta as previously described [14]. Assay thresholds for seropositivity were set at  $\geq 99\%$  relative light units (RLU) limits of children's sera that fit a Johnson-Su distribution [14].

DNA was extracted from anogenital samples as previously described [15]. Extracts were tested for HPV using L1 consensus primer polymerase chain reaction (PCR) with MY09/MY11 primers sets and  $\beta$ -globin as an internal control for sample amplification. PCR products from positive samples were typed for 38 HPV types by dot-blot hybridization using type-specific probes and two mixes, as previously described [15]. Samples negative for  $\beta$ -globin were considered inadequate and excluded from the analysis.

### 2.3. Statistical analysis

Frequency distributions were used to describe the study population and HPV seroprevalence, both overall and by specific HPV types evaluated. Bivariate associations between two HPV outcomes [seropositive for any (1) HPV types included in the 2vHPV (HPV 16 or 18) and (2)

HPV types included in the 4vHPV (HPV types 6, 11, 16 or 18)] and potential correlates were performed using the chi-square statistic. A multivariable logistic regression model (MLRM) using an estimable generalized equations approach for controlling the correlation between the measurements of women living in the same households' block was fitted. Significant correlates associated to any of the two HPV outcomes in the age-adjusted analyses ( $p < 0.05$ ) were included in the MLRM. Prevalence odds ratios (POR) with 95% confidence interval (CI) of seropositivity outcomes were estimated. We assessed antibody levels among seropositive women, for each HPV type, using Mann-Whitney or Kruskal-Wallis tests. Data was analyzed using STATA/SE 13.0 (Stata Corporation, College Station, TX).

## 3. Results

### 3.1. Characteristics of the study population

The majority of women in the study had healthcare coverage (90%), about half were married/cohabitating (53%), and 32% of women reported history of smoking. Most of the respondents initiated sexual activity at 15 years or older (85%), more than two thirds reported having at least three lifetime sexual partners (68%), 70% reported having had anal sex, and 90% had engaged in oral sex. Overall, 53% were positive for anogenital HPV DNA infection at the time of study participation, and 35% had a history of abnormal pap smears (Table 1). Only 2 women reported history of cervical cancer, and none reported history of anal cancer.

### 3.2. HPV seroprevalence

Overall 47% ( $n = 246$ ) of women were seropositive for at least one of the HPV vaccine types evaluated (HPV 6, 11, 16 and 18), 35% ( $n = 185$ ) were positive for HPV 6 or 11%, and 32% ( $n = 166$ ) were positive for oncogenic HPV 16 or 18. Type-specific seroprevalence was highest for HPV 6 ( $n = 151$ , 29%) and 16 ( $n = 122$ , 23%), followed by HPV 11 ( $n = 95$ , 18%) and 18 ( $n = 87$ , 17%). Seroprevalence was high in the youngest age-group (16–19 year old), ranging from 26% for HPV 6–37% for HPV 16. Only 4% ( $n = 20$ ) of women were seropositive for all types, 6% ( $n = 33$ ) for 3 types, 16% ( $n = 83$ ) for two types and 21% ( $n = 110$ ) for a single HPV type (data not shown). The trends in type-specific antibodies by age groups is shown in Fig. 1. While HPV 6 and HPV 11 showed no significant trend, HPV 16 and HPV 18 both showed significant decreases with increasing age group ( $p < 0.05$ ). We found no evidence of significant differences of antibody levels of the HPV types evaluated between age categories or lifetime sexual partners among women seropositive for each HPV type (data not shown).

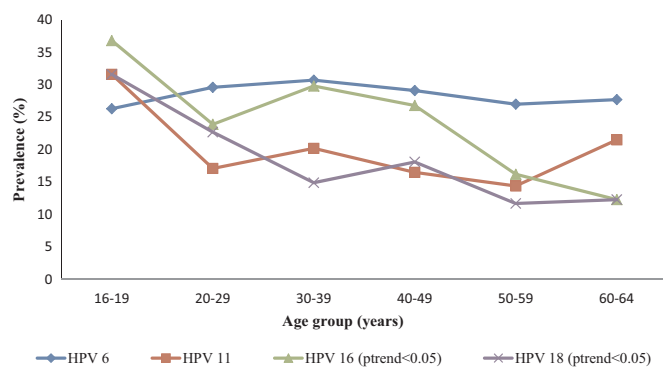
### 3.3. Correlates of HPV 16/18 and 6/11/16/18 seroprevalence

In agreement with trends by age-group shown in Fig. 1, the seroprevalence of HPV 16/18 and HPV 6/11/16/18 was higher in younger women, with significant results for HPV 16/18 (Table 1). The prevalence of HPV 16/18 types was also higher for women with public health insurance (37.6%), those with age of sexual debut  $< 15$  years (42.9%), those with at least three lifetime sexual partners (38.3%), and those with current anogenital HPV DNA infection (37.4%). Higher seroprevalence for HPV 6/11/16/18 was observed for single women (51.3%) and those divorced, separated or widowed (53.9%) ( $p = 0.043$ ). Higher seroprevalence for HPV 6/11/16/18 vaccine types was also observed for women with public health insurance (54.6%), those with at least three lifetime sexual partners (55.5%), those who had ever had anal sex (50.0%), and those with current anogenital HPV infection (56.5%) ( $p < 0.05$ ) (Table 2).

**Table 1**  
Characteristics of study population, unvaccinated women aged 16–64 years living in the San Juan metropolitan area of Puerto Rico (n = 524).

Variable	Overall n (Column%)
All Respondents	524 (100)
Age (years)	
16–34	166 (31.7)
35–49	182 (34.7)
50–64	176 (33.6)
Education	
≤ 12 years	180 (34.5)
13–15	198 (37.8)
≥ 16	145 (27.7)
Marital Status	
Single	119 (22.7)
Married/Cohabit	275 (52.5)
Div/Sep/Widow	130 (24.8)
Health Care Coverage	
Private	260 (49.6)
Public	213 (40.7)
None	51 (9.7)
Smoking	
Never	356 (67.9)
Ever	168 (32.1)
Drugs Use	
Never	308 (58.8)
Ever	216 (41.2)
Age of Sexual Debut	
< 15 years	77 (14.7)
≥ 15 years	447 (85.3)
Lifetime sexual partners	
1–2	165 (31.7)
≥ 3	355 (68.3)
Anal Sex	
Never	158 (30.3)
Ever	364 (69.7)
Oral Sex (n = 522)	
Never	52 (10.0)
Ever	470 (90.0)
HPV any anogenital Infection	
No	244 (46.7)
Yes	278 (53.3)
History of Abnormal Pap Test (n = 505) <sup>a</sup>	
No	395 (78.2)
Yes	110 (21.7)

<sup>a</sup> On women who have ever had a pap test.



**Fig. 1.** Seroprevalence to HPV types 6, 11, 16 and 18 among unvaccinated women in Puerto Rico by age group (n = 524).

### 3.4. Multivariate analyses of factors associated with HPV 16/18 and HPV 6/11/16/18 seroprevalence

The fully adjusted logistic regression models showed that the number of lifetime sexual partners was the strongest factor associated with HPV seropositivity (POR<sub>HPV16/18</sub>: 2.4, 95% CI: 1.5–3.9; POR<sub>HPV6/11/16/18</sub>: 2.5, 95% CI: 1.7–3.9). Anogenital HPV DNA infection with HPV types 6/11/16/18 was associated with seropositivity to these same

**Table 2**  
Seroprevalence for HPV-vaccine types by demographic and lifestyle characteristics among unvaccinated women aged 16–64 years living in the San Juan metropolitan area of Puerto Rico (n = 524).

	HPV 16 /18 <sup>a</sup> n (Row %)	Chi-square P <sub>value</sub>	HPV 6/11/16/18 <sup>a</sup> n (Row %)	Chi-square P <sub>value</sub>
All Respondents	166 (31.7)		246 (47.0)	
Age (years)		0.001		0.077
16–34	<b>65 (39.2)</b>		89 (53.6)	
35–49	<b>63 (34.6)</b>		84 (46.2)	
50–64	<b>38 (21.6)</b>		73 (41.5)	
	<b>P<sub>trend</sub> &lt; 0.001</b>		<b>P<sub>trend</sub> = 0.025</b>	
Education (years)		0.424		0.205
≤ 12 years	62 (34.3)		90 (49.7)	
13–15	64 (32.3)		97 (49.0)	
≥ 16	40 (27.6)		59 (40.7)	
Marital status		0.299		<b>0.043</b>
Single	44 (37.0)		<b>61 (51.3)</b>	
Married/ Cohabiting	80 (29.1)		<b>115 (41.8)</b>	
Divorced/ Separated/ Widowed	42 (32.3)		<b>70 (53.9)</b>	
Health care coverage		<b>0.036</b>		<b>0.012</b>
Private	<b>69 (26.5)</b>		<b>106 (40.8)</b>	
Public	<b>80 (37.6)</b>		<b>116 (54.5)</b>	
None	<b>17 (33.3)</b>		<b>24 (47.1)</b>	
Smoking		0.964		0.087
Never	113 (31.7)		158 (44.4)	
Ever	53 (31.6)		88 (52.4)	
Age of sexual debut (years)		<b>0.022</b>		0.148
< 15	<b>33 (42.9)</b>		42 (54.6)	
≥ 15	<b>133 (29.8)</b>		204 (45.6)	
Lifetime number of sexual partners		<b>&lt; 0.001</b>		<b>&lt; 0.001</b>
1–2	<b>29 (17.6)</b>		<b>48 (29.1)</b>	
≥ 3	<b>136 (38.3)</b>		<b>197 (55.5)</b>	
Anal sex		0.104		<b>0.033</b>
Never	42 (26.6)		<b>63 (39.9)</b>	
Ever	123 (33.8)		<b>182 (50.0)</b>	
Oral sex (n = 522)		0.444		0.481
Never	14 (26.9)		22 (42.3)	
Ever	151 (32.1)		223 (47.5)	
HPV any anogenital infection		<b>0.002</b>		<b>&lt; 0.001</b>
No	<b>61 (25.0)</b>		<b>88 (36.1)</b>	
Yes	<b>104 (37.4)</b>		<b>157 (56.5)</b>	
History of Abnormal Pap Test (n = 505) <sup>b</sup>		0.336		0.265
No	121 (30.6)		181 (45.8)	
Yes	39 (35.45)		57 (51.8)	

<sup>a</sup> Refers to seroprevalence to any of the types indicated in each column.

<sup>b</sup> Among women that have ever had a Pap test.

HPV types (POR<sub>HPV6/11/16/18</sub>: 1.8, 95% CI: 1.2–2.6). No other significant associations (p < 0.05) were observed in the adjusted models (Table 3).

## 4. Discussion

This is the first study to describe the seroprevalence of HPV types 6, 11, 16 and 18 in a population-based sample of unvaccinated Hispanic women from Puerto Rico. The prevalence of HPV serum antibodies in our study ranged from 17% for HPV 18–29% for HPV 6. A direct comparison between HPV serology studies is difficult because methods are not standardized [16]. Although the type-specific estimates in our study are higher than those reported in women from the USA [10],

**Table 3**  
Multivariable logistic regression for HPV seropositivity according to demographic, life-style, sexual, and clinical characteristics.

Variable	HPV 16/18 OR <sub>adjusted</sub> (95% CI)	HPV 6/11/16/18 OR <sub>adjusted</sub> (95% CI)
Age (years)		
16–34	1.8 (1.0–3.1) *	1.2 (0.7–2.0)
35–49	1.6 (1.0–2.7)*	1.0 (0.6–1.6)
50–64	1.00	1.00
Marital status		
Married/Cohabiting	1.0	1.0
Single	1.0 (0.6–1.6)	0.9 (0.6–1.5)
Divorced/Separated/ Widowed	1.0 (0.6–1.6)	1.2 (0.7–1.9)
Health care coverage		
Private	1.0	1.0
Public	1.4 (0.9–2.1)	1.4 (1.0–2.1) ‡
None	1.1 (0.6–2.2)	1.1 (0.6–2.1)
Lifetime sexual partners		
1–2	1.0	1.0
≥ 3	2.4 (1.5–3.9) †	2.5 (1.7–3.9) †
HPV anogenital infection (any)		
No	1.0	1.0
Yes	1.4 (0.9–2.1)	1.8 (1.2–2.6) †

† p < 0.05.  
\* 0.05 < p < 0.10.

Australia [17], England [18], Slovenia (except for HPV 16) [19] and China [20] (Refer to Table 4 for individual seroprevalence estimates), the trend we observed for higher HPV 6 and 16 seroprevalences than HPV 11 and 18 was in agreement with all these studies except China. Detection of antibodies to one of more of the quadrivalent HPV vaccine types was also higher in our study (53%) than in USA (32%) [10] and in Slovenia (41%) [19].

Our study showed a decreasing trend in HPV seropositivity with increasing age for HPV 16 and HPV 18; higher HPV 16 seroprevalence was also previously reported in younger Puerto Rican women, although no significant differences were observed across age-groups in that smaller study [12]. However, some epidemiological studies report a seropositivity peak between 30 and 44 years and then a decline through older ages [9,10,17] and others report an increasing trend of seropositivity as age increases [21,22]. Our observed pattern could be attributed to waning of antibodies with time in the older age groups, or a cohort effect, with increased HPV infection exposure among women from the younger cohorts due to their higher-risk sexual practices, as has been documented in Puerto Rico [23]. The sexual behavior pattern among younger women highlights the necessity to reinforce education on HPV vaccination and safer sexual practices to prevent not only HPV transmission, but STIs in general.

While age trends were noted, we found that the strongest predictor of seropositivity to HPV types 16/18 and HPV6/11/16/18 was higher number of lifetime sexual partners, in agreement with previous studies

**Table 4**  
Seroprevalence of HPV types in women from population-based studies in different countries.

Setting	Study Characteristics			HPV Type Seroprevalence (%)			
	Study period	Age-group (years)	Sample Size (n)	6	11	16	18
<b>Puerto Rico (current study)</b>	<b>2010–2013</b>	<b>16–64</b>	<b>524</b>	<b>29</b>	<b>18</b>	<b>23</b>	<b>17</b>
Puerto Rico [12]	2007–2008	21–64	253	–	–	16	–
Slovenia [19]	2010	20–64	3259	19	6	25	9
USA (NHANES) [10]	2003–2006	14–59	4531	18	7	15	6
Australia [17]	2005	0–69	1523	13	5	12	6
England [18]	2002–2004	10–49	4647 <sup>a</sup>	16	6	15	6
China [20]	2006–2007	14–54	4731	7	3	6	2
Costa Rica [9]	1993–1994	18–97	9949	–	–	15	15

<sup>a</sup> Includes male and women; –: not tested for that type.

[9,22,24,25]. HPV serologic results are influenced by HPV exposure through sexual contact which is higher in those with riskier sexual practices. In this same cohort we previously reported that women with risky sexual behaviors were less likely to undergo Pap test [26], emphasizing the importance of continuing to promote cervical cancer control with both screening and HPV vaccination.

HPV seroprevalence and detection of HPV DNA do not always show consistent associations for several reasons [27,28]. HPV DNA is a measure of current infection, and seroconversion may be delayed, or not occur at all. HPV serology is a measure of cumulative exposure and HPV DNA may have cleared [8,9,24,25]. We found a two-fold increased risk of seropositivity to HPV 6/11/16/18 in women with current anogenital infection, but results for HPV 16/18 were not significant. Although HPV cumulative exposure in women in the San Juan metropolitan area of Puerto Rico is high, seropositivity to all 4 types included in the quadrivalent vaccine is low (4%).

Study limitations consist of possible bias related to self-reporting of risky behaviors due to social desirability, self-report of vaccination history and difference in immunoassays as previously noted. Despite these limitations, this is the first population-based study of correlates of HPV 6/11/16 and 18 in a population-based sample of women in Puerto Rico. Although our seroprevalence estimates could have been affected by HPV vaccination, we expect this to have limited impact on our results because women with self-reported HPV vaccination were excluded and most of the study population were older than the age groups recommended for HPV vaccination.

### 5. Conclusions

We conclude that the baseline assessment highlights the need for HPV vaccination and the potential impact widespread vaccination can confer in the population. High seroprevalence in the youngest age-group (16–19 years) indicates early age of exposure to HPV in PR and supports the need to vaccinate prior to the age of 16. Given that even young women have been exposed to multiple vaccine types, it is important to vaccinate at age 11–12 year old as recommended by the Advisory Committee on Immunization Practices [29]. PR initiated HPV vaccination in 2006 following FDA approval. Initially coverage was quite low [30], but recently initiation of the vaccine series among adolescent girls was higher in PR than the US. However, series completion remains low in both populations [31,32]. Thus, coverage still needs to be improved; continued efforts should be made for vaccine series completion, within recommended time intervals, as coverage is still below Healthy People 2020 objectives [33].

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### Conflict of interest

We wish to confirm that there are no other known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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