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Effectiveness of a universal vaccination program with an HPV quadrivalent vaccine in young Brazilian women

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ABSTRACT

We examined human papillomavirus (HPV) vaccine effectiveness in a nationwide sample of women aged 16 to 25 years who utilized the public health system in Brazil. This was a cross-sectional, multicentric survey conducted between September 2016 and November 2017 (POP-Brazil Study). A total of 5,945 young adult women were recruited from 119 public primary care units from all 27 federative units of Brazil by trained health professionals. The participants participated in a face-to-face interview and provided biological samples for genital HPV analysis. HPV genotyping was performed using a Linear Array HPV genotyping test in a central laboratory. Sampling weights were applied to the data. Overall, 11.92% (95% CI 10.65, 13.20) of the participants reported having been vaccinated. The frequency of vaccination was highest in 16- to 17-year-old women, with a decreasing vaccination rate with increasing age, and vaccinated women were more likely to belong to the high socioeconomic status group. The use of a quadrivalent vaccine decreased the HPV types 6, 11, 16, and 18 by 56.78%, from 15.64% in unvaccinated women to 6.76% in vaccinated women ($P < 0.01$), even after adjustment for age. Those who received the vaccine had lower HPV 16 (2.34% in vaccinated vs 8.91% in unvaccinated, $P < 0.01$) and 6 rates (2.06% vs 5.77%, $P < 0.01$). Additionally, a higher rate of high-risk HPV types other than HPV 16 and 18 (40.47% in vaccinated vs 32.63% in unvaccinated, $P < 0.01$) was observed. In conclusion, the results of this study support the effectiveness of HPV vaccination in Brazil. Continuous surveillance must be assured to monitor the HPV infection rate in the vaccination era.

Human papillomavirus (HPV) is a risk factor for cervical and other HPV-driven cancers, providing an opportunity for primary cancer prevention [1]. HPV vaccination programs aim to decrease the burden of cervical cancer by reducing the HPV infection rate [2]. Since the introduction of the HPV vaccine, infection rates have decreased worldwide [3]. Cervical cancer incidence and mortality rates have decreased at an unequal rate in recent years due to multiple factors, such as screening and an increase in socioeconomic level [4]. Approximately 90% of all cervical cancer deaths occur in low- and middle-income countries, where the introduction of efficient screening and preventive strategies is still limited by cost and cultural challenges [5]. In a recent *meta*-analysis, the prevalence of both HPV 16 and 18 decreased significantly by 83% among girls aged 13–19 years and by 66% among women aged 20–24 years after vaccination programs had been implemented for 5–8 years [6]. The cervical precancer incidence has declined by 56% among those aged 18–20 years and by 39% among those aged 21–24 years [7], and the effect of the vaccine seems to be greatest for lesions associated with HPV16 and 18 than for lesions due to other HPV types [8].

Currently, three prophylactic HPV vaccines are available worldwide: the bivalent (2vHPV), quadrivalent (4vHPV), and nonavalent (9vHPV) vaccines [1]. The three vaccines prevent infections by high-risk HPV 16 and 18, which are responsible for the majority of cervical cancer cases [7]. The 4vHPV vaccine also protects against HPV types 6 and 11, which cause 90% of genital warts

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[4], and the 9vHPV vaccine targets the same types included in the 4vHPV plus five additional oncogenic types (31/33/45/52/58) [9]. Public health vaccination against HPV should be primarily focused on adolescents before the first sexual intercourse [10].

HPV vaccines can provide partial protection against other HPV types that can cause cancer but are not included in the vaccine; this phenomenon is called cross-protection [1]. The vaccine appears to exhibit partial cross-protection against other HPV types phylogenetically related to HPV 16 and 18, which may be beneficial in some individuals. However, studies have not been able to determine the clinical relevance or the duration of this protection [11].

In 2014, Brazil introduced the quadrivalent vaccine in a public immunization program for girls (11–13 years) for primary prevention of cervical cancer. The implementation was expanded to those aged 9 to 13 years in 2015 and 9 to 14 years in 2017; at that time, boys aged 11–14 years and other at-risk populations, such as HIV-positive people aged 9 to 26 years, oncologic patients and people who had undergone solid organs or bone marrow transplantation, were included [12].

The efficacy of HPV vaccines has been demonstrated in clinical trials [13,14]. However, vaccine effectiveness and vaccine program performance in community settings may be lower than those reported in clinical trials; women may be infected prior to vaccination or have poor compliance with vaccination schedules. The present manuscript reports data from a baseline nationwide survey of HPV prevalence in Brazil that was designed to measure the impact of HPV vaccination in groups before and after quadrivalent HPV vaccine uptake [15]. In this manuscript we have evaluated participants who have received the HPV vaccine and compared with those non-vaccinated in a cross-sectional analysis. Therefore, we examined differences in the HPV infection rate according to vaccination status in a nationwide sample of women aged 16 to 25 years who utilized the Public Health System in Brazil.

1. Methods

1.1. Study design/population

This cross-sectional study included 5,945 sexually active young adult women from 119 public primary health care units from 26 state capitals and the Federal District of Brazil; participants were recruited from September 2016 to November 2017. We excluded women who were not sexually active, pregnant women, and women who had given birth with in the previous 6 months, women who had undergone hysterectomy or trachelectomy, and women who had ever had grade 2 or higher cervical intraepithelial neoplasia. Details regarding the study design and methods have been provided elsewhere [16].

The participants were recruited from the community and schools and were interviewed by trained primary care professionals using a structured questionnaire. Vaccination status was self-reported and was independent of number of doses and intervals.

Race/skin color was self-reported, and socioeconomic status was calculated from a score considering the number of goods in the household [17]. We also asked about the living area (urban, periurban or rural), frequency of health care unit attendance in the past year, education level, marital status, smoking status, drug use, alcohol consumption, number of sexual partners in the last 12 months, age at first sexual intercourse, condom use, and use of hormonal contraceptives. To characterize sexually transmitted infections (STI), we asked the participants if they had ever been diagnosed with HIV, syphilis, gonorrhea, genital warts and/or herpes. Additionally, participants were invited to undergo a rapid HIV test. Individuals who reported having STI and/or had a positive rapid test result at the time of the interview were considered positive. Genital HPV-suggestive lesions were reported by primary care professionals after clinical examination.

Cervical samples were obtained using a Qiagen HC2 DNA collection device according to the manufacturer's instructions. Genital swabs were placed in a tube containing 1 mL of Qiagen's Specimen Transport Medium (STM), stored at controlled room temperature (15–25 °C) and shipped to a central laboratory weekly where the samples were aliquoted and stored at −80 °C until processing [16].

DNA was extracted from 0.5 mL of STM using magnetic beads from an LC DNA Isolation Kit III for isolation and purification by a robotic system (MagNA Pure LC 2.0; Roche) according to the manufacturer's instructions. The DNA concentration was determined using a NanoDrop 2000 (Thermo Scientific™).

HPV genotyping was performed using a Linear Array® (LA) genotyping test (Roche), which amplified a 450-bp fragment from the L1 gene by polymerase chain reaction (PCR) followed by nucleic acid hybridization. For each reaction, 25 µl of working master mix was combined with DNA extract (between 100 and 150 ng) in a final volume of 50 µl. PCR cycling conditions and hybridization were performed as recommended by the manufacturer. The assay included primers for β-globin as an internal control for sample amplification. To ensure reproducibility of the LA test, an automated AutoBlot instrument (Fujirebio) was used for the hybridization and wash steps [18]. As the HPV 52 probe cross-reacts with types 33, 35 and 58, additional analyses were performed using a type-specific real-time PCR assay if needed [19,20].

The HPV results were grouped as follows: positive for any HPV type, positive for high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), positive for high-risk HPV types excluding HPV16 and HPV18, positive for low-risk HPV types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82,82v, 83, 84, 89), and positive for vaccine types (4vHPV: 6, 11, 16, 18 and high-risk 4vHPV: 16 and 18).

This research received approval from the Ethics Committee of the Moinhos de Vento Hospital research board and from the centers that participated in the data collection. Written informed consent was obtained from all participants (Approval No. 1607032). Confidentiality was ensured during data collection and subsequent publication of the results.

1.2. Statistical analysis

Descriptive analysis was used to characterize the study population. Categorical variables were summarized using absolute frequencies and percentages and the chi-square test was used to detect differences between groups. Crude and adjusted prevalence rates and 95% confidence intervals (95% CIs) were calculated for each HPV genotype group. The Cochran-Armitage trend test was applied to determine how the prevalence of HPV changes with age (16–17, 18–19, 20–21, 22–23, 24–25 years) in vaccinated and unvaccinated women. For each HPV genotype group, vaccine effectiveness was estimated through Poisson regression to determine the difference in risk between the vaccinated and unvaccinated women [21].

Sample size was based on the main objective of the POP-Brazil Study, namely, establishing the prevalence of HPV in Brazil. It was calculated according to sex and considering study design. It was purposely equal in all regions to maximize diversity in less populated areas. Sampling weights were applied to the data from our convenience samples in each capital to estimate HPV prevalence among women aged 16 to 25 years according to the Brazilian census [22]. SAS software (Statistical Analysis System, SAS Institute Inc., Cary, N.C.) version 9.4 was used to conduct the analyses, and a

2-sided confidence level of 5% was determined to be statistically significant.

2. Results

A total of 5,945 women were included in the analysis, of which 677 (11.92%; 95% CI 10.65, 13.20) were vaccinated against HPV. Overall, most declared their skin color as brown/pardo (58.15%) followed by white, and reported living in urban (78.90%) or periurban (19.59%) areas.

As expected, vaccination decreased with age, and more than half of all vaccinated women were<17 years old. Additionally, vaccinated participants were more likely to belong to social classes A-B (16.10%) than to classes C (11.68%) or D-E (10.63%) (P = 0.03) (Table 1). No significant difference was found regarding skin color. Most vaccinated participants reported that they were actively dating (16.10%), not currently using condoms, and had had two or more sexual partners in the past year. The mean age at first sexual intercourse was higher among unvaccinated women (15.48 years, 95% CI 15.42–15.53) than among vaccinated women (14.98 years, 95% CI 14.85–15.11, P < 0.01). Despite the significantly higher rate of alcohol consumption in vaccinated women than in unvaccinated women, the rates of tobacco use and drug use were not significantly different between the groups. The geographic region of Brazil with the highest rate of vaccinated participants was the Central-West region (14.57%), followed by the Southeast (13.47%), South (10.77%), Northeast (10.31), and North regions (9.24%) (p = 0.02).

There were no differences in the prevalence of STI (12.07% vs. 10.02%; P = 0.35) or HIV prevalence (0.58% vs. 1.37%; P = 0.32) between the unvaccinated women and vaccinated women. Similar results were found for suggestive-HPV genital lesions (2.40% in unvaccinated and 2.98% in vaccinated participants, P = 0.59).

The use of a quadrivalent vaccine decreased the prevalence rate of HPV types 6, 11, 16, and 18 by 56.78%; vaccinated women had a lower prevalence (6.76%) of HPV types included in the quadrivalent vaccine than unvaccinated women (15.64%; P < 0.01) (Table 2). These data were consistent even after adjustment for age (7.15% vs. 12.56%; P < 0.01). We also observed a reduction in the prevalence of the high-risk 4vHPV types (16 and 18), from 12.24% in unvaccinated women (P < 0.01) to 4.85% in vaccinated women. The prevalence rates of overall, high- and low-risk HPV infections were similar between the vaccinated and unvaccinated groups. In contrast, there were increases in the prevalence rates of some high-risk HPV types, excluding HPV 16 and 18, in vaccinated women (40.47% vs 32.63%, P < 0.01).

The reduction in the HPV infection rate was even higher than 56.78% for some specific types; the infection rate of HPV 16 was reduced by 73.74% and that of HPV 6 was reduced by 64.3% (Fig. 1). On the other hand, the rates of high-risk HPV types 59 and 39 were higher among vaccinated women than among unvaccinated women (data not shown).

The HPV infection rate showed a significant decreasing trend with increasing age in all HPV groups (P < 0.01) in unvaccinated women. This trend was observed in vaccinated participants for only the HPV types included in the quadrivalent vaccine

Table 1
Characteristics of adolescents and young adult women according to vaccination status. Brazil, 2016–2017.

	N	Vaccinated (n = 677) %	Unvaccinated (n = 5,268) 95% CI	P %	95% CI	
Age, y						< 0.01
16–17	787	51.34	46.23,56.45	48.66	43.55,53.77	
18–19	1,208	7.47	5.47,9.46	92.53	90.54,94.52	
20–21	1,282	6.81	4.44,9.19	93.19	90.81,95.56	
22–23	1,306	3.89	2.59,5.19	96.11	94.81,97.41	
24–25	1,362	4.30	2.86,5.74	95.70	2.59,5.19	
Race/color						0.88
White	1,429	12.50	9.64,15.36	87.50	84.64,90.36	
Black	932	11.11	8.47,13.75	88.89	86.25,91.53	
Brown/pardo	3,407	11.87	10.19,13.56	88.13	86.44,89.81	
Other	153	13.81	4.67,22.95	86.19	77.05,95.33	
Socioeconomic status[a]						0.03
A-B	896	16.10	12.11,20.09	83.90	79.91,87.90	
C	3,158	11.68	9.95,13.42	88.32	86.58,90.05	
D-E	1,891	10.63	8.57,12.70	89.37	87.30,91.43	
Living area						0.20
Periurban area	352	13.89	9.66,18.12	86.11	81.88,90.34	
Rural area	4,885	19.40	5.32,33.48	80.60	66.52,94.68	
Urban area	5,504	11.29	10.10,12.48	88.71	87.52,89.90	
Alcohol consumption						0.02
Yes	4,059	13.99	11.46,16.51	86.01	83.49,88.54	
No	1,881	10.82	9.42,12.23	89.18	87.77,90.58	
Marital status						< 0.01
Single	1,127	14.20	11.06,17.33	85.80	82.67,88.94	
Dating	2,271	16.10	13.74,18.46	84.00	81.54,86.26	
Married/living with partner	2,474	7.00	5.51,8.47	93.00	91.53,94.49	
Widowed/divorced/separated	72	10.64	0,00,23.56	89.36	5.51,8.47	
Hormonal contraceptive						0.50
Yes	2,911	11.52	9.78,13.27	88.48	86.73,90.22	
No	3,006	12.40	10.53,14.27	87.60	85.73,89.47	
Current condom						< 0.01
Yes	2,958	8.87	7.36,10.39	91.13	89.61,92.64	
No	2,959	15.02	12.99,17.05	84.98	82.95,87.01	
No. of sexual partners in the past year						< 0.01
< 2	4,456	10.94	9.52,12.35	89.06	87.65,90.48	
≥ 2	1,329	15.32	12.34,18.30	84.68	81.70,87.66	

Abbreviations: CI, confidence interval; [a]The social class distribution reflects the mean household monthly income: A-B = R$ 13,031 (US$ 3458), C = R$2328 ($582), D-E = R $708 ($177).

Table 2
Prevalence of human papillomavirus (HPV) in women aged 16 to 25 years according to the vaccination status. Brazil, 2016–2017.

	Prevalence (Confidence Interval 95%)		*P*
	Vaccinated	Unvaccinated	
Overall HPV	55.61 (49.89, 62.33)	54.60 (52.56, 56.63)	0.744
High-risk HPV	42.48 (36.84, 48.11)	38.59 (36.60, 40.58)	0.197
High-risk HPV types excluding 16 and 18	40.47 (34.86, 46.08)	32.63 (30.71, 34.54)	< 0.001
Low-risk HPV	39.38 (33.89, 44.87)	40.34 (38.32, 42.35)	0.749
Vaccine HPV types			
16 and 18	4.85 (2.85, 6.87)	12.24 (10.92, 13.55)	< 0.001
6, 11, 16, and 18	6.76 (4.42, 9.10)	15.64 (14.17, 17.11)	< 0.001

High-risk HPV: 6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Low-risk HPV: 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82,82v, 83, 84, and 89.

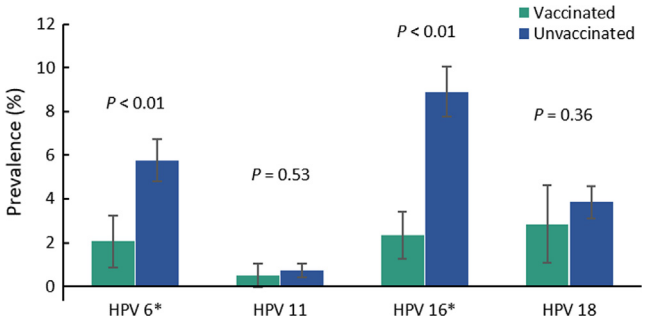

Fig. 1. HPV types in vaccinated and unvaccinated women in the POP-Brazil Study. Legend: a) Prevalence of HPV types in vaccinated and unvaccinated participants. b) Risk differences and 95% confidence intervals between vaccinated and unvaccinated women by HPV type. *Significance change.

(P < 0.01) (Table 3). When we stratified specific HPV types by age, the HPV 16 infection rates were significantly lower in vaccinated women than in unvaccinated women in the 16 to 17 (1.10% vs 10.96%, *P* < 0.01), 18 to 19 (3.70% vs 11.50%, *P* < 0.01) and 20 to 21 years (3.04% vs 9.17%, *P* = 0.02) (Fig. 2).

3. Discussion

This is the first nationwide study to evaluate the effectiveness of the quadrivalent vaccine by comparing vaccinated and unvaccinated young women. We found a significant difference in the HPV prevalence of the types included in the quadrivalent vaccine,

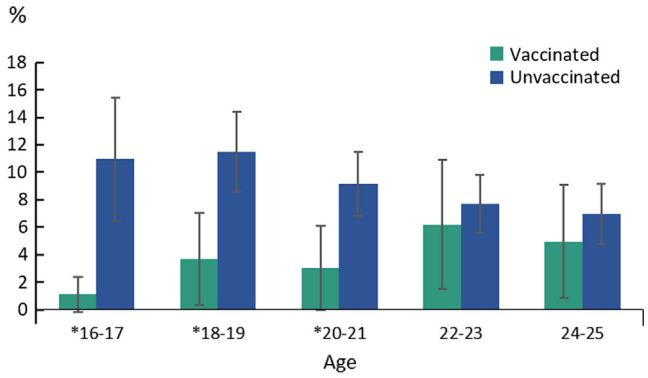

Fig. 2. HPV 16 in vaccinated and unvaccinated women by age. *$P < 0.01$.

mainly due to differences in the HPV 16 infection rate. On the other hand, the high-risk HPV types excluding HPV 16 and 18 were higher among vaccinated women than among unvaccinated women.

Notably, the effectiveness of the bi- and quadrivalent HPV vaccines has already been demonstrated worldwide in adolescent girls and young women aged 15 to 26 years [8,10,23]. In the United States, the effectiveness was high regardless of the number of doses [24], but the direct impact and herd effect were proportional to vaccine coverage [6]. In Sweden, vaccination with the quadrivalent vaccine significantly decreased the HPV vaccine type prevalence a decade after the introduction of the HPV vaccine [25]. We are able to show a significant reduction in HPV infection only four to five years after the introduction of the HPV vaccination program by the public health system of Brazil.

In this study, younger women and those with a higher socioeconomic level had the highest rates of vaccination. As also observed in previous studies [26], there was an inverse association of age with HPV prevalence in the years following sexual debut. As we evaluated a narrow age range, we were not able to demonstrate the usual increase later in life, around the fifth decade[27]. However, this trend was observed in only vaccinated women when we evaluated all HPV types included in the quadrivalent vaccine together. The introduction of HPV vaccination in Brazil was recent, and younger females had higher rates of vaccination, which could explain the lack of differences between age groups.

Although participants with higher socioeconomic levels had higher rates of vaccination, there was no difference in vaccine status according to self-declared skin color. In the United States, a *meta*-analysis including over three million people showed no overall racial or ethnic differences in HPV vaccine uptake overall [28]. As the vaccine program was introduced by the public health

Table 3
Impact of age on the prevalence of HPV infection in vaccinated and unvaccinated women in the POP-Brazil Study.

	Prevalence (Confidence Interval 95%) and *P* value										*P* for trend
	16 to 17 years		18 to 19 years		20 to 21 years		22 to 23 years		24 to 25 years		
Overall HPV											
Vaccinated	47.61 (41.04, 54.19)	0.086	64.08 (59.94, 68.68)	0.847	52.45 (34.17, 70.72)	0.523	48.55 (31.84, 65.26)	0.994	62.90 (47.85, 77.95)	0.038	0.960
Unvaccinated	52.39 (45.81, 58.06)		62.71 (49.24, 76.17)		58.48 (54.26, 62.69)		48.62 (44.36, 52.89)		45.91 (41.72, 50.10)		< 0.01
High-risk HPV types excluding 16 and 18											
Vaccinated	39.04 (31.47, 46.60)	0.260	54.58 (40.95, 68.22)	0.044	36.66 (19.13, 54.19)	0.707	31.28 (16.55, 46.01)	0.797	42.19 (25.18, 59.19)	0.029	0.470
Unvaccinated	44.87 (38.13, 51.60)		40.01 (35.69, 44.33)		33.29 (29.28, 37.30)		29.32 (25.43, 33.20)		24.98 (21.37, 28.59)		< 0.01
16 and 18 HPV types											
Vaccinated	1.87 (0.12, 3.61)	< 0.001	14.22 (3.19, 25.25)	0.915	5.05 (1.19, 8.92)	0.012	9.72 (2.97, 16.48)	0.692	9.11 (6.68, 11.54)	0.571	0.370
Unvaccinated	15.84 (10.77, 20.90)		14.86 (11.70, 18.02)		12.99 (10.19, 15.78)		11.25 (8.72, 13.78)		7.37 (2.26, 12.47)		< 0.01
6, 11, 16, and 18 HPV types											
Vaccinated	3.61 (1.13, 6.08)	< 0.001	18.06 (6.68, 29.44)	0.576	6.75 (2.11, 11.39)	0.006	11.41 (4.15, 18.68)	0.696	7.93 (2.65, 13.20)	0.363	< 0.01
Unvaccinated	18.65 (13.44, 23.85)		21.67 (17.96, 25.37)		16.80 (13.62, 19.99)		13.02 (10.34, 15.72)		10.94 (8.32, 13.55)		< 0.01

system in Brazil in 2014, we expected to find the highest rates in the young population and in women with a high socioeconomic level who were willing to pay for vaccination.

However, the effect on nonvaccine HPV types remains controversial [25]. Cross-protection and replacement are key elements in the choice of HPV vaccines for immunization programs. In a *meta*-analysis of 9 studies (2016), both bi- and quadrivalent vaccines were associated with a slight increase in HPV 39 and HPV 52 and a decrease in HPV 31 [29]. Another previous *meta*-analysis including two important clinical trials also found that the 2vHPV vaccine decreased the rates of HPV 31, 33, and 45 [11]. HPV 39 is among the ten most frequent HPV types in women with invasive cervical cancer [30].

Brazil is a large and populated country in South America with high socioeconomic inequality and cultural diversity. In addition to providing cervical cancer screening, the control of cervical cancer is one of the country's health priorities, leading to the introduction of the public health HPV vaccination program as a tool to decrease morbidity and mortality associated with cervical cancer.

Despite the magnitude and importance of the study, some limitations should be noted. Although a large sample of sexually active young adult women was included, public vaccination started only in 2014; thus, the proportion of vaccinated participants was small and did not allow us to show differences in other HPV vaccine types, such as HPV 18, which has a low frequency in the population. Further studies with larger sample sizes are needed to investigate the impact of vaccination on specific HPV types. Additionally, the vaccination status was self-reported and may have been either under- or over-reported. An HPV prevalence analysis was performed considering sexually active women, and we did not obtain information about whether the participants were vaccinated before or after their first sexual contact or the number of doses received, which could impact in prevalence trends according to age.

4. Conclusions

In summary, a major reduction in the prevalence of HPV types included in the vaccine, especially HPV 16, was observed, and the infection rates were the lowest in the younger age groups. Importantly, the prevalence of other high-risk HPV types has increased, and surveillance should be continued. Our findings demonstrate the effectiveness of HPV vaccination in a cohort of young women from Brazil, which was estimated few years after vaccination introduction. Continuous monitoring of HPV infection is an important strategy to evaluate the public vaccination program and evaluate the prevalence of specific HPV types and herd effects.

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CRediT authorship contribution statement

Eliana M. Wendland: Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **Natália Luiza Kops:** Investigation, Resources, Writing - original draft. **Marina Bessel:** Formal analysis, Writing - review & editing. **Juliana Comerlato:** Investigation, Writing - review & editing. **Ana Goretti Kalume Maranhão:** Writing - review & editing. **Flávia Moreno Alves Souza:** Writing - review & editing. **Luisa Lina Villa:** Investigation, Writing - review & editing. **Gerson Fernando Mendes Pereira:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Dr. Villa is an occasional consultant and speaker for HPV vaccines at Merck, Sharp & Dohme and an occasional consultant for HPV tests at BD, Roche and Qiagen. All other authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.040.

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