Short Communications

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Regional Disparities in the Impact of Human Papillomavirus–Induced Lesions after 10 Years of HPV Vaccination Program in Brazil

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Abstract

Background and objective: Human papillomavirus (HPV) causes almost all cases of cervical cancer and its prevalence can be significantly reduced by vaccines. This study aimed to compare the prevalence of preneoplastic and neoplastic uterine cervix lesions in the cytology of Brazilian women aged 20–24 yr before and after the HPV vaccination campaign. The study also correlates these findings with the proportional coverage of first and second doses for this population. **Methods:** An ecological study was conducted and data from DATASUS were analyzed from 2020 to 2024. Data were collected from women aged 20–24 yr who had oncotic pap smears between 2020 and 2024, and the prevalence ratios (PRs) were calculated in relation to 2020. **Results:** Following the vaccination program, the prevalence rate of tests with HPV-induced lesions in Brazil and the north, southeast, and south regions decreased by 0.85, 0.75, and 0.83, respectively, in 2023. No significant reductions were observed in the northeast and central-west regions. **Conclusion:** Although the second dose had reduced coverage, HPV-induced lesions were observed to decrease in Brazil and the north, southeast, and south after 10 yr of the beginning of the vaccination program. Decrease in HPV-induced lesions over time after vaccination did not follow similar trend in the northeast or central-west regions as in other parts.

Keywords: Brazil- cervical cancer- HPV vaccine- human papillomavirus

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Introduction

Cervical cancer is among the leading causes of morbidity and mortality globally [1]. , the incidence of cervical cancer has been increasing steadily in Brazil; however, it has the best prevention prospects among all types of cancer [2]. The human papillomavirus (HPV) causes almost all cases of cervical cancer. HPV vaccines have the potential to significantly reduce its prevalence. Many countries have implemented national HPV vaccination programs, with vaccination rates of 9%, 32%, and 76% in Greece, the United States, and the United Kingdom, respectively [3, 4] .

Increasing HPV vaccination rates in low- and middle-income countries is critical to eradicate cervical cancer [5]. In 2014, the Ministry of Health of Brazil launched an HPV vaccination campaign to vaccinate 80% of the target population [6]. In April 2022, the World Health Organization Strategic Advisory Group of Experts advised nations to incorporate a single-dose option into their dosing regimens [7].

The multiple-dose regimen is a known impediment to successful HPV vaccination. This study aimed to compare the prevalence of preneoplastic and neoplastic uterine cervix lesions in the cytology of Brazilian women aged 20–24 yr before and after the HPV vaccination campaign and to correlate these findings with proportional coverage of first and second doses for this population.

Materials and Methods

This ecological study examined data from DATASUS from 2020 to 2024. The prevalence of preneoplastic and neoplastic lesions was determined by accessing the Cervical Cancer Information System (SISCAN), which is a part of the Epidemiological and Morbidity Information System.

This information is available on the internet for free consultation as aggregated data and was not collected on an individual basis. There was no risk of physical or moral damage to individuals and communities as the principles outlined in resolution 466 on December 12, 2012, were followed. This article did not require submission to the Research Ethics Committee [8]. Population projections by age were used to calculate the first- and second dose vaccination coverage variables by year of birth for the years 2021 to 2023. The first dose coverage was calculated as the first doses administered in a given year divided by the target population (20–24 yr) multiplied by 100. Second dose coverage was calculated by multiplying the number

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of second doses administered in a given year by the target population (20–24 yr) × 100.

Vaccination data were extracted from the Information System of the National Immunization Program of the Ministry of Health (SI-PNI). Statistical programs were used to conduct comparative analyses. The 2014 campaign targeted girls aged 11 to 13 yr who were born between 2001 and 2003. The group aged 20-24 yr included women who were born before 2000 and thus, had not been vaccinated. Until 2023, a mix of vaccinated and unvaccinated women was observed.

The impact of the vaccine was calculated using the incidence of precursor lesions in the cytology of women aged 20–24 yr in cohorts with varying proportions of vaccinated women. The proportion of altered cytology per 100,000 women aged 20–24 yr was calculated. Cytology data classified as normal (no squamous preneoplastic changes) or with squamous changes in cohorts from 2020 and 2023 were used, with prevaccination cohorts (from 2020) serving as a comparison group. Vaccination coverage was compared with the prevalence of HPV-induced lesions at the national and regional levels using cohorts of vaccinated and unvaccinated women.

The chi-square test was used to calculate the prevalence ratio (PR) in relation to 2020 (patients not vaccinated). Pearson's correlation coefficient was used to assess the relationship between first- and second dose coverage and the presence of HPV-induced lesions on cytology. A p value of <0.05 was considered significant. The R program (v.4.3.3, 2024-02-29 ucrt) and its tidyverse package were used to link and analyze databases.

Results

Data on coverage of the first dose, second dose, total, and positive examinations for HPV-induced lesions among women aged 20–24 yr in Brazil and regions from 2020 to 2023 are shown in Table 1. Following the vaccination program, Brazil, the north, southeast and south regions showed a decrease in the prevalence of HPV-induced lesion tests, not observed in the northeast and central-west regions.

In Brazil, the correlation coefficient (CCR) for vaccination access and the occurrence of HPV-induced cytologic lesions per 100,000 women was $R^2 = 0.99$ ($p = 0.002$). The CCR between second dose coverage and the presence of HPV-induced lesions on cytology was $R^2 = 0.99$ ($p = 0.005$). Both showed a strong negative correlation.

The CCR for first dose coverage in the southeast region was $R^2 = 0.86$ ($p = 0.048$). Second dose coverage had an $R^2 = 0.90$ ($p = 0.03$), indicating a strong and significant correlation for both. For the southern region, the correlation coefficient for first dose coverage was $R^2 = 0.98$ ($p = 0.007$). For second dose coverage, it was $R^2 = 0.99$ ($p = 0.004$), indicating a strong and significant correlation between the two.

In the north region, despite a significant decrease in examinations with HPV-induced lesions over the years, the correlation coefficient for first dose coverage was $R^2 = 0.62$ ($p = 0.21$), and for second dose coverage dose, it was $R^2 = 0.62$ ($p = 0.14$), both non-significant.

In the northeast region, the CCR between first dose coverage and the occurrence of HPV-induced lesions on cytology for every 100,000 women was $R^2 = 0.40$ ($p = 0.74$, not significant), and for second dose coverage, it was $R^2 = -0.41$ ($p = 0.76$, not significant). In the central-west region, the adjusted CCR for both first- and second dose coverage was $R^2 = -0.05$ ($p = 0.45$), indicating a negligible and non-significant correlation.

Discussion

HPV infection is involved in almost all cases of cervical cancer and in significant proportion of oropharyngeal, anal, and genital malignancies. [9]. Clinical trial data with long-term follow-up show that the HPV vaccine permanently prevents high-grade precursor lesions in males and females. The findings were consistent across studies with different populations in terms of age and gender as well as socioeconomic status and geographic location [10].

In 2014, the Brazilian Ministry of Health included the quadrivalent HPV vaccine in the National Immunization Program (PNI) for girls aged 9 to 14 yr and, since 2017, for boys aged 11 to 14 yr [11]. In this study, we found that in Brazil, with a first dose coverage of just over 40% of the population, the prevalence of HPV-induced lesions dropped by around 10% in 2022, which increased to around 15% in 2023, coinciding with an increase in the proportion of vaccinated women in the cohorts, demonstrating a strong correlation between vaccination and impact on the reduction of HPV-induced lesions on cytology. The southeast and south regions also showed a strong correlation with reduction.

Although the northern region had the lowest vaccine uptake, it did not have the most negative impact. In 2023, 52.3% of the region's 20- and 24-year-old population received their first dose. Even though no significant correlation coefficient between access and impact was found, the PRs decreased the most among the regions (0.75%). Despite excellent adherence to first dose coverage comparable with the south and southeast regions of the 2014 campaign, there was no impact on the reduction in the prevalence of HPV-induced lesions, with the northeast region demonstrating an even greater significant increase in prevalence in 2022. In the central-west region, the main assumption was that the campaign by the Federal District initiated before 2014 was responsible for the lack of impact demonstration; however, even after excluding the Federal District from the analysis, we were unable to demonstrate an impact on reducing prevalence.

We try to explain these findings using some hypotheses. Differences in vaccination adherence may account for these regional differences. Furthermore, potential regional differences in HPV prevalence, with more types covered by the quadrivalent vaccine in other regions, may favor a greater impact. HPV replacement may have occurred more consistently in these regions, and the persistence of high-grade lesions in these regions may have had a lower potential for progression after vaccination, implying that there is no difference in protection between regions with

Table 1. Proportional 1st Dose Coverage, Proportional Coverage, Total and Positive Exams for HPV-Induced Lesions of Women Aged 20-24 Years. Brazil andregions.

Region	Year	First dose coverage (%)	Second dose coverage (%)	Total number of exams performed	Exams with HPV-induced lesions	Number of positive exams/100 thousand exams	Prevalence Ratio (PR) and confidence interval (CI)
Brazil	2020	-------	----------	354,184	6389	1803.,86	—----------
	2021	20.18	8.08	494,721	8603	1738.96	0.9646 (0.9342- 0.9961) p=0,02*
	2022	40.36	21.16	563,020	9222	1637.95	0.908 (0.8793 - 0.9377) p<0.0000001***
	2023	63.67	29.37	590,030	9082	1539.24	0.851 (0.824, 0.8789), p<0.0000001***
North	2020	----------	----------	27,880	563	2019.37	----------
	2021	20.9	7.2	43,978	951	2162.44	1.07 (0.97, 1.19), p>0.05
	2022	31.8	15.5	57,891	966	1668.65	0.82 (0.74 0.91), p=0.0003***
	2023	52.3	26	68,677	1036	1508.51	0.75 (0.67, 0.83), p<0.0000001***
Southeast	2020	------	----------	101,610	2103	2069.68	----------
	2021	20.68	14.3	134,875	2628	1948.47	0.9403(0.8874-0.9963), p=0,037*
	2022	41.16	28.6	150,946	2632	1743.67	0.8397 (0.7925, 0.8897), p<0,00001***
	2023	65.25	41.6	152,442	2629	1724.59	0.83 (0.79, 0.88), p<0.0000001***
South	2020	---------	----------	82,690	1600	1934.94	----------
	2021	20.82	14.8	107,681	1977	1835.98	0.95 ((0.89,1,01), p>0,05
	2022	41.04	29.5	115,662	1938	1675.57	0,91 (0.89, 0.93), p<0,00001***
	2023	64.58	42.3	119,970	1889	1574.56	0.81 (0.76, 0.87), p<0,00001***
Northeast	2020	----------	--------	115,040	1560	1356.05	----------
	2021	21.4	13.6	170,842	2328	1362.66	1.01 (0.94-1.07). p>0.05
	2022	43.38	26.2	196,590	2841	1445.14	1.07 (1.00. 1.14), p<0.04*
	2023	66.85	39	201,723	2599	1288.4	0.95 (0.89. 1.01) p=0.11
Mid-west	2020	---------	------	26,958	563	2088.43	----------
	2021	16.54	10.1	35701	693	1941.12	0.93 (0.83-1.04) p=0.19
	2022	35.7	22.1	41931	845	2015.22	0.96 (0.87. 1.07), p=0.51
	2023	57.85	35.5	47218	929	1967.47	0.94 (0.85. 1.05), p=0.27

* p<0.05; **p<0.001; ***p<0.0001

different prevalences.

The prevalence and distribution of HPV types may differ according to region and age. In Malaysia, the most common high-risk HPV type among women living in urban areas is HPV 52, which is not covered by the current HPV vaccine for female protection.

In a meta-analysis, Colpani et al. [12] observed significant variation in the prevalence of HPV between different geographic areas of Brazil, with an increased prevalence of cervical HPV in the northeast and central-west regions, precisely the two regions where the impact of vaccination was not observed. Martins et al. [13] found that HPVs 31 and 33 were the second most common types among populations in the northeast and central-west regions, demonstrating the geographic variability of HPV types in Brazil. Surprisingly, HPV 66 was detected in 22% of HPV-positive samples from Campo Grande, Mato Grosso do Sul. According to Glehn et al. [14], HPV vaccination coverage in Northeastern states between 2014 and 2021 was, on average, lower than the target of 80% recommended by the PNI. Vaccination coverage was higher for females and both sexes in the first dose, whereas vaccination coverage for males was lower in all states and for both doses.

Type replacement has not been observed in clinical trial cohorts, despite being proposed as a possible explanation for the increased prevalence of high-risk HPV in nonvaccinated individuals. According to Schelecht et al. [15] (39, 51, 56, 68), some nonvaccine types have become more prevalent over time, but the findings are insufficient to support type replacement [13].

Following immunization, lesions with a lower carcinogenic potential are also possible. Using methylation markers, Louvanto et al. [16] found that high-grade cervical lesions were still present in vaccinated women after a long period of follow-up. Women who received the HPV vaccination with LSIL and controls had low methylation levels, just like those with HSIL. The severity of the injury tends to increase the level of methylation. Women who have received an HPV vaccination may benefit more from close monitoring of their high-grade squamous intraepithelial lesions than from immediate treatment, due to low methylation levels and the possibility of lesion reversal. This indicates that HSIL lesions can still be seen in women who received the vaccination in their early adolescence and that even if the lesions are high-grade, they are unlikely to progress to cancer [14].

Furthermore, when we compare the results of coverage of the first and second doses, we see that the northeast, north, and central-west regions had the worst accumulated results in 2023 for the first dose, at 43.38%, 52.3%, and 57.85%, respectively, and 26%, 39%, and

35.5% for the second dose. It is possible that this had a real effect in reducing the impact in the northeast and central-west regions while having no effect in the north due to lower demographic density. The north region is the least populated, accounting for nearly half of the national territory and the majority of the Brazilian Legal Amazon (Demographics of Brazil - Statistics & Facts, n.d.) [17]. According to Xing et al. [18], high population density and mobility may increase the risk of HPV infection.

These observations of regional differences may allow us to develop public policies that focus on areas with less impact. These findings could have implications for the screening and treatment of HPV-induced disease. The primary limitation of this study is the use of secondary data, which requires accuracy in DATASUS and PNI data.

In conclusion, ten years after the vaccination program began, even with lower second dose coverage, there is a reduction in HPV-induced lesions in Brazil and the north, southeast, and south regions. In terms of the decrease in HPV-induced lesions over time postvaccination, the northeast and central-west regions did not follow the other regions. Differences in vaccination adherence, potential regional variations in HPV prevalence, more consistent replacement of HPV types after vaccination in these regions, and persistence of high-grade lesions with less potential for progression could be hypotheses to explain these findings.

Author Contribution Statement

Adriana do Valle Graça - acquisition of data, conception and design, drafting the article, revising critically, final approval. Leila Cristina Soares Brollo - conception and design, drafting the article, revising critically, final approval

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Availability of data

The information contained in this study is available on the internet for free consultation.

Ethical issue

The information contained in this study is available on the internet for free consultation and is not collected individually. For this reason, there is no possibility of physical or moral harm from the perspective of the individual or the collective, as the principles contained in resolution 466 of December 12, 2012 were respected. Therefore, this article did not require submission to the Research Ethics Committee.

Cnflict of interest

The authors declare no conflict of interest

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