

Downward Trend In The Hpv-Induced Lesions Among The Vaccinated Female Population In Brazil

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Abstract:

Background: This study aimed to analyze the impact of the HPV vaccine by comparing the incidence of pre-neoplastic and neoplastic HPV-induced histological lesions in age groups with and without vaccination coverage in Brazil and its regions from 2015 to 2021.

Materials and Methods: This longitudinal study utilized data on the incidence of HPV-induced lesions obtained from the Cancer Information System (SISCAN) of the Brazilian Unified Health System's Information Technology Department (DATASUS). Data on vaccination coverage were collected from the Information System of the National Immunization Program (SI-PNI). Trend analysis was conducted using the non-parametric Mann-Kendall test.

Results: The incidence of histological exams with HPV-induced lesions in Brazil between 2015 and 2021, among the 15–19-year-old age group, exhibited a significant tendency toward progressive and continuous decrease ($z = -2.70$; $p = 0.006$) with a pronounced linear fall ($\tau = -0.90$). The northern region had the lowest vaccination coverage compared to other regions, and the incidence of HPV-induced histological lesions did not show a declining trend, with some age groups showing significant upward trends. In contrast, the Northeast region showed better vaccination coverage in the years 2018, 2019, 2020, and 2021. There was a downward trend in the incidence of HPV-induced lesions among the 15 to 19-year-old group in the Southeast ($p = 0.03$), South ($p = 0.007$), Northeast ($p = 0.01$), and Midwest ($p = 0.003$) regions, with the most significant decline observed in the Midwest.

Conclusion: Despite vaccination coverage not consistently reaching the target, there was a noticeable trend toward a decline in the incidence of histological lesions induced by HPV in Brazil and most regions.

Key Word: Human papillomavirus; Papillomavirus Vaccines; Vaccination Coverage; Brazil.

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I. Introduction

Cervical cancer is a significant cause of morbidity and mortality worldwide, particularly in low-, and middle-income countries with limited resources to support an organized screening program¹.

To prevent infection and reduce the risk of cancer, some models suggest that 80% of the world's population should be immunized against HPV². The World Health Organization (WHO) plan to eliminate cervical cancer by implementing specific measures, including achieving full immunization of 90% of girls up to 15 years of age by 2030 because cervical cancer is predominantly caused by HPV³.

In Brazil, limited access to healthcare, and geographical challenges contribute to cervical cancer being a public health concern. In 2014, Brazil initiated an HPV vaccination campaign with a goal to vaccinate 80% of the population. Initial doubts regarding the feasibility of achieving this goal due to geographical and cultural factors were dispelled, as high adherence rates were observed in most states, reaching approximately 100% compliance⁴. While cervical cancer screening is recommended from the age of 25 according to the Ministry of Health, opportunistic screening practices enable data collection from age groups that would not typically be covered by screening. Therefore, this study aimed to conduct a preliminary analysis of the impact of the vaccine by comparing the incidence of pre-neoplastic and neoplastic lesions with histological evidence in age groups with and without vaccination coverage in Brazil and its regions.

II. Material And Methods

This longitudinal study utilized data on the incidence of HPV-induced lesions obtained from the Cancer Information System (SISCAN) of the Brazilian Unified Health System's (DATASUS) Information Technology Department for the period from 2015 to 2021.

To calculate vaccine coverage, data were extracted from the Information System of the National Program for Immunizations (SI-PNI) of the Ministry of Health. The data included information on the first and second HPV vaccines administered to individuals born from the years 2001 to 2005. The data covered all available periods starting from 2014, which marked the beginning of the vaccination campaign. Vaccine coverage was calculated according to the population projection for each year of vaccination, using the coverage method recommended by the Pan American Health Organization⁵.

The outcome variables extracted from SISCAN were the prevalence of HPV-induced lesions in histology, analyzed both at the national level and for specific regions. The analysis covered the period from 2015 to 2021 and focused on age groups between 15 and 64 years, categorized in 5-year intervals. The HPV-induced lesions with high-grade features that cannot exclude microinvasion and invasive squamous cell carcinoma.

Trend analysis was performed using the non-parametric Mann-Kendall test. The z value was examined with $z > 0$ indicating a positive trend, $z < 0$, a negative trend, and $z = 0$, no trend. The significant level was set at $p < 0.05$. The strength of the trend was assessed through the significance test on Kendall's tau value. A tau value less than 0.3 indicates a weak linear relationship, tau less than 0.7 is a moderate linear relationship, and tau greater than, or equal to 0.7 indicates a strong linear relationship. The statistical analysis was performed using R software version 4.2.2 (2022-10-31 ucrt).

III. Result

Regarding vaccination coverage, the analysis of DATASUS data on second doses based on population projections revealed that until 2015, there was no age group covered by the campaign for girls aged 15–19 years. The vaccination had not yet been covered for other age groups, except for the 20–24 age group in 2021, which included those born in 2006.

In Brazil, the calculated coverage for the first dose among individuals aged 15–19 years was 20.14% in 2016, 40.35% in 2017, 68.19% in 2018, and 85.59% in 2019. Notably, in 2020, the coverage exceeded 100% of the projected population (110.51%) (Table 1).

Regarding the second dose of the HPV vaccine, the calculated coverage for 2016 was 12.93%, which increased to 27.34% in 2017, 40.56% in 2018, and 54.30% in 2019. For 2020 and 2021, the entire group of individuals 15–19 years was covered by the vaccine, with a coverage rate of 82.35% and 82.44%, respectively.

Table 1. Coverage of first and second doses in the 15-19 age groups according to the population projection for the years, Brazil and regions.

	Brasil		Norte		Nordeste		Sudeste		Sul		Centro-oeste	
	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose
2016	20.14	11.90	15.48	7.12	21.05	13.08	20.94	14.52	20.89	14.89	17.40	10.55
2017	40.35	25.37	31.76	15.86	41.79	25.66	41.74	41.74	41.22	30.08	37.62	23.66
2018	68.19	41.88	56.34	30.25	66.00	45.10	67.35	46.44	65.69	45.62	64.44	41.56
2019	85.59	61.26	72.26	47.00	84.25	56.75	81.82	67.56	79.76	65.01	78.54	57.23
2020	110.51	82.93	94.54	66.71	101.41	78.26	103.50	91.14	99.38	83.90	98.05	74.64

The incidence of histological examinations with HPV-induced lesions in Brazil from 2015 to 2020 revealed a significant and consistent decrease in the age group of 15–19 years ($z = -2.70$; $p = 0.006$), demonstrating a strong linear downward trend ($\tau = -0.90$) (Figure 1). However, there was no statistically significant trend observed in other age groups: 20–24 years ($z = -0.60$, $p = 0.55$), 25–29 years ($z = 0$; $p = 1$), 30–34 years ($z = 0$, $p = 1$), 35–39 years ($z = 0.60$; $p = 0.55$), 40–44 years ($z = 0.60$; $p = 0.55$), 45–49 years ($z = 0.60$; $p = 0.55$), 50–54 years ($z = 0.30$; $p = 0.76$), 55–59 years ($z = 0.60$; $p = 0.55$), and 60–64 years ($z = 0.30$; $p = 0.76$).

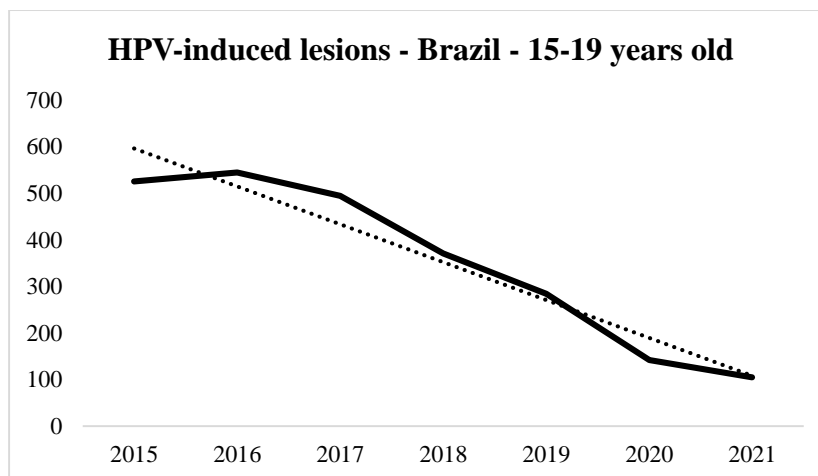


Figure 1. Incidence of HPV-induced lesions in Brazil among individuals aged 15 to 19 years from 2015 to 2021, demonstrating a declining trend.

In the northern region, the calculated coverage of the first dose of the HPV vaccine among the 15–19 age group was 15.48% in 2016, 31.76% in 2017, 56.34% in 2018, 72.26% in 2019, and 94.54% in 2020. For the second dose, was 8.38% in 2016, 18.51% in 2017, 30.42% in 2018, 41.85% in 2019, 66, 01% in 2020 and 70.21% in 2021. There was no statistically significant trend observed in any age group: in the age group of 15–19 years ($z = -1.37$, $p=0.17$), 20–24 years ($z=0$; $p=1$), 25–29 years ($z=1.20$; $p=0.22$), 30–34 years ($z=1.50$, $p=0.13$), 35–39 years old ($z=1.50$, $p=0.13$), 44–49 years ($z=1.20$; $p=0.23$). The ranges 40–44 years ($z=2.40$; $p=0.01$; $\tau=0.81$) and 50–54 years old ($z=2.10$; $p=0.03$; $\tau=0.71$), 55–59 years ($z=1.99$; $p=0.048$; $\tau=0.68$) and 60–64 years ($z=2.40$; $p=0.02$; $\tau=0.81$) showed increasing trend.

In the Northeast region, the calculated coverage for the first dose among individuals aged 15–19 years was 21,05% in 2016, 41.79% in 2017, 66% in 2018, 84.25% in 2019 and 101.41% in 2020. Regarding the second dose, the calculated coverage for 2016 was 13.06%, 27.79% in 2017, 58.28% in 2018, 72.03% in 2019, 100.08% in 2020 and 100,47 in 2021. The incidence of histological examinations with HPV-induced lesions in the age group of 15–19 years showed a significant decreasing tendency ($z=-2.58$, $p=0.01$; $\tau=-0.88$). No trend was observed for individuals aged 20–24 years ($z=0$; $p=1$), 25–29 years ($z=0$; $p=1$), 30–34 years ($z=0.30$; $p=0.76$), 35–39 years ($z=0.30$; $p=0.76$), 40–44 years ($z=1.20$; $p=0.23$), 45–49 years ($z=0.60$; $p=0.55$), 50–54 years old ($z=1.20$; $p=0.23$), 55–59 years ($z=1.20$; $p=0.23$) and 60–64 years ($z=0.90$; $p=0.37$).

In the Southeast region, the calculated coverage for the first dose among individuals aged 15–19 years was 20.94% in 2016, 41.74% in 2017, 67.35% in 2018, 81.82% in 2019 and 103.5% in 2020. Regarding the second dose, the calculated coverage for 2016 was 14.51%, 30.16% in 2017, of 44.04% in 2018, 58.78% in 2019, 89.34% in 2020 and 87.89 in 2021. The 15–19 age group showed a significant downward trend for positive histological exams for HPV-induced lesions ($z=-2.10$, $p=0.03$), with a high linear downward trend ($\tau=-0.71$). The other age groups, 20–24 years ($z=-1.20$, $p=0.23$), 25–29 years ($z=0$; $p=1$), 30–34 years ($z=0.30$, $p=0.76$), 35–39 years ($z=0.30$, $p=0.76$), 40–44 years ($z=0.60$, $p=0.55$), 45–49 years ($z=0.60$, $p=0.55$), 50–54 years ($z=0.60$, $p=0.55$), 55–60 years ($z=0$, $p=1$), 60–64 years ($z=0.60$; $p=0.55$) showed no significant trend.

In the southern region, the calculated coverage for the first dose among individuals aged 15–19 years was 20.89% in 2016, 41.22% in 2017, 65.69% in 2018, 79.76% in 2019 and 99.38% in 2020. Regarding the second dose, the calculated coverage for 2016 was 13.7%, 28.3% in 2017, 40.48% in 2018, 54.96% in 2019, 83.02% in 2020 and 82.42% in 2021. There was a significant trend towards a decrease in positive diagnoses for HPV-induced lesions in the 15–19 age group ($z=-2.70$; $p=0.007$, $\tau=-0.90$) with a high linear trend. The ranges of 20–24 years old ($z=-0.60$, $p=0.55$), 25–29 years old ($z=0.30$; $p=0.76$), 30–34 years old ($z=-0.60$, $p=0.55$), 35–39 years old ($z=0$; $p=1$), 40–44 years old ($z=0$; $p=1$), 45–49 years old ($z=-0.45$; $p=0.65$), 50–54 years old ($z=-0.60$; $p=0.55$), 55–59 years old ($z=-0.45$; $p=0.65$) and 60–64 years old ($z=0$; $p=1$) did not show this trend.

In the Midwest region, the calculated coverage for the first dose among individuals aged 15–19 years was 17.40% in 2016, 37.62% in 2017, 64.44% in 2018, 78.54% in 2019 and 98.05% in 2020. The second dose coverage was 9.05% in 2016, 20.95% in 2017, 33.08% in 2018, 44.17% in 2019 and 66.11% in 2020 and 69.23% in 2021. This region presented the most expressive result of all regions in the 15–19 age group ($z = -3.00$; $p = 0.003$) with maximum trend strength ($\tau = -1$). The 20–24 age group also showed a trend for a substantial decline ($z = -2.70$, $p\text{-value} = 0.007$) and a strong linear trend ($\tau=-0.90$), which might be an effect of district federal campaigns in the years before the national campaign. Regarding other groups, 25–29 years ($z = -1.50$; $p = 0.13$), 30–34 years ($z = -1.80$; $p=0.07$), 35–39 years ($z=-0.45$; $p=0.65$), 40–44 years ($z=0$; $p=1$), 45–49 years ($z=-0.90$;

p=0.37), 50-54 (z=0.60; p=0.55) years, 55-59 years (z= -0.60; p=0.55) and 60-64 years (z= -0.90; p=0.37), there was no significant trend (Figures 2 and 3).

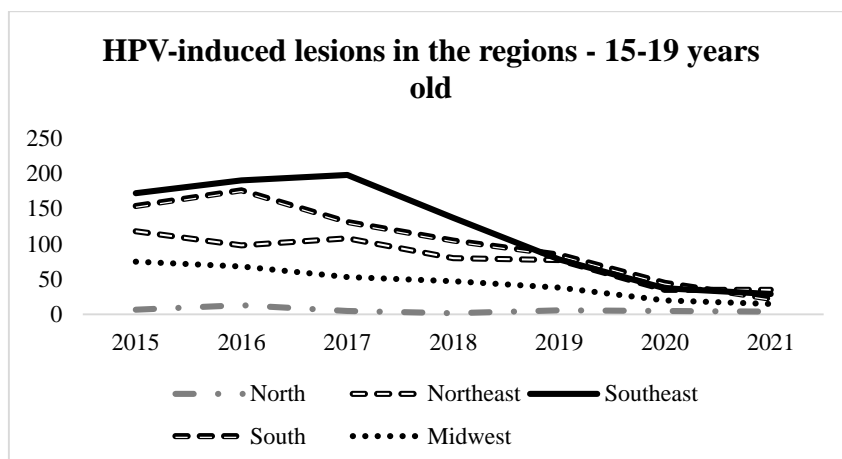


Figure 2. Region-specific prevalence of HPV-induced lesions in Brazil among individuals aged 15 to 19 years from 2015 to 2021.

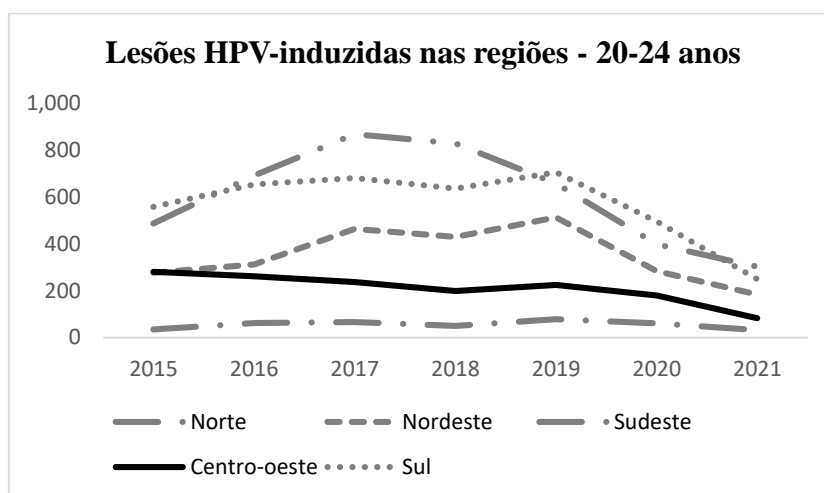


Figure 3. Region-specific prevalence of HPV-induced lesions in Brazil among individuals aged 20 to 24 years from 2015 to 2021.

IV. Discussion

HPV infection is a significant contributing factor in the development of cervical cancer and epidemiological research indicates that the infection rate can reach 80% in sexually active women. While the immune system can naturally eliminate the majority of viral infections, some persist, and can lead to cancer overtime⁶. Implementing widespread vaccination programs has the potential to significantly decrease mortality rates and the occurrence of HPV-related cancers, thereby reducing the financial burden associated with treating these diseases⁷.

Tabibi et al. demonstrated a reduction in cervical cancer and mortality rates following the introduction of HPV vaccination in the United States in 2006. The study specifically focused on girls and women aged 11-26 years, revealing a more substantial reduction in cervical cancer cases among women aged 15-24 years compared to those aged 25-39 years⁸. Additionally, Caskey conducted a database analysis comparing pre- and post-vaccination populations, which demonstrated a decline in cervical cancer incidence and mortality rates associated with the introduction of the HPV vaccine⁹.

In Brazil, the Unified Health System (SUS) offers free vaccines against numerous diseases to individuals across all age groups, attaining a national coverage rate exceeding 90%. Nonetheless, vaccination coverage in Brazil has experienced a decline since 2013, accompanied by an increase in vaccine hesitancy within the country. These trends have been closely linked to disinformation campaigns, posing significant challenges for the PNI in recent years¹⁰.

However, in 2014, during the first year of the vaccination campaign, 87% of Brazilian municipalities achieved the target of 80% coverage for the first dose among eligible girls. However, this number decreased to 32% of municipalities for the second dose¹¹. Consequently, there is a limited time frame for impact assessment. Nevertheless, the results of the analysis of histopathological exams with HPV-induced lesions in the 15–19 age group, which was partially covered by the vaccine until 2019 and fully covered from 2020, revealed a decreasing trend in the incidence of these lesions in Brazil and nearly all regions, which was not observed in other age groups. These results demonstrate that, despite Brazil falling short of the WHO's target of 90% HPV vaccination coverage by 2030, a tangible impact is already being observed in the majority of the vaccinated populations.

It is crucial to disseminate these findings publicly, particularly considering the significant rise in vaccine hesitancy within Brazil. Despite the proven efficacy and accessibility of vaccines, they are often rejected due to various concerns and misconceptions¹². Notably, vaccination rates for diseases such as measles, mumps, and rubella have consistently declined since 2013, raising concerns about potential outbreaks of preventable diseases¹³. Numerous personal and political viewpoints pose obstacles to vaccination efforts. In the case of HPV, being a sexually transmitted infection, many parents express apprehension that vaccination may inadvertently encourage teenage sexual activity or promote risky behavior¹⁴.

The northern region stands out as the only one region that did not demonstrate a decline in the incidence of HPV-induced lesions among the 15–19 age group. Furthermore, there is an observed trend of increasing incidence of these lesions in other groups, including 40–44 years, 50–54 years, 55–59 years, and 60–64 years. It is worth noting that this region also exhibits the lowest coverage rates based on DATASUS data.

However, similar observations regarding low coverage rates have been made in other vaccines, such as hepatitis, particularly in states located in the North region¹⁵.

Interestingly, the North, and Midwest regions exhibited comparable results, with coverage rates of 70.21% and 69.23%, respectively. However, a notable difference between these regions is that the Federal District in the Midwest region initiated the HPV vaccination campaign before the national campaign. This early implementation in the Federal District may have contributed to higher coverage rates in the region, which is reflected in the stronger downward trend observed in the 20–24 years age group, indicating that expanding the vaccine coverage to additional age ranges enhances the vaccine's effectiveness in providing protection.

The requirement for multiple doses has been recognized as a barrier to achieving successful HPV vaccination¹⁶. However, in December 2022, WHO authorized countries to use a single dose of the HPV vaccine at their discretion, which has had a significant impact on public health. This recommendation was based on strong evidence generated from several observational and ecological studies, as well as a randomized clinical trial. The UK's Vaccines Advisory Committee also deemed the evidence robust and convincing enough to recommend the adoption of a single-dose regimen in its national immunization program¹⁷. Considering projections of coverage of the first dose only, Brazil is expected to reach the WHO target of 90% coverage for this population by 2030.

Targeted outreach efforts aimed at specific populations can significantly enhance the acceptance and uptake of the HPV vaccine. To ensure high vaccination rates for future generations, it is crucial to identify and address barriers to immunization. Implementing educational incentive campaigns and school-based vaccination programs, which were successful during the initial phase of the 2014 campaign, can help maintain a strong adherence to vaccination protocols. Additionally, to achieve the goal of 90% coverage by 2030, it is important to consider the implementation of second-dose rescue vaccination strategies¹².

The findings of this study suggest that the current coverage of the HPV vaccine is effective in preventing HPV-induced diseases. The potential effectiveness of single-dose vaccination is likely contributing to a higher percentage of the vaccinated population. However, as the vaccination campaign progresses, further studies should be conducted in Brazil to gather more data. Despite the need for continued research, this initial analysis presents promising results that can guide further vaccination campaigns, with particular attention to the northern region.

V. Conclusion

Despite vaccination coverage not consistently reaching the target, there was a noticeable trend toward a decline in the incidence of histological lesions induced by HPV in Brazil and most regions. The northern region, which has the worst outcomes, should receive more attention when adopting public policy.

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