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ANALYSIS OF HPV MORBIDITY BEFORE AND AFTER IMPLEMENTATION OF VACCINATION IN BRAZIL: AN EPIDEMIOLOGICAL STUDY

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Abstract: **INTRODUCTION**: Genital human papillomavirus (HPV) infections are transmitted mainly through unprotected sexual intercourse. In women, it is related to cervical cancer (CCC) – the fourth most common type of cancer in this population. Since 2014, the National Immunization Program has implemented the quadrivalent HPV vaccine, currently targeting boys and girls aged 9 and 14 and people aged 9 to 45 with special clinical conditions. **OBJECTIVE:** To analyze the behavior of HPV morbidity before and after the start of vaccination in Brazil. **METHODOLOGY:** This study is observational, descriptive, analytical, retrospective and has a quantitative approach, with data collection in the IT Department of the Unified Health System. The number of CC cases in Brazil and in the regions in the pre- and post-vaccination, as well as the doses of HPV vaccines applied and the amounts spent on the pathology. **RESULTS:** In the pre-vaccination period, the morbidity rate in Brazil and the North, Northeast, Central-West, South and Southeast regions were, respectively, 88/100,000 inhabitants, 56.9/100,000, 86.6/100,000, 88,2/100,000, 133.4/100,000 and 79.5/100,000, while in the post-vaccination period they were 80.2/100,000, 71.7/100,000, 77.6/100,000, 83.6/100,000, 106, 4/100,000 and 74.2/100,000, respectively. **DISCUSSION:** Research data revealed that the morbidity rate due to CC in the pre- and post-vaccination period is quite variable, with an increase in the North region and a decrease in Brazil and other regions. It was also observed that the South region significantly exceeds the national average morbidity standard, while in the analyzed interval this rate decreases by approximately 20%. **CONCLUSION:** A reduction in the prevalence of HPV morbidity was observed in Brazil, suggesting that prevention strategies, such as the vaccine, have generated a positive impact over the years. However, unlike the other regions, the morbidity rate in the North region increased in the post-vaccination period, even with the highest vaccination coverage.

Keywords: Human Papilloma Virus; Cervix; Vaccination.

INTRODUCTION

The Human Papilloma Virus (HPV) is a small, non-enveloped, double-stranded deoxyribonucleic acid (DNA) virus belonging to the genus Papillomavirus of the Papillomaviridae family (Palefsky, 2022a). Genital infections are transmitted through unprotected penetrative sexual intercourse or close physical skin-to-skin contact involving an infected area (Palefsky, 2022b), making this one of the most common sexually transmitted infections in the world (Moura, 2021).

HPV, in women, is related to cervical cancer (CCU) – the fourth most common type of cancer in this population – and vulvar and vaginal cancer, being uncommon throughout the world. Regarding diseases associated with HPV in women and men, there are non-genital warts, genital warts, anal cancer, oropharyngeal cancer and recurrent respiratory papillomatosis. In men, the virus is associated with penile cancer and precursor lesions, occurring mainly at a younger age (Palefsky, 2022a).

The relationship between HPV and cancer risk varies depending on your genotype. Thus, it is known that HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are associated with a high risk of cervical cancer - HPV being 16 and 18 are the most frequently isolated in this type of cancer - while genotypes 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81 are related to a low risk of colon cancer. of uterus (Palefsky, 2022b).

Given this, it is worth highlighting that the vaccine is one of the public health actions that

has the greatest impact on society. Currently, two prophylactic vaccines against HPV are available, regulated for use in the population in several countries, including Brazil: the bivalent vaccine that acts against viruses 16 and 18 and the tetravalent or quadrivalent vaccine that acts against serotypes 6, 11, 16 and 18. Both vaccines are produced from the L1 protein of the viral capsid by recombinant DNA technology resulting in virus-like particles (VLP), particles similar to viruses, but which do not have DNA and, therefore, do not are infectious. They are capable of inducing the production of antibodies against specific types of HPV contained in the vaccine (Calumby, 2020).

Since 2014, the National Immunization Program of the Ministry of Health (PNI-MS) has implemented the quadrivalent vaccine (6,11,16 and 18) for HPV for girls aged 9-14, expanding it to women living with AIDS up to 26 years (Sorpreso; Kelly, 2018) and, currently, boys and girls aged 9 and 14 and people aged 9 to 45 with special clinical conditions (living with AIDS, solid organ or bone marrow transplant recipients and oncology patients, immunosuppressed due to diseases and/or treatment with immunosuppressive drugs) (Brazil, 2023). Brazil has good experience in vaccination coverage with national programs, enabling efficient promotion of vaccination against oncogenic HPV types in the target population.

These prophylactic vaccines have proven their effectiveness in countries that have already implemented them in their vaccination calendar, with a reduction in virus manifestations by up to 90%. (Pinho, 2018) The effectiveness of the vaccine in men and women suggests that immunization is more effective among individuals who have not been infected with HPV and reduces morbidity in young women related to precursor lesions and in situ cancer. (Calumby, 2020)

In Brazil, and as in other low- and middle-income countries, where 56% of the global burden of this neoplasm resides, only 1.0% and 0.1%, respectively, of women aged between 10 and 20 years were vaccinated. It is worth noting that the success of a vaccination program, however, does not depend only on the biological effectiveness of the vaccine, but on several other local factors, such as poverty, inequality, gender, cultural or religious traditions and beliefs, which can restrict significantly the success of any vaccination program (Luvisaro, 2018).

Unfortunately, mortality from HPV-related cervical cancer has remained constant in recent decades in Brazil, even with several vaccination campaign initiatives and screening programs for Pap smears (Zerlotti et al., 2018).

The proportion of mortality due to CC is 5.19% throughout Brazil, with the global standard rate being 4.8%, indicating that Brazil needs to strengthen prevention, diagnosis and early treatment campaigns for women diagnosed with cervical cancer. uterus (Cheffer et al., 2022).

The study aimed to analyze Brazilian regions regarding HPV vaccination coverage data, correlating with morbidity rates before and after the implementation of the HPV vaccine.

Therefore, this study is relevant because complications resulting from HPV infection can be serious and lead to death, making it necessary to monitor the HPV vaccine and evaluate the behavior of morbidity due to malignant neoplasia of the cervix in Brazil, since HPV infection is directly related to the main cause of cervical cancer, the fourth most common type of cancer and the fourth most frequent cause of death from cancer in females (Ferreira et al., 2022).

METHODOLOGY

STUDY DESIGN

This study is observational, descriptive, analytical, retrospective, sectional and has a quantitative approach and aims to analyze HPV morbidity in Brazilian regions, through data collection at the Department of Informatics of the Unified Health System (DataSUS), a bank of public domain data, and TabNet, in order to obtain information about HPV morbidity before and after the start of vaccination in Brazil.

SAMPLE POPULATION

The population defined in the 2010 demographic census by the Brazilian Institute of Geography and Statistics (IBGE) was used, in which Brazil had 190,755,799 inhabitants and the North, Northeast, Southeast, South and Center-West regions had 15,864,454, 53,081,950, 80,364,410, 27,386,891 and 14,058,094 inhabitants, respectively.

DATA COLLECTION

Data collection was carried out on March 10, 2023 at DataSUS/TabNet, evaluating HPV morbidity in the regions of Brazil, in the years 2007 to 2013 and 2015 to 2021 (7 years before and 7 after the implementation of the HPV vaccine). HPV in Brazil), and comparing the values presented, relating them to the doses of HPV vaccines applied in each region. To this end, the "Health Information" category was chosen in TabNet and, in the "Epidemiological and Morbidity" option, "Hospital Morbidity in the SUS" was selected, subsequently "General by place of residence, from 1995 to 2007" and "General by place of residence, as of 2008", followed by the option "Brazil by regions/states" in the "geographical coverage" category. The "Region" option was included in the "Line" category; years from 2007 to 2021 in the "Available Periods" category and, in the "Available selections" category, the following variables were selected: Region (North, Northeast, South, Central-West and Southeast) and ICD-10 Morb List (Malignant neoplasm of cervix).

To collect data on HPV vaccine doses administered in Brazil, the DataSUS/TabNet website was accessed on March 30 and 31, 2023. In TabNet, the categories "Health Care" and "Immunizations - since 1994", followed by the option "Doses applied". The "Year" option was included in the "Line" category; "Immunobiologicals" in the "column" category; years from 2014 to 2021 in the "Available Periods" category and, in the "Available selections" category, the following variables were selected: Region (North, Northeast, South, Central-West and Southeast) and Immunobiologicals (Quadrivalent HPV - Female and Quadrivalent HPV - Masculine).

To collect data on the total amounts spent in Brazil and regions, the "Health Information" category was accessed on TabNet and, in the "Epidemiology and Morbidity" option, "Hospital Morbidity in the SUS" was selected, then "General by location of residence, from 1995 to 2007" and "General by place of residence, from 2008 onwards", followed by the option "Brazil by regions/states" in the "geographical coverage" category. The option "Morb List - ICD-10" was included in the "Line" category; "Region" in the "Column" category and "Total value" in the "Content" category. The years 2007 to 2021 were also selected individually in the "Available Periods" category and, in the "Available selections" category, the following variables were selected: Region (North, Northeast, South, Central-West and Southeast) and ICD-10 Morb List (Malignant neoplasm of the cervix).

DATA ANALYSIS

After data collection, the authors began analyzing the behavior of morbidity due to malignant neoplasia of the cervix in the pre- and post-vaccination period (from 2007 to 2013 and from 2015 to 2021) in Brazil and regions, analyzing the evolution of these values and evaluated the vaccination coverage of HPV vaccine doses applied in the country, from 2014 to 2021, with the aim of correlating information on the number of vaccine doses applied and morbidity in Brazilian regions.

RESULTS

In Brazil, morbidity in the pre-vaccination period - from 2007 to 2013 - was 88 cases for every hundred thousand inhabitants. The North, Northeast, Central-West, South and Southeast regions had, respectively, the following morbidities: 56.9/100 thousand, 86.6/100 thousand, 88.2/100 thousand, 133.4/100 thousand and 79.5/100 thousand.

Furthermore, in Brazil, morbidity in the post-vaccination period - from 2015 to 2021 - was 80.2 cases for every hundred thousand inhabitants. The North, Northeast, Central-West, South and Southeast regions had, respectively, the following morbidities: 71.7/100 thousand, 77.6/100 thousand, 83.6/100 thousand, 106.4/100 thousand and 74.2/100 thousand.

In Brazil, vaccination coverage was 213 doses/thousand inhabitants. The regions that had the highest vaccination coverage against HPV were the North and Northeast, followed by the Central-West, South and Southeast regions, with 238 doses/thousand inhabitant, 219 doses/thousand inhabitant, 217 doses/thousand inhabitant, 214 doses/thousand inhabitant and 204 doses/thousand inhabitants, respectively.

It is important to highlight that in the pre-vaccination and post-vaccination period there is a Brazilian population of 190,755,799, Southeast 80,364,410 (41.12%), Northeast 53,081,950 (27.82%), South 27,386,891 (14.35%), North 15,864,454 (8.31%) and Central-West 14,058,094 (7.36%).

In Brazil, the average annual expenditure in the pre-vaccination period was 23,986,622.24 reais. The regions with the highest spending averages were the Southeast and Northeast, followed by the South, Central-West and North, with 8,615,878.63, 7,590,241.67, 4,861,345.84, 1,577,511.28 and 1,341,644.81 reais spent on average, respectively.

It was observed that in Brazil, on average, 41,797,483.76 reais were spent in the post-vaccination period. The regions with the highest average spending were the Northeast and Southeast, followed by the South, Central-West and North regions, with average spending values of 14,513,993.51, 13,731,653.69, 7,967,717.64, 2,915,788.64 and 2,668,330.26 reais, respectively.

DISCUSSION

Research data revealed that the rate of morbidity due to cervical neoplasia in the pre-vaccination and post-vaccination period is quite variable in Brazil and regions, with an increase in the North region and a decrease in Brazil and the Southeast, Central-West, South and Northeast in the periods studied.

A study carried out in 2019 showed that the HPV virus is more prevalent in countries on the poorest continents in the world: Africa and South America, including Brazil, and the lowest rates are found in countries in Europe and Asia. Central. This situation also reflects the rates of morbidity and mortality from cervical cancer, since measures to combat the disease also depend on the implementation of the disease prevention and control program adopted in each country. This also occurs in Brazilian regions (Simoes; Junior, 2019).

Data from the present study showed that the North region has a lower morbidity rate from

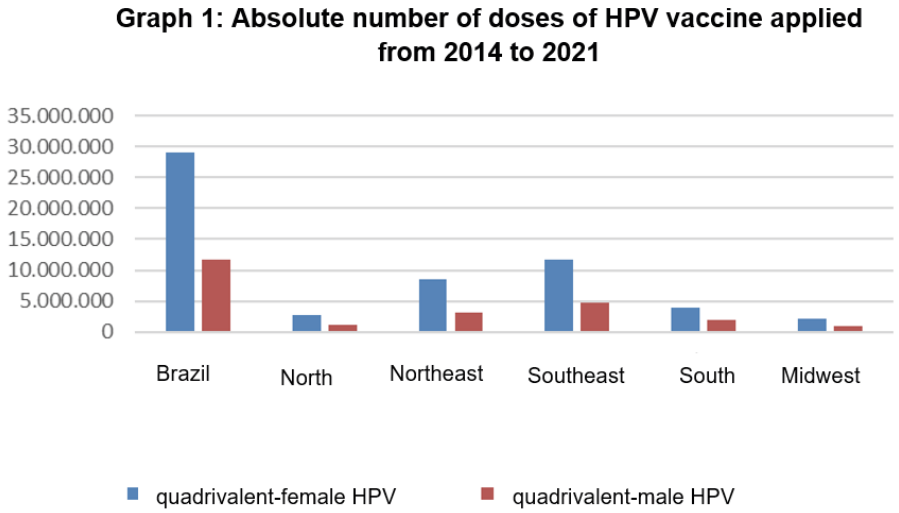
Regions	Morbidity rate in the pre-vaccination period* (for every 100 thousand inhabitants)	Morbidity rate in the post-vaccination period** (for every 100 thousand inhabitants)
Brazil	88	80,2
Midwest	88,2	83,6
Northeast	86,6	77,6
North	56,9	71,7
Southeast	79,5	74,2
South	133,4	106,4

Table 1 – Morbidity of cervical neoplasia by Brazilian region

Source: Data collected in the research

*2007 to 2013

** 2015 to 2021



Graph 1: Absolute number of doses of HPV vaccine applied from 2014 to 2021

Source: Data collected in the research

cervical cancer both in the pre-vaccination and post-vaccination periods and is the region with the highest vaccination coverage against HPV. However, this territory stands out for being the only one among the regions that had an increase in rates between the pre- and post-vaccination periods, corroborating the study by Da Silva, et al. 2023, which states that cervical cancer has a heterogeneous disposition, with a higher incidence in low- and middle-income countries. This demonstrates different exposures to risk factors, which may be inserted in the socioeconomic context, lifestyle and habits, as well as access to care and health services.

Cervical cancer in Brazil, in the pre-vaccination period, has a morbidity rate of 88/100 thousand inhabitants, while in the South region this rate is equivalent to 133.4/100 thousand; post-vaccination, Brazil has a morbidity rate of 80.2/100 thousand inhabitants and in the South region of 106.4/100 thousand inhabitants. Therefore, it is clear that the South region in terms of cervical cancer significantly exceeds the national average standard. In the same scenario, it was observed that in the South region, in the pre- and post-vaccination interval, the morbidity rate decreases by approximately 20%.

According to Oliveira's 2023 study, the

process of colonization and exploration in Brazil generated inter-territorial inequalities, with productive activities and economic complexes centralized in the South and Southeast regions. Inequalities that are also reflected in the unequal health conditions of different populations, in the level of exposure to risk and protective factors, causes of illness and death, and in the differentiated access to resources and services available in the health system.

Medium and high complexity services and equipment were concentrated in capitals and metropolises, notably located in the Center-South axis of the country. This pattern of distribution and fragmentation of supply results in geographic inequities in access to health services in the country (Oliveira, 2023). What contributes to the discrepancies in CC morbidity rates in residents of the Northern Regions, which was observed an increase from the pre- to post-vaccination period, compared to those in the South, which decreased in relation to the time interval analyzed, as previously reported.

Furthermore, between regions of Brazil, vaccination coverage varies greatly. The Southeast region stands out for being below the value of Brazil. In the Northeast, Central-West and South there is less variability in vaccination coverage, being higher than the value in Brazil, and the North region stands out as the region with the highest vaccination coverage. It is important that vaccination coverage is high and adequately distributed, which was not observed even in regions with the largest population.

Many countries have already recorded a significant reduction in HPV after adhering to vaccination in young people, such as Australia, Europe, North America and New Zealand, which reduced the number of HPV infections by approximately 90%. In the United States and Australia, the reduction was demonstrated in less than 4 years (Coelho et al., 2015). Corroborating this, a study, by Lusivaro in 2022, showed that Australia -a pioneering country in introducing the HPV vaccine into its national vaccination program- currently has good results in reducing the incidence of cervical cancer thanks to the rate of vaccination coverage, which varies from 70% to 80% throughout its territory.

A study conducted in 2017 showed that, of 12 countries in Latin America and the Caribbean (LAC) that had not yet implemented an HPV vaccination program in 2015, 10 had a cervical cancer incidence rate above the LAC average. Furthermore, the introduction of a universal vaccine for boys, as occurred in Brazil, could lead to faster control of cancer and other HPV-associated lesions (Restrepo et al., 2017).

Based on research data, it was observed that, in the Southeast region, the total amount spent on hospital morbidity from cervical cancer in the pre-vaccination period was 60,311,150.42 reais, with an annual average of 8,615,878.63 reais and in the post-vaccination period 109,853,229.57 reais were spent, with an annual average of 13,731,653.69 reais. Being the region in Brazil with the biggest expenses during the period analyzed.

In view of this, government incentives for the private network aimed at marketing health plans and insurance, associated with greater formalization of jobs and income, helped the expansion of the market and the expansion of segmentation and fragmentation of the health system (Bahia, 2018a). Parallel to this, the Southeast region is where public units, philanthropic-private and private hospitals designed to serve the public on the most expensive health plans are concentrated (Bahia, 2018b).

Still based on the research data, it was observed that, in Brazil, the total amount spent on hospital morbidity from cervical

cancer in the pre-vaccination period was 167,906,355.71 reais, with the annual average being 23,986. 622.24 reais and in the post-vaccination period 334,379,870.11 reais were spent, on average 41,797,483.76 reais per year.

However, in a 2020 study by De Oliveira Mendes, it was found that with successful immunization, the vaccine can reduce the number of colposcopy and biopsy exams and the number of treatments for precursor lesions of cervical cancer. When an immunization service is effective, the expectation is that cases of cervical cancer and hospital expenses linked to it practically disappear. What is observed in the present study is that increases occur progressively, as demonstrated by the data mentioned above.

The study carried out by Silveira and collaborators in 2022 obtained results on the performance of the Pap smear test and showed differences between regions, being higher in the Southeast (37.1%) and lower in the North (5.6%). The present study obtained similar results.

The Southeast region has the largest population, around 41.12%, and was the region with the highest expenditure in the pre-vaccination period, with 35.91% of the total, while in the post-vaccination period it was characterized by the second highest expenditure: 32.75% of the total. The North has the fourth largest population, with around 8.31%, and had the lowest expenditure in the pre-vaccination period, around 5.59% of the total, while in the post-vaccination period it had an expenditure of 6.38% of the total, the lowest of the period.

CONCLUSION

After analyzing the data from the present study, a reduction in the prevalence of HPV morbidity in Brazil was observed in the pre- and post-vaccination periods, suggesting that prevention strategies, such as the vaccine, have generated a positive impact over the years. However, the North region, which had the lowest expenditure during the periods evaluated, differed from the other regions by presenting an increase in the morbidity rate, despite having the highest vaccination coverage. Furthermore, the Southeast region is characterized by the lowest vaccination coverage and, even so, has the second lowest morbidity rate in the post-vaccination period. It is worth mentioning that the data from the South region is surprising, given that it has the second lowest vaccination rate, but showed a significant decrease between the periods studied. Therefore, it is essential to identify the challenges that this scenario entails, suggesting an improvement in prevention strategies, aiming at full access to vaccination and strengthening early detection of cervical cancer to continue advancing in the fight against HPV infection.

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