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IMPACT OF IMMUNOBIOLOGICALS AGAINST HPV ON THE OUTCOME OF MALIGNANT NEOPLASM OF THE CERVIX IN BRAZIL

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Marcela Nazareth Souza[1], Jakeline Resende Carvalho[2], Maria Clara Ribeiro Figueiredo[3], Flávia Dias Barbosa[4], Juliana Fagundes Pacheco[5], Laila Carrijo Borges Limberger[6], Letícia Nogueira Resende[7], Daniel Silva Nascimento[8], Carlo José Freire de Oliveira[9], Melissa Carvalho Martins de Abreu[10], Camila Botelho Miguel[11] and Wellington Francisco Rodrigues[12]

ABSTRACT

Cervical cancer is an important public health issue, associated with high morbidity and mortality rates in Brazil and worldwide. Infection with oncogenic subtypes of the Human Papilloma Virus (HPV) is one of the main risk factors for this neoplasm, which motivated the implementation of vaccination programs. This study aims to analyze the impact of HPV vaccination on cervical cancer morbidity and mortality in Brazil between 2011 and 2020. An ecological and time-series study was carried out using data from the Ministry of Health and the Brazilian Institute of Geography and Statistics (IBGE). Morbidity and mortality rates

[1] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[2] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[3] Postgraduate Course in Tropical Medicine and Infectious Diseases, Federal University of Triângulo Mineiro – UFTM, Uberaba/MG, Brazil
[4] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[5] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[6] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[7] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[8] Postgraduate Course in Tropical Medicine and Infectious Diseases, Federal University of Triângulo Mineiro – UFTM, Uberaba/MG, Brazil
[9] Postgraduate Course in Tropical Medicine and Infectious Diseases, Federal University of Triângulo Mineiro – UFTM, Uberaba/MG, Brazil
[10] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
[11] Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
Postgraduate Course in Tropical Medicine and Infectious Diseases, Federal University of Triângulo Mineiro – UFTM, Uberaba/MG, Brazil
[12] Corresponding author
Multidisciplinary Laboratory of Scientific Evidence, Centro Universitário de Mineiros – UNIFIMES, Mineiros/GO, Brazil
Postgraduate Course in Tropical Medicine and Infectious Diseases, Federal University of Triângulo Mineiro – UFTM, Uberaba/MG, Brazil
E-mail: wellington.frodrigues@unifimes.edu.br

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were adjusted for population density and age groups, and data were analyzed using the "R" program. Although no significant correlation was found between vaccination and morbidity, the negative relationship between vaccination coverage and mortality suggests a protective effect of immunization, corroborating the literature that highlights the efficacy of the vaccine in preventing this cancer. These results reinforce the need to intensify vaccination campaigns as a crucial strategy for reducing mortality from cervical cancer in Brazil, highlighting, however, that other factors such as access to health services also influence outcomes.

Keywords: Cervical Cancer, Vaccination Coverage, Immunization.

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INTRODUCTION

Cancer is a broad denomination that encompasses an extensive set of diseases with the potential to affect any part of the body. Other commonly used expressions are malignant tumors and neoplasms. A distinctive feature of cancer is the proliferation of anomalous cells that multiply beyond their normal limits, with the ability to invade adjacent structures of the body and spread to distant organs; this last process is recognized as metastasis, being the main cause of cancer-related deaths (WHO, 2021).

Cancer is one of the main reasons for death globally, resulting in approximately 9.6 million deaths in the year. In 2018, it stopped one in six deaths and almost 10 million in 2020 (FERLAY et al., 2020). The global impact of cancer in 2020, according to estimates by the World Cancer Observatory (Globocan), prepared by the International Agency for Research on Cancer (IARC), indicates that there were 19.3 million new occurrences of cancer worldwide (18.1 million, if we exclude cases of non-melanoma skin cancer). About one in five people will be diagnosed with cancer at some point in their lives (Ferlay et al., 2021).

The ten most frequent types of cancer represent more than 60% of the new occurrences of the disease. Among women, breast cancer is the most prevalent, with 2.3 million new cases (24.5%), followed by colon and rectal cancers, with 865 thousand (9.4%); lung, with 771 thousand (8.4%); cervix, with 604 thousand (6.5%); and non-melanoma skin, with 475 thousand (5.2%) new cases worldwide (Sung et al., 2021). In Brazil, the forecast for new cases of cervical cancer in the period from 2023 to 2025 is 17,010, which corresponds to an estimated risk of 15.38 cases per 100 thousand women. (INCA, 2022).

Cancer rates in the world continue to increase, exerting significant pressure on the physical, emotional and financial aspects of individuals, families, communities and the public health system. In many low- and middle-income countries, health systems are not adequately prepared to cope with this increase, resulting in a lack of access to quality diagnosis and treatment in a timely manner for many patients. In countries where healthcare systems are consistent and considered good, survival rates for many cancers are improving thanks to affordable early detection, quality treatment, and survivorship care (Martel et al., 2020; Wild et al., 2020), but still among women, a cancer that stands out is uterine cancer.

In the last decade, cervical cancer has ranked third among the most common types of cancer in women worldwide. However, a study showed that in 42 countries with few

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resources, it was the most prevalent type of cancer in women, thus demonstrating its close relationship with socioeconomic development (Arbyn et al., 2020).

The precursor lesions of cervical cancer are usually asymptomatic and are detected by cytopathological tests (Barcelos et al., 2017). Secondary prevention aims to identify and treat high-grade lesions, such as CIN2 or CIN3. Considering that these lesions are more frequent in women between 35 and 40 years of age, and that invasive carcinoma is extremely rare in immunocompetent women aged 25 years or younger, it is recommended to start screening from 21 or 25 years of age (Lopes; Ribeiro, 2019).

In 2020, the World Health Organization (WHO) estimated that 604,000 women were diagnosed with cervical cancer globally, resulting in an estimated 342,000 deaths. Cervical cancer is the most frequently diagnosed type in 23 countries and the leading cause of cancer death in 36 nations. Most of these countries are located in sub-Saharan Africa, Melanesia, South America, and Southeast Asia (WHO, 2021).

In Brazil, given its socioeconomic and cultural plurality, the rates of malignant neoplasm of the cervix are heterogeneous among different communities. Cervical cancer occupies the third position in incidence in the Central-West, with a rate of 16.66 cases per 100 thousand inhabitants, the fourth place in the South region, with 14.55 cases per 100 thousand, and the fifth in the Southeast region, with 12.93 cases per 100 thousand. On the other hand, in regions with lower levels of development, such as the North, with 20.48 cases per 100 thousand, and the Northeast, with 17.59 cases per 100 thousand inhabitants, cervical cancer is the second most common type among women (Brasil, 2022).

As for mortality in Brazil, 6,627 deaths related to cervical cancer were recorded in 2020, resulting in a crude mortality rate of 6.12 deaths per 100 thousand women (Brasil, 2022; National Cancer Institute José Alencar Gomes da Silva, 2020a). Some factors recognized as associated with disease progression include Human Immunodeficiency Virus (HIV) infection and other conditions that cause immunosuppression, such as smoking, multiple births, and long-term use of oral contraceptives (Wild; Weiderpass; Stewart, 2020).

At the moment, eradication of cervical cancer is seen as a viable possibility. This can be achieved through vaccination against the most common cancer-related HPV types, as well as by screening and treatment of precursor lesions. The World Health Organization's (WHO) global strategy to accelerate the elimination of this public health problem includes targets to be achieved by 2030: ensuring that 90% of girls are fully vaccinated against HPV by the age of 15, ensuring that 70% of women have high-quality screening tests by the age

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of 35 and 45, and ensure that 90% of women diagnosed with precursor lesions and cancer receive treatment (WHO, 2020).

In sum, cervical cancer represents a significant burden for global public health, especially in countries with limited resources, where the absence of access to adequate prevention and treatment programs amplifies the impact of this disease. However, advances in understanding its pathogenesis and implementing prevention strategies, including HPV immunization and screening for precursor lesions, offer a promising prospect for eradication.

The use of immunobiologicals as primary prevention measures has a protective effect against vaccine-preventable diseases. In addition, cervical cancer is known to be a malignant pathology with a great impact on morbidity and mortality. The existence of the immunizer against HPV subtypes 16 and 18, epidermally the most responsible for cervical neoplasia, has been in the vaccination schedule of the Ministry of Health since 2014. Thus, this study aims to evaluate the impact of immunobiologicals against the human papillomavirus on the outcome for malignant neoplasm of the cervix in Brazil. To this end, an ecological and time-series study will be carried out in the period from 2011 to 2020 on the impact of HPV immunobiologicals on the outcome for malignant cervical neoplasm in Brazil.

METHODOLOGY

This study was carried out using public data from secondary sources, and ethical approval was not required for its realization. The protocol meets the current principles of resolution number 466, of 2012, of the National Health Council. In addition, the data does not contain personal identifiers of the cases, containing only information related to public health or social situation.

An ecological study with a retrospective time series covering a period of ten years (2011 to 2020) was carried out, using data from the Ministry of Health (Datasus), the National Immunization Program Information System, and the Brazilian Institute of Geography and Statistics (IBGE). Data on malignant neoplasms of the uterus and HPV vaccination coverage in the different macro-regions of Brazil were analyzed.

Data related to mortality and morbidity due to malignant neoplasm of the uterus (C10: C53) - period from 2011 to 2020 and HPV vaccination coverage in females aged 09 to 12 years for the year 2015 in the different macro-regions, available in the Ministry of

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Health database, were included. Inconsistent data after reviewing the generated database (lack of information or numbers incompatible with the distribution evaluated), as well as data not validated by the Ministry of Health were excluded.

The collection of information containing morbidity and mortality data was accessed after consulting DATASUS via TABNET, through the Ministry of Health making available on its access page (http://tabnet.datasus.gov.br). Vaccination coverage was accessed through the National Immunization Program (http://pni.datasus.gov.br) Information System Age and population size estimates were obtained from the database of the Brazilian Institute of Geography and Statistics (IBGE) for each year analyzed.

For data analysis, the information was tabulated in the Excel program (Microsoft Office Professional Plus, 2016). Statistical analyses were performed using the "R" program through packages available for the "R studio" study. The distribution was tested for all variables (D'Agostino & Pearson or Shapiro-Wilk test). Parametric tests (one-way ANOVA with Tukey's multiple comparison) were used to compare the groups. For correlation, Pearson's and Spearman's tests for Gaussian and non-Gaussian distributions, respectively.

RESULTS

After analyzing morbidity and mortality due to malignant cervical neoplasia among the different macro-regions of Brazil, a significant discrepancy was identified between them ($p<0.05$). The macro-region with the highest average morbidity rate per 100 thousand inhabitants was the South (14.47 ± 1.39), followed by the Northeast (10.50 ± 0.77), Southeast (9.95 ± 0.65), Central-West (9.73 ± 1.00) and North (7.73 ± 1.14) (Figure 1A). On the other hand, the highest mortality rates were recorded in the North (4.43 ± 0.38) and Northeast (3.25 ± 0.26) regions, followed by the Central-West (2.96 ± 0.26), South (2.91 ± 0.31) and Southeast (2.28 ± 0.14) (Figure 1B). Contrary to what was expected, i.e., that regions with higher morbidity rates also had higher mortality rates, the opposite was observed, with a negative and significant correlation between morbidity and mortality rates ($rho = -0.40$; $p<0.05$) (Figure 1C).

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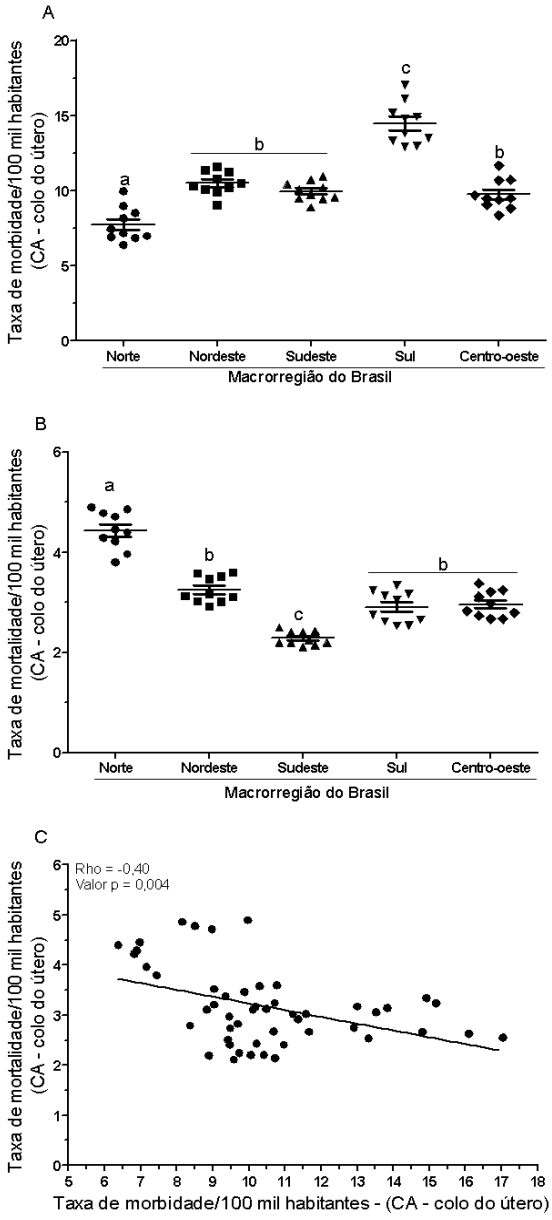
Figure 1. Effect of morbidity and mortality due to malignant cervical neoplasm among the macro-regions of Brazil.



Source: Data on morbidity and mortality were taken from the Ministry of Health database (DataSus) through Tabnet, and the rates obtained were compared between the macro-regions. (A) In-hospital morbidity rate due to malignant cervical neoplasm. (B) Mortality rate due to malignant neoplasm of the cervix. (C) Correlation between morbidity and mortality rates due to malignant neoplasm of the cervix. The letters a, b and c indicate significant differences between the macro-regions. The level of significance adopted was 5%.

After comparing morbidity and mortality rates between the macro-regions of Brazil, potential temporal correlations for the study period (2011 to 2020) and the rates found (Figure 2) were evaluated. For morbidity due to malignant cervical neoplasms, a positive and significant correlation was found ($r = 0.75$; $p = 0.01$) only for the northern region of the country, on the other hand, a negative and significant correlation ($r = - 0.79$; $p = 0.01$) was

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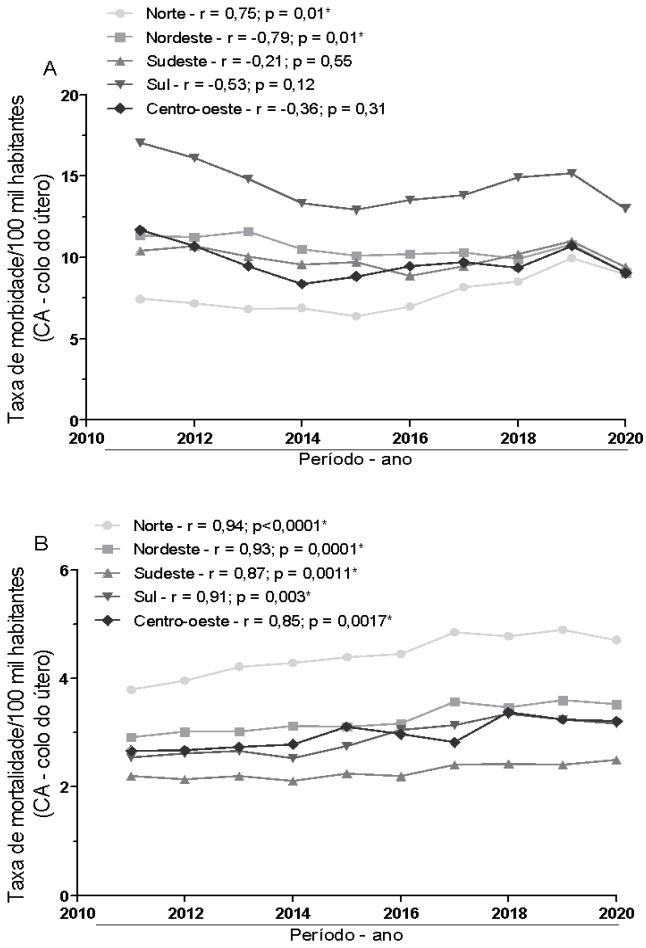
observed for the northeast region. The other regions did not show significant correlations (p>0.05) (Figure 2A). In the correlations for mortality rates, positive, predictor and significant correlations were evidenced for all the macro-regions evaluated (r>0.8; p<0.05) (Figure 2B).

Figure 2. Temporal correlations for morbidity and mortality due to malignant cervical neoplasm for the different Brazilian macro-regions.



Source: Morbidity and mortality data were extracted from the Ministry of Health database (DataSus) via Tabnet and the rates obtained were correlated with the survey period (2011 to 2020). (A) Correlation for morbidity. (B) Correlation for mortality. A * demonstrates a significant difference for correlation. The level of significance used was 5%.

In the end, possible correlations were found between the mean morbidity and mortality rates and the vaccination coverage for the second stage among individuals aged 9 to 12 years for the year 2015 (Figure 3). For the average morbidity rates per 100 thousand inhabitants, vaccination coverage did not show a significant correlation (rho = 0.39; p>0.05) (Figure 3A), on the other hand, vaccination coverage observed in 2015 was negatively correlated with the mortality rate for malignant cervical neoplasm (rho = - 0.80; p<0.05) (Figure 3B).

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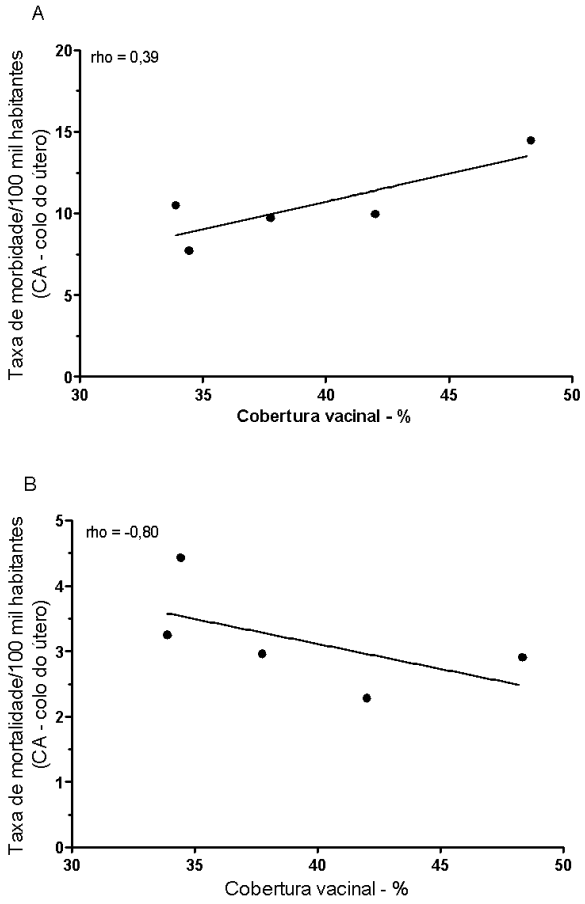
Figure 3. Correlation between morbidity and mortality rates and vaccination coverage for the Human Papillomavirus.



Source: Morbidity and mortality data were extracted from the Ministry of Health database (DataSus) via Tabnet, and vaccination coverage was extracted from the National Immunization Program Information System. The means were obtained by the period evaluated (morbidity and mortality) or by the states belonging to each macro-region (vaccination coverage). The level of significance used was 5%.

DISCUSSION

The discrepancy in morbidity and mortality rates due to malignant cervical cancer between the macro-regions of Brazil is a relevant finding, highlighting significant inequalities in possible gaps in access to health services and in the effectiveness of prevention and treatment programs. Although the South has the highest morbidity rate, it is surprising to observe that the North and Northeast regions exhibit the highest mortality rates, which indicates possible failures in the health systems in these regions, which may result in late diagnosis or lack of access to effective treatments. According to the study by Guedes (2022), this inverse correlation between morbidity and mortality between different regions suggests the existence of additional factors in addition to the incidence of the disease, such as the quality of health services, availability of appropriate treatments, and the population's awareness of prevention and early detection.

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These results contrast with some expectations previously established in the scientific literature, which generally associate higher morbidity rates with higher mortality rates. However, they highlight the complexity of public health issues, which go beyond the simple incidence of the disease. As pointed out in the study conducted by Ferreira *et al.,* (2021), there is a need for strategies targeted and adapted to each region, considering not only the prevalence of the disease, but also the social, economic, and cultural determinants that impact the effectiveness of health interventions. Thus, this deeper understanding of regional disparities in cervical cancer morbidity and mortality can direct more effective public policies and distribute resources more equitably to improve health outcomes, early diagnosis, treatment, and prevention for populations across the country.

By evaluating the data from the temporal analysis of morbidity and mortality rates due to malignant cervical neoplasm among the macro-regions of Brazil, they reveal interesting patterns and important nuances. The presence of significant correlations between morbidity and mortality in different regions suggests that the determinants and risk factors related to cervical cancer may vary considerably across the country (Tibes, 2024). The positive correlation observed in the North region for morbidity indicates a possible consistent increase in the detection of cervical cancer cases over time, which may reflect improvements in health services or an increase in awareness and access to preventive screenings. On the other hand, the negative correlation in the Northeast region indicates a reduction in the incidence of the disease during the study period, which can be attributed to several preventive interventions or changes in risk factors in this region.

These findings partially corroborate the scientific literature, which already highlights the regional variability in cervical cancer morbidity and mortality rates in Brazil. However, the presence of positive and significant correlations between mortality rates in all macro-regions contradicts the expectation that greater early detection would lead to a decrease in mortality rates. This suggests that other factors such as access to appropriate treatment, quality of health services, and socioeconomic factors may be playing a crucial role in determining cervical cancer mortality outcomes in the country (Tibes, 2024; Nascimento *et al.,* 2023).

The results of the correlations between morbidity and mortality rates due to malignant cervical neoplasm and vaccination coverage in the second stage among individuals aged 9 to 12 years for the year 2015 provide important information on the possible influence of HPV vaccination in reducing mortality related to this disease. Although

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no significant correlation was found between vaccination coverage and morbidity rates, the finding of a significant negative correlation between vaccination coverage and mortality rate suggests that vaccination can play a significant role in preventing more severe forms of the disease and, consequently, in reducing mortality.

These findings are in line with previous research that has highlighted the effectiveness of HPV vaccination in preventing cervical cancer and its precursors. The negative correlation observed here suggests that increased vaccination coverage may be associated with a decrease in the incidence of severe cases of cervical cancer, which are more likely to result in death. This finding highlights the continued importance of promoting and implementing HPV vaccination programs, not only to reduce the incidence of the disease, but also to mitigate its impacts on morbidity and mortality (Calumby *et al.,* 2020). However, it is crucial to emphasize that the correlation found does not necessarily imply direct causality. Other factors, such as improvements in healthcare systems, access to screening tests, and effective treatments, may also influence observed mortality rates (Silva *et al.,* 2020). Therefore, additional studies are needed to further evaluate the relationship between HPV vaccination coverage and cervical cancer mortality, taking into account different variables and regional contexts.

CONCLUSION

This study provides important data on the relationship between HPV vaccination coverage and cervical cancer morbidity and mortality rates in the different macro-regions of the country. Although no significant correlation was found between vaccination coverage and morbidity rates, the significant negative correlation between vaccination coverage and mortality rate suggests a possible protective effect of vaccination in reducing mortality related to this disease.

These findings are consistent with the existing scientific literature, which already highlights the efficacy of HPV vaccination in preventing cervical cancer. The negative correlation between vaccination coverage and mortality reinforces the importance of promoting and implementing HPV vaccination programs as a fundamental strategy to reduce the burden of cervical cancer in Brazil. However, it is important to emphasize that the correlation found does not necessarily imply direct causality, and other factors, such as access to health services and quality of screening and treatment programs, may also influence the observed results.

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Ultimately, this research enriches the understanding of the role of HPV vaccination in public health in Brazil, providing relevant evidence on its potential impact on reducing cervical cancer morbidity and mortality. These results can inform health policies and direct efforts to strengthen immunization and cancer prevention programs, aiming to achieve the goal of cervical cancer eradication by 2030, as established by the World Health Organization (WHO).

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