

RESEARCH ARTICLE



Impact of HPV vaccination on the hospitalizations for anogenital warts and high-grade cervical intraepithelial neoplasia in Brazil: A national analysis

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ABSTRACT

The HPV vaccination program in Brazil, introduced in 2014 for girls and 2017 for boys, aims to reduce HPV-related diseases, including anogenital warts (AGW) and high-grade cervical intraepithelial neoplasia (CIN). This descriptive ecological study evaluated the program's impact on hospitalizations for AGW and high-grade-CIN using interrupted time series analysis of data from the Brazilian Hospital Information System from 2011 to 2019. From 2011 to 2019, there were 4,312 AGW hospitalizations among females, 7,295 AGW hospitalizations among males, and 84,306 hospitalizations for high-grade CIN. Following the implementation of the HPV vaccination program, significant reductions in hospitalizations for AGW and high-grade CIN were observed, particularly in the targeted 15–19-year-old age group. In this group, the median number of hospitalizations prevented was 174 (95% CI: 154–193) for AGW among females, 116 (95% CI: 86–147) for AGW among males, and 217 (95% CI: 94–339) for high-grade CIN, with strong model fits. Downward trends were also noted in older age groups, though with poorer model fits. The HPV vaccination program has significantly reduced hospitalizations for AGW and high-grade CIN in Brazil, particularly among the targeted age group. Local evidence of early disease benefits reinforces the importance of HPV immunization in reducing the burden of HPV-related diseases and support expanding vaccination efforts for broader public health benefits. Reductions of AGW and high-grade CIN in older age groups may reflect indirect vaccination effects and treatment strategies, respectively.

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Introduction

Human papillomavirus (HPV) is the primary cause of cervical cancer and anogenital warts (AGW), both significant health issues in Brazil.^{1–3} To combat these issues, Brazil introduced a quadrivalent HPV vaccination program in March 2014. Initially targeting girls aged 11–14 years with a three-dose regimen, it was later adjusted to two doses and expanded to include girls aged 9–11 years by 2015.⁴ In 2017, it was expanded to boys aged 11–14 years, and by 2018, to boys aged 9–10 years.⁵ Since 2015, populations with medical conditions up to 45 years at higher risk of HPV-related disease have been progressively included.^{6,7}

Initial coverage rates for girls in 2014 reached 87% for the first dose and around 60% for the second dose. Between 2015 and 2019, first-dose coverage for girls consistently exceeded 90% by age 15. However, vaccination coverage for boys lagged, with fewer than 30% of boys receiving the first dose by age 15 in 2017. This increased to 48% in 2019, although still lower than the rates for girls.⁸

Since 1988, the Brazilian Ministry of Health has recommended that women aged 25 to 60 undergo a Pap smear annually, transitioning to every 3 years after two consecutive negative results.⁹ However, women younger than 25 can still undergo a Pap smear if they have specific risk factors or if their healthcare provider deems

it necessary based on their medical history.⁹ Additionally, annual screening for sexually transmitted infections for sexually active adolescents is recommended, including a Pap smear if there is any suspicion of cervical or vaginal disease.¹⁰ Data from the Brazilian Cervical Cancer Information System for the period 2013–2019 indicate that approximately 20% of Pap smears were conducted in women under 20 years of age.¹¹

Given the early age of sexual initiation in Brazil, with a mean age of approximately 14 years, monitoring AGW and high-grade cervical intraepithelial neoplasia (CIN) can serve as early indicators of vaccination impact.^{12–15} In high-income countries with high vaccination coverage, significant decreases in HPV-related diseases have been reported shortly after the implementation of HPV vaccination programs.^{16–19} The POP-Brazil study demonstrated an 80.6% reduction in the prevalence of HPV types 6, 11, 16, and 18 in vaccinated girls aged 16–17 years compared to unvaccinated counterparts (2.6% vs. 18.6%) after 3 years of HPV vaccine introduction.²⁰ However, no evaluation of the vaccine's impact on disease reduction has been reported in Brazil.

This study aims to fill this gap by utilizing national secondary hospitalization data to assess the trends in AGW and high-grade CIN hospitalization rates over a nine-year period, including 5 years post-vaccination. By examining these early disease outcomes, this study seeks to determine whether the HPV

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vaccination program is producing the expected effect in reducing these HPV-related diseases. Understanding the impact of vaccination in Brazil is crucial for improving public health policies and supporting the importance of HPV immunization.

Materials and methods

Study design and population

This descriptive ecological interrupted time series (ITS) study utilized secondary data from the Brazilian Hospital Information System (SIH) from 2011 to 2019, excluding data from 2020 onwards due to the impact of the COVID-19 pandemic on healthcare.²¹

Age groups were categorized as 10–14, 15–19, 20–24, 25–29, 30–39, 40–49 and 50+ years. Both sexes were analyzed for AGW, while only females were included for high-grade CIN.

Data sources

Hospitalization data were obtained from the SIH database, covering approximately 75% of hospitalizations in Brazil.²² This database contains anonymized records without unique identifiers, thus the unit of analysis is individual hospitalization. Population data were obtained from the Brazilian Institute of Geography and Statistics.²³

Case definitions

AGW and high-grade CIN (CIN 2, CIN 3, and carcinoma *in situ*) hospitalizations were identified using ICD-10 codes in the main diagnosis field. Only records with definitive surgical procedures were included for high-grade CIN, while no procedure codes were used for AGW. A detailed list of ICD-10 codes and surgical procedures is in the supplementary materials (Table S1).

Data analysis

Hospitalization rates per 100,000 population and the number of hospitalizations for AGW and high-grade CIN were analyzed by year and age group. For AGW, analysis was also by sex. Separate generalized linear models with a negative binomial distribution, stratified by age group and sex, were used for the ITS analysis. These models predicted AGW and high-grade CIN-related hospitalizations in the post-vaccination period, to estimate counterfactual hospitalization counts. We then compared these estimates with observed hospitalizations to evaluate the impact of HPV vaccination.

A time-series regression approach estimated changes in half-yearly hospitalization rates before and after HPV vaccination program. For females, the pre-vaccination period was January 2011 to January 2014, and the post-vaccination period was July 2014 to December 2019. For males, the periods were January 2011 to January 2017, and July 2017 to December 2019. The models included terms for the pre-intervention trend, the immediate level change at intervention, and the post-intervention trend. The logarithm of the population divided by 100,000 was an offset variable to adjust for potential population changes over time.

Potential leverage points (influential outliers) were analyzed by comparing actual and adjusted values. An influential leverage point in the 15 to 19 age group for AGW among females caused an overestimation of counterfactual hospitalizations in the postvaccination period. To address this, we replaced the outlier with the average of its preceding and succeeding values, resulting in a more parsimonious model.²⁴

Goodness-of-fit for models was evaluated using the simulated envelope method and pseudo- R^2 values (poor < 0.5, moderate = 0.5–0.6, or good > 0.6).^{24,25} Immediate level changes and pre- and post-vaccination trends were calculated for all age groups, regardless of the pseudo- R^2 value. The primary measure of impact compared observed rates to estimated counterfactual counts in the post-vaccination period.

To determine the statistical significance of the differences between observed and counterfactual counts, we used a bootstrap simulation with 1,000 replications. This approach estimated the total number of averted HPV-related hospitalizations by resampling the data and generating a distribution of differences. Results were represented as median differences and percentiles (2.5 and 97.5).

To assess the robustness of findings, two types of sensitivity analysis were conducted. First, quarterly data were used instead of half-yearly data to increase data points and potentially provide a more detailed view of trends. It was also assessed if this granularity led to greater data dispersion, affecting estimate stability. Second, a model using the full dataset with covariates for sex, age, time (in days), and an indicator for pre- and post-vaccine implementation was fitted. Interaction terms between sex and age, and between time and the indicator variable, were added to assess their combined influence. By comparing these models, we aimed to confirm similar findings, demonstrating the robustness of our results when accounting for these additional factors.

Results

From 2011 to 2019, there were 11,607 AGW hospitalizations (4,312 females and 7,295 males), and 84,306 high-grade CIN hospitalizations. Table 1 shows hospitalization rates and counts for 2011, 2015, and 2019 by age group. Males consistently had higher hospitalization rates for AGW than females. In females, the 15–19 age group had the highest AGW hospitalization rate in 2011 and 2015. By 2019, this age group had the largest decline, with the highest rates shifting to the 20–24 age group. In males, the highest AGW hospitalization rates were consistently observed in the 20–24 age group throughout the period. The 15–19 age group experienced nearly double the incidence from 2011 to 2015, returning to 2011 levels by 2019.

For high-grade CIN, the 30–39 age group consistently had the highest hospitalization rates, rising from 15.3 per 100,000 in 2011 to 24.3 per 100,000 in 2019. The 15–19 age group saw a decrease in hospitalization rates, dropping from 1.0 per 100,000 in 2011 to 0.5 per 100,000 in 2019 (Table 1).

For AGW hospitalization trends among females (Figure 1), the 15–19 age group exhibited a strong model fit and a significant post-vaccination reduction in hospitalizations. Hospitalizations dropped significantly compared to both the observed pre-vaccination levels and the counterfactual

Table 1. Hospitalizations and rates per 100,000 for anogenital warts (females and males) and high-grade cervical intraepithelial neoplasia, by age group. Brazilian data, 2011, 2015 and 2019.

Year	Age group (years)	Female Anogenital Warts		Male Anogenital Warts		High-grade Cervical Intraepithelial Neoplasia	
		n	Rate/100,000	n	Rate/100,000	n	Rate/100,000
2011	10–14	19	0.2	11	0.1	7	0.1
	15–19	100	1.2	64	0.7	89	1.0
	20–24	75	0.9	116	1.3	559	6.4
	25–29	43	0.5	97	1.1	1,111	12.6
	30–39	78	0.5	142	0.9	2,389	15.3
	40–49	53	0.4	115	0.9	2,016	15.3
	50+	54	0.2	67	0.4	1,495	6.8
2015	All ages	422	0.5	612	0.8	7,666	9.0
	10–14	14	0.2	15	0.2	1	0.0
	15–19	124	1.5	110	1.3	117	1.4
	20–24	92	1.1	198	2.3	615	7.2
	25–29	45	0.5	143	1.7	1,325	15.2
	30–39	94	0.6	155	1.0	3,443	20.5
	40–49	90	0.6	108	0.8	2,244	16.2
2019	50+	107	0.4	124	0.6	1,901	7.5
	All ages	566	0.6	853	1.0	9,646	10.8
	10–14	8	0.1	8	0.1	2	0.0
	15–19	28	0.4	54	0.7	40	0.5
	20–24	67	0.8	218	2.5	596	6.9
	25–29	39	0.5	131	1.5	1,467	17.2
	30–39	86	0.5	198	1.2	4,201	24.3
	40–49	86	0.6	117	0.8	2,808	19.0
	50+	100	0.3	139	0.6	2,141	7.5
	All ages	424	0.5	865	1.0	11,255	12.1

estimate. The 50+ age group also demonstrated a good fit, with a moderate decrease after 2014. The 40–49 age group had a moderate fit, with hospitalization rates stabilizing post-vaccination, while the counterfactual suggests these rates would have increased without the vaccine.

Models with pseudo- R^2 values close to or above 0.5 generally yielded more statistically significant results (Table 2). Among the 15–19 age group, the median number of hospitalizations prevented was 174 (95% CI: 154, 193) for AGW among females, 116 (95% CI: 86, 147) for AGW among males, and 217 (95% CI: 94, 339) for high-grade CIN. For older age groups, significant reductions were observed in non-targeted populations. Among females aged 40–49, 301 hospitalizations for AGW were prevented (95% CI: 266, 334), and among males, reductions were seen across several age groups, including 20–24 years, 25–29 years, and 50+ years. For high-grade CIN, the most significant reduction was observed in the 30–39 age group, with a median of 3,920 hospitalizations prevented (95% CI: 2,603, 5,238). In the 50+ age group, the model also showed a strong fit, with a significant reduction of 1,204 hospitalizations (95% CI: 301, 2,107). Conversely, no statistically significant changes were found in some other age groups, particularly the 40–49 age group, where confidence intervals included zero, reflecting a poorer model fit.

For AGW hospitalization trends among males (Figure 2), the 15–19 age group exhibited the most significant reduction, with hospitalizations falling below both the counterfactual and pre-vaccination levels. The 20–24 age group had the strongest model fit, with reduced hospitalizations compared to counterfactual, but not below pre-vaccination levels. The 25–29, 30–39, and 50+ age groups showed declines or stabilization, but hospitalization levels remained higher than those observed before vaccination, despite reductions compared to the counterfactual.

For high-grade CIN hospitalization trends (Figure 3), the 15–19 age group saw significant decreases post-vaccination, dropping below both pre-vaccination levels and the counterfactual estimate. Other age groups, such as 25–29, 30–39, 40–49, and 50+, showed stabilization or slight declines post-vaccination compared to the counterfactual. Hospitalization levels in these groups remained higher than pre-vaccination levels though lower than expected based on the counterfactual scenario. The 10–14-year-old age group showed a reduction in hospitalizations, but the model fit was weaker.

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The sensitivity analyses using quarterly data instead of half-yearly data showed similar results but with poorer model fits (Figure S1–S3, Table S2). In the full model with covariates and interaction terms, the main findings

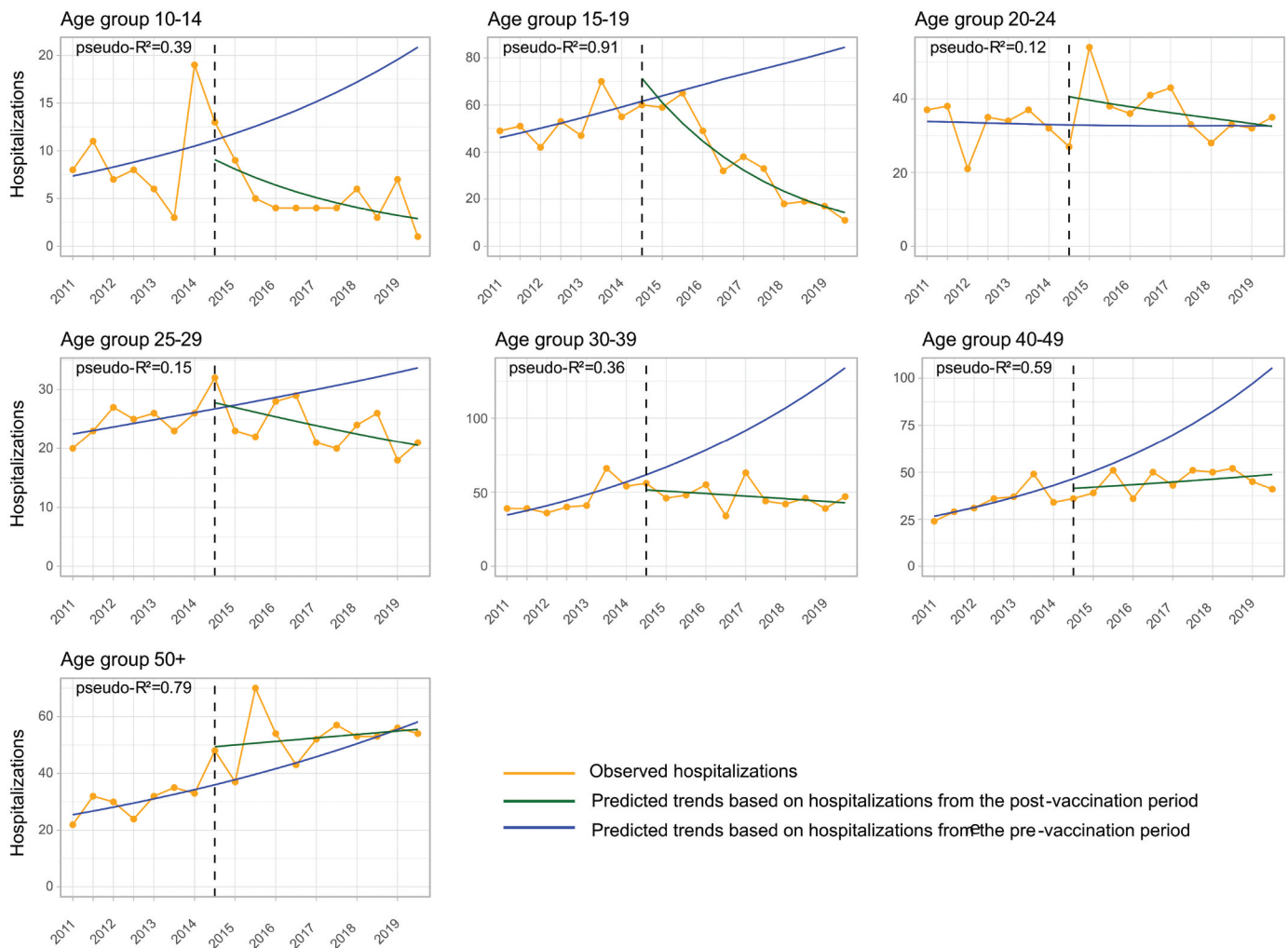


Figure 1. Age-specific time series of hospitalizations for anogenital warts among females: Observed data vs. counterfactual and post-vaccination estimates. For AGW hospitalization trends among males (Figure 2), the 15–19 age group exhibited the most significant reduction, with hospitalizations falling below both the counterfactual and pre-vaccination levels. The 20–24 age group had the strongest model fit, with reduced hospitalizations compared to counterfactual, but not below pre-vaccination levels. The 25–29, 30–39, and 50+ age groups showed declines or stabilization, but hospitalization levels remained higher than those observed before vaccination, despite reductions compared to the counterfactual.

aligned with the age- and sex-specific models, showing a moderate fit and similar issues, thereby reinforcing the consistency of results.

Within the 15–19 age group, a detailed breakdown by individual years showed an increasing trend in the proportions of AGW and high-grade CIN hospitalizations as age increased. Among males, the proportion of AGW rose from 5.4% at age 15% to 37.8% at age 19. In females, the proportion peaked earlier, increasing from 11.9% at age 15% to 24.2% at age 17, before decreasing slightly to 22.1% at age 19. For CIN, the increase was pronounced, starting at 4.5% at age 15 and rising to 40.7% by age 19 (Figure S4, Table S3).

Discussion

Our study evaluated the national impact of HPV vaccination on hospitalizations for AGW and high-grade CIN in Brazil using an ITS analysis. We observed significant reductions in HPV-related hospitalizations post-vaccination compared to counterfactual and prevaccination levels, particularly in the

targeted 15–19-year-old age group. The more pronounced decline in AGW hospitalization rates among female adolescents is likely due to the longer duration since vaccination and higher coverage compared to males. These findings align with prior research on HPV effectiveness in adolescents.^{18,26–28}

We did not observe significant reductions in adolescents aged 10–14 years across the outcomes studied. For some older age groups in females, observed AGW hospitalizations were lower than counterfactual projections, although many models had poor or only moderate fits. In males, older age groups showed reduced AGW hospitalizations compared to counterfactual projections, but not below pre-vaccination levels. Most changes reflected a shift from an increasing pre-vaccination trend to a more stable or decreasing post-vaccination trend. Reductions in AGW among non-targeted ages may be due to indirect effects.^{18,29–32}

Additional factors may also contribute to the observed reductions in AGW hospitalizations among older age groups. One of them is the expansion of the public HPV vaccination for immunocompromised individuals up to 45 years. Although these individuals are a small fraction of the population, they

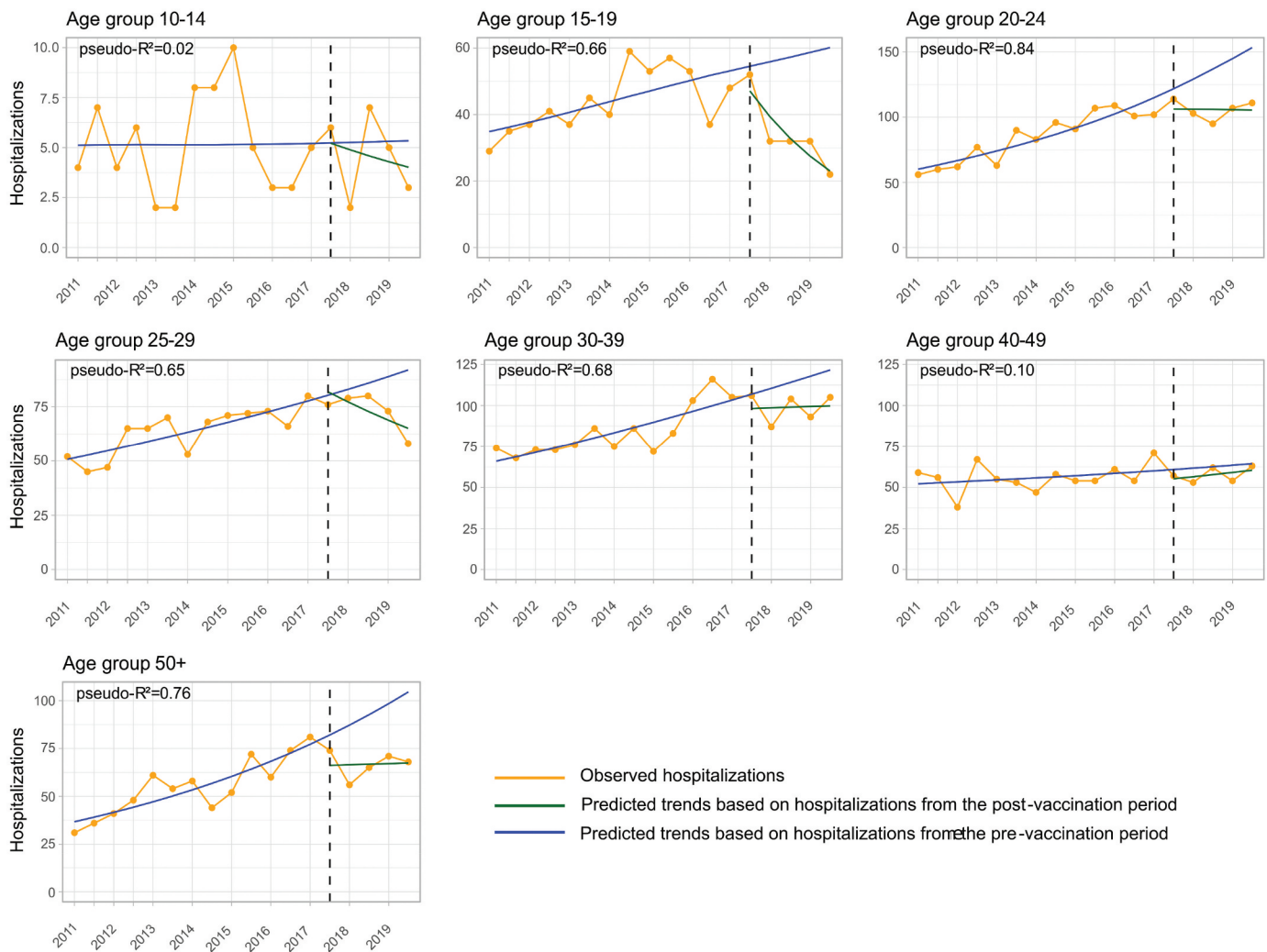


Figure 2. Age-specific time series of hospitalizations for anogenital warts among males: Observed data vs. counterfactual and post-vaccination estimates. For high-grade CIN hospitalization trends (Figure 3), the 15–19 age group saw significant decreases post-vaccination, dropping below both pre-vaccination levels and the counterfactual estimate. Other age groups, such as 25–29, 30–39, 40–49, and 50+, showed stabilization or slight declines post-vaccination compared to the counterfactual. Hospitalization levels in these groups remained higher than pre-vaccination levels, though lower than expected based on the counterfactual scenario. The 10–14-year-old age group showed a reduction in hospitalizations, but the model fit was weaker.

may be disproportionately represented among those requiring hospitalization for AGW. In industrialized countries, AGW hospitalization rates range from 7% to 19%.³³ This could partially explain the reductions in certain older age groups. However, verifying these hypotheses is challenging due to the lack of mandatory comorbidity data in the SIH database and limited detail on reporting practices.

Regarding high-grade CIN, our study found a reduction in hospitalizations in 15–19 age group, consistent with the POP-Brazil study, which reported a 73.7% reduction in HPV 16 prevalence.²⁰ Other studies support this early impact: a meta-analysis by Drolet et al. reported a 51% reduction in high-grade CIN rates 5 to 8 years post-vaccination. Ellingson et al. found the vaccine 86% effective in preventing CIN3+ in girls vaccinated at ages 12–13, and Hofstetter et al. observed a 76% lower risk of cervical abnormalities in those vaccinated between ages 11–14.^{18,34,35}

Reductions (or stabilization of slightly increasing trends) were also observed for high-grade CIN among older age

groups in our study. Since CIN incidence peaks in older age groups compared to AGW, these reductions had a greater numerical impact than in the vaccine-targeted age group. In addition, unlike AGW, which is mostly managed outpatient, a larger proportion of CIN require hospitalization for treatment.³⁶ These trends in older women are likely more influenced by cervical cancer screening and early detection efforts, including the amplification of *see and treat* interventions for high-grade CIN performed on an outpatient basis, rather than recent changes in HPV transmission or vaccination effects.^{37–41}

Monitoring trends in AGW and high-grade CIN provides an early and sensitive measure of HPV vaccine impact, well before reductions in cervical cancer rates become evident. Our results reinforce the critical role of HPV vaccination in the national strategy to eliminate cervical cancer as a public health problem. Brazilian NIP has made continuous efforts to expand HPV vaccination for populations of high-risk to develop HPV-disease. An additional group that stands to benefit from

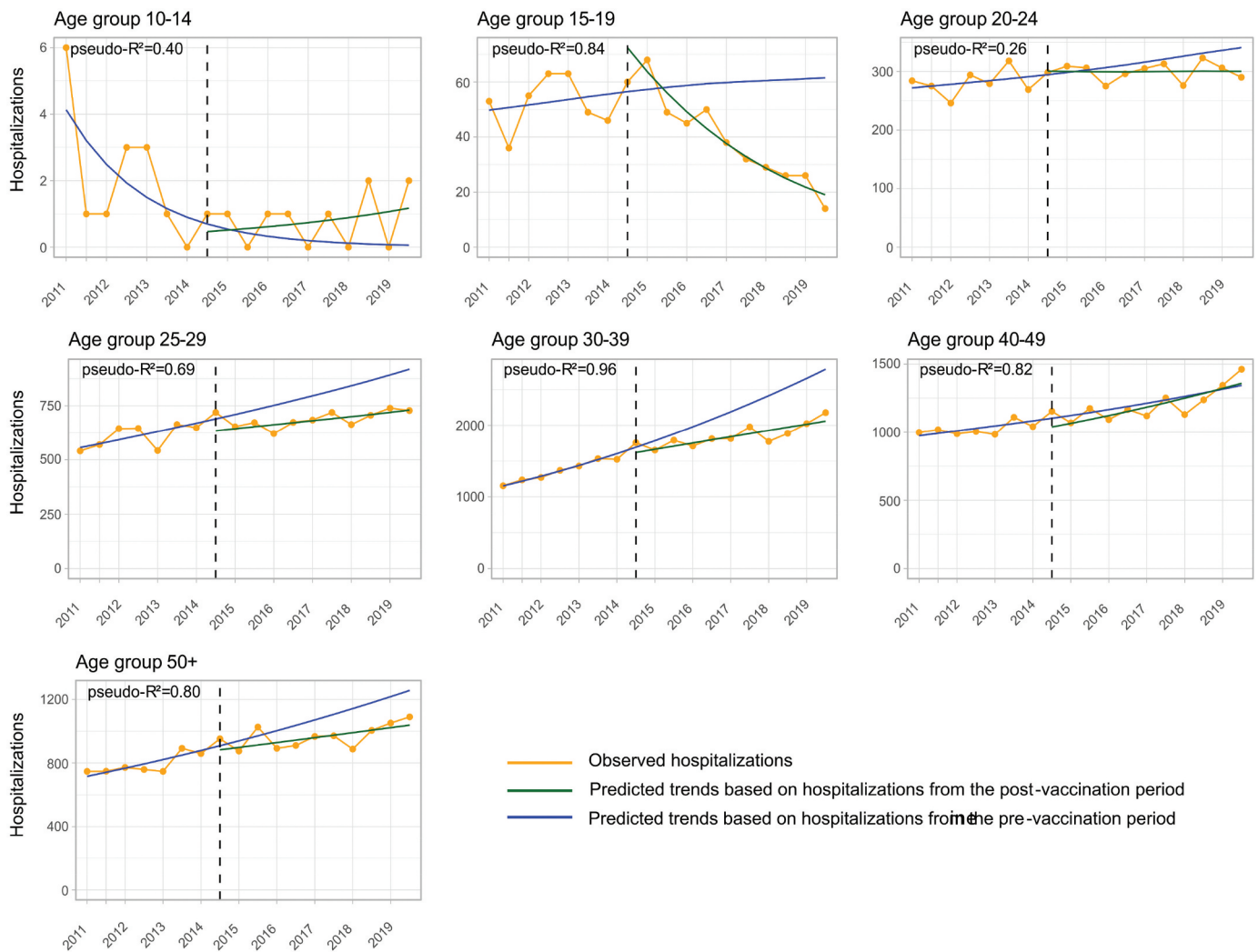


Figure 3. Age-specific time series of hospitalizations for cervical intraepithelial neoplasia – Surgical procedures: Observed data vs. counterfactual and postVaccination estimates.

vaccination includes women previously diagnosed with high-grade CIN. Growing evidence indicates that women previously treated for high-grade CIN face a significantly elevated risk of recurrence, either due to persistent high-risk HPV infections or reinfection with new HPV genotypes.^{42–46} Importantly, post-treatment HPV vaccination has been shown to reduce this risk, offering a valuable secondary prevention strategy for this high-risk group.⁴⁴ These findings support continued efforts to broaden vaccine access and coverage to maximize the protective benefits of the HPV immunization program.

Several methodological considerations arise in this study. ITS analysis is prone to ecological fallacy, as it assumes that observed changes are primarily attributed to the intervention – here, HPV vaccination – without fully accounting for other concurrent factors. While this approach controls trends and seasonality, it cannot entirely rule out other confounding environmental factors, like improved healthcare access or shifts in public health policies coinciding with the intervention. As discussed earlier, other factors occurring during the study period likely contributed to the observed trends; however, we are unaware of any major changes in reporting or recording practices that could have significantly influenced the

results. Additionally, it is important to acknowledge some diagnostic challenges in our models, specifically issues with dispersion, heteroscedasticity, and small sample sizes, particularly for the younger age group. We found some evidence of these challenges, but not to a degree that would undermine the findings. However, they could still affect the robustness of the results and should be considered when interpreting them.

We acknowledge the risk of false positives due to the multiplicity of tests. Rather than applying statistical corrections, we present the full p-values for the reader's discretion. If more stringent p-value thresholds were used, many models, especially those for older individuals, would lose significance. Thus, caution is needed when interpreting the results based on conventional p-values alone. Additionally, while the model fit was low for some age groups, it represented the best achievable fit given the available data. Our use of semester data points, complemented by a sensitivity analysis using quarterly data, yielded consistent findings, reinforcing the reliability of our conclusions despite fit limitations and the multiple tests.

This study's reliance on national SIH data provides broad coverage of HPV-related hospitalizations across Brazil but introduces challenges such as potential coding inaccuracies

Table 2. Hospitalizations for genital warts among females and males, cervical intraepithelial neoplasia-surgical procedures. Model fit assessment and impact estimates by age group: pre- and post-vaccination trends, immediate level change, and differences between observed and estimated hospitalizations in the post-vaccination period.

Age groups (years)	Pseudo-R ²	p-values			Model estimates			Hospitalizations in the post-vaccination period			
		Pre-vaccination trend	Immediate level change	Post-vaccination trend	Pre-vaccination trend	Immediate level change	Post-vaccination trend	Observed	Estimated without vaccine	Median Difference	95% CI
Genital warts among females											
10–14	0.393*	0.381	0.947	0.060	1.073	0.973	0.837	60	170	110	92; 128
15–19	0.906	0.704	<0.001	<0.001	1.010	1.631	0.850	401	575	174	154; 193
20–24	0.124*	0.970	0.169	0.582	0.999	1.260	0.979	400	360	−40	−56; −25
25–29	0.148*	0.504	0.620	0.215	1.026	1.096	0.948	264	331	67	50; 83
30–39	0.360*	0.013	0.532	0.003	1.076	0.918	0.909	520	1,035	515	474; 553
40–49	0.594	0.023	0.725	0.065	1.076	0.950	0.937	494	795	301	266; 334
50+	0.786	0.351	0.019	0.330	1.033	1.432	0.964	577	510	−67	−109; −31
Genital warts among males											
10–14	0.019*	0.743	0.898	0.645	1.011	1.071	0.932	23	26	3	−5; 12
15–19	0.657	0.002	0.753	<0.001	1.036	1.059	0.816	170	286	116	86; 147
20–24	0.836	<0.001	0.501	0.061	1.057	0.926	0.942	530	686	156	105; 208
25–29	0.637	<0.001	0.410	0.017	1.036	1.117	0.913	366	430	64	26; 102
30–39	0.680	<0.001	0.630	0.390	1.029	0.944	0.972	495	571	76	33; 120
40–49	0.105*	0.602	0.499	0.847	1.005	0.900	1.008	289	313	24	−6; 54
50+	0.756	<0.001	0.269	0.161	1.047	0.853	0.945	334	465	131	88; 174
High-grade Cervical Intraepithelial Neoplasia											
10–14	0.399*	0.043	0.710	0.049	0.784	0.673	1.409	9	3	−6	−9; −3
15–19	0.841	0.422	0.057	<0.001	1.017	1.283	0.867	437	654	217	94; 339
20–24	0.261*	0.122	0.708	0.188	1.014	1.021	0.985	3,297	3,483	186	−100; 471
25–29	0.689	<0.001	0.071	0.114	1.032	0.921	0.985	7,577	8,786	1,209	600; 1,817
30–39	0.956	<0.001	0.202	<0.001	1.046	0.957	0.974	20,375	24,295	3,920	2,603; 5,238
40–49	0.816	0.112	0.178	0.428	1.012	0.942	1.007	13,206	13,389	183	−707; 1072
50+	0.804	0.043	0.565	0.111	1.017	0.972	0.984	10,626	11,830	1,204	301; 2,107

* These rows have models with pseudo-R² values below 0.5 indicating a poor fit and suggesting that the estimates derived from these models should be interpreted with caution, if not altogether disregarded.

and regional variations in data completeness. Additionally, the SIH database reflects only public hospitalizations, excluding private or out-of-pocket settings. One positive aspect is that, during the study period, recording and reporting practices within the SIH database remained relatively stable. Another important limitation is that our analysis relied solely on hospitalization records. In Brazil, many high-grade CIN (CIN 2/3) cases are treated entirely in outpatient settings. Procedures like loop electrosurgical excision (LEEP), commonly performed without admission, are not captured in the hospital database (SIH). This is particularly relevant for younger women, who often present with less advanced disease and, when fertility preservation is a concern, are more likely to receive conservative or outpatient-based treatment.⁹ Capturing these cases would require outpatient data analysis, which is structurally distinct and planned for future work.

Overall, our study provides compelling evidence that the HPV vaccination program has significantly reduced hospitalizations for AGW in Brazil, with indirect benefits extending beyond targeted individuals, suggesting a possible herd effect for AGW in older age groups. The reductions in high-grade CIN are likely due to direct vaccination effects, while those in older age groups may result from enhanced cervical cancer screening programs. These findings underscore the importance of expanding and promoting the HPV vaccination program to maximize public health outcomes. Future research should focus on the long-term impact of the vaccine on HPV-related cancers in both genders and strategies to increase vaccine coverage across diverse populations.⁴⁷

Conclusion

In conclusion, our study shows that Brazil's HPV vaccination program significantly reduced hospitalizations for AGW and high-grade CIN among targeted age groups, especially adolescents aged 15–19. These findings align with previous research on HPV vaccine effectiveness and highlight its substantial public health benefits. Reductions in older age groups may reflect indirect vaccination effects and ongoing early treatment efforts, respectively. Our results emphasize the importance of expanding HPV vaccination efforts. Local evidence of these early benefits could help sustain and increase coverage, particularly in Latin American and Caribbean countries that rely on publicly funded programs. The success of Brazil's program exemplifies how targeted immunization strategies lead to significant health improvements and reinforces the need for continued support.

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Author contributions

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Notes on contributor

Cintia Irene Parellada is a physician who graduated from the Evangelical Medical School of Paraná, Brazil (1993), with a residency in Gynecology and Obstetrics at Londrina University Hospital (1995), followed by a fellowship in Gynecological Endocrinology and Lower Genital Tract Pathology and Colposcopy at Hospital das Clínicas, University of São Paulo (1996). In 2002, she received her PhD in Health Sciences, in the field of Obstetrics and Gynecology, from the same institution. She held a position on the executive board of the Brazilian Association for Lower Genital Tract Disease and Colposcopy (ABPTGIC) from 1998 to 2012, including roles as Scientific Director and editor of its journal and website. During this period, she led major initiatives in continuing medical education, including in-person and e-learning courses, newsletters, and scientific publications. Since 2006, Dr Parellada has worked at MSD in medical affairs and outcomes research, contributing across various therapeutic areas such as vaccines/immunology, respiratory diseases, human reproduction, and gynecology. Her academic background includes over 120 contributions to the scientific community, including journal articles, book chapters, congress presentations, and newsletters—demonstrating a strong commitment to advancing medical science and improving public health.

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Data availability statement

Data available on request from the authors.

Ethics approval statement

Ethics approval was not applicable for this study as all data were extracted from public and structured databases that contain anonymized and aggregated information. Specifically, the data were obtained from DATASUS: <https://datasus.saude.gov.br/informacoes-de-saude-tabnet/>

Generative artificial intelligence (AI)

During the preparation of this work the author(s) used Chat-GPT in order to assist with language editing and refinement of text structure. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

References

1. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664–670. doi:10.1002/ijc.30716.
2. Instituto Nacional de Câncer – INCA. Estimativa 2023 : Incidência de Câncer No Brasil. 2023. <https://Www.Inca.Gov.Br/Sites/Ufu.Sti.Inca.Local/Files/Media/Document/Estimativa-2023.Pdf>.
3. Ministério da Saúde S de V em S e A Departamento do Programa Nacional de Imunizações, Coordenação Geral de Incorporação Cien. Nota Técnica No 41/2024-CGICI/DPNI/SVSA/MS. Atualização Das Recomendações Da Vacinação Contra HPV No Brasil. Adotar a Dose Única Da Vacina HPV No Brasil Para Os Adolescentes de 9 a 14 Anos e Incorporar a Vacinação Contra HPV Nos Pacientes Com Diagnos. 2017.
4. Baker ML, Figueroa-Downing D, Chiang ED, Villa L, Baggio ML, Eluf-Neto J, Bednarczyk RA, Evans, DP. Paving pathways: Brazil's implementation of a national human papillomavirus immunization campaign. *Rev Panam Salud Publica*. 2015;38(2):163–166.
5. Brasil. Ministério da Saúde. Nota informativa nº 311/2016/CGPNI/DEVIT/SVS/MS. <https://antigo.aids.gov.br/pt-br/legislaao/nota-informativa-no-3112016cgpniidevitsvms>.
6. Carvalho NS, Silva R, Val ICD, Bazzo ML, Silveira MFD. Brazilian protocol for sexually transmitted infections 2020: human papillomavirus (HPV) infection. *Rev Soc Bras Med Trop*. 2021;54(suppl 1):e2020790. doi: 10.1590/0037-8682-790-2020.
7. Ministério da Saúde. Instrução Normativa Do Calendário Nacional De Vacinação 2024. <https://Sbim.Org.Br/Noticias/1885-Ms-Vacina-Hpv4-Para-Pessoas-Com-Papilomatose-Respiratoria-Recorrente-Prr>.
8. World Health Organization. Human papillomavirus (HPV) vaccination coverage. [https://immunizationdata.who.int/global/wiise-detail-page/human-papillomavirus-\(hpv\)-vaccination-coverage?CODE=BRA&ANTIGEN=15HPV1_F&YEAR=](https://immunizationdata.who.int/global/wiise-detail-page/human-papillomavirus-(hpv)-vaccination-coverage?CODE=BRA&ANTIGEN=15HPV1_F&YEAR=).
9. Brasil. Ministério Da Saúde. Instituto Nacional de Câncer José Alencar Gomes Da Silva. Diretrizes Brasileiras Para o Rastreamento Do Câncer Do Colo Do Útero, 2ª Edição Atualizada. Rio (de) Janeiro: INCA 2016 https://Www.Inca.Gov.Br/Sites/Ufu.Sti.Inca.Local/Files//Media/Document//Diretrizes_para_o_rastreamento_do_cancer_do_colo_do_uterio_2016_corrigido.Pdf.
10. Ministério da Saúde Secretaria de Vigilância em Saúde Departamento de DST AeHV. Protocolo Clínico e Diretrizes Terapêuticas para Atenção Integral às Pessoas com Infecções Sexualmente Transmissíveis.

11. DataSUS. Sistema de Informação do Câncer - SISCAN. Citologia do Colo Uterino por Faixa Etária. http://tabnet.datasus.gov.br/cgi/dhdat.exe?SISCAN/cito_colo_pacbr.def.
12. Castellsagué X, Paavonen J, Jaisamrarn U, Wheeler CM, Skinner SR, Lehtinen M, Naud P, Chow S-N, Del rosario-Raymundo MR, Teixeira JC, et al. Risk of first cervical HPV infection and pre-cancerous lesions after onset of sexual activity: analysis of women in the control arm of the randomized, controlled PATRICIA trial. *BMC Infect Dis.* 2014;14(1):551. doi: 10.1186/s12879-014-0551-y.
13. Stanley M. Pathology and epidemiology of HPV infection in females. *Gynecologic Oncol.* 2010;117(2 Suppl):S5–10. doi: 10.1016/j.ygyno.2010.01.024.
14. Wiley DJ, Douglas J, Beutner K, Cox T, Fife K, Moscicki AB, Fukumoto L. External genital warts: diagnosis, treatment, and prevention. *Clin Infect Dis: Off Publ Infect Dis Soc Am.* 2002;35 (Suppl 2):S210–24. doi: 10.1086/342109.
15. Cunha KS, Okada LM, Rinaldi AEM, Marques ES, da Silva Paro HBM, Azeredo CM. Sexual initiation before age 14 and Co-occurrence of Health risk behaviors among Brazilian adolescents: data from the national school Health survey 2015. *Sex Res Soc Policy.* 2023;20(1):120–133. doi: 10.1007/s13178-022-00715-w.
16. Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, Fairley CK, Guy RJ. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ.* 2013;346(apr18 1):f2032. doi: 10.1136/bmj.f2032.
17. Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early impact of human papillomavirus vaccination on cervical neoplasia—nationwide follow-up of young Danish women. *J Natl Cancer Inst.* 2014;106(3):djt460. doi: 10.1093/jnci/djt460.
18. Drolet M, Bénard É, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet.* 2019;394(10197):497–509. doi: 10.1016/s0140-6736(19)30298-3.
19. Mesher D, Panwar K, Thomas SL, Edmundson C, Choi YH, Beddows S, Soldan K. The impact of the national HPV vaccination program in England using the bivalent HPV vaccine: surveillance of type-specific HPV in young females, 2010–2016. *The J. Infect. Dis.* 2018;218(6):911–921. doi: 10.1093/infdis/jiy249.
20. Wendland EM, Kops NL, Bessel M, Comerlato J, Maranhão AGK, Souza FMA, Villa LL, Pereira GFM. Effectiveness of a universal vaccination program with an HPV quadrivalent vaccine in young Brazilian women. *Vaccine.* 2021;39(13):1840–1845. doi: 10.1016/j.vaccine.2021.02.040.
21. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, Jones M, Kitchen E, Fox M, Johansson M, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open.* 2021;11(3):e045343. doi: 10.1136/bmjopen-2020-045343.
22. Massuda A, Andrade MV, Atun R, Castro MC. Brazil - international health care system profiles - commonwealth fund 2020. <https://www.commonwealthfund.org/International-Health-Policy-Center/Countries/Brazil>.
23. Brazilian Institute of Geography and Statistics. Projeção da população residente, segundo o sexo e os grupos de idade. [accessed 2024 Dec 2]. <https://anuario.ibge.gov.br/2023/caracteristicas-da-populacao/demografia/aeb-2023-tabelas-demografia/22076-projecao-da-populacao-residente.html>.
24. Paula GA. Modelos de Regressão: Com Apoio Computacional. 2024. IME-USP. https://www.ime.usp.br/~giapaula/Texto_2024.Pdf.
25. Scott Long J. Regression models for categorical and limited dependent variables. Advanced quantitative techniques in the social Sciences number 7. Thousand Oaks, CA: Sage Publications; 1997.
26. Smith LM, Strumpf EC, Kaufman JS, Lofthers A, Schwandt M, Lévesque LE. The early benefits of human papillomavirus vaccination on cervical dysplasia and anogenital warts. *Pediatrics.* 2015;135(5):e1131–40. doi:10.1542/peds.2014-2961.
27. Mikalsen MP, Simonsen GS, Sørbye SW. Impact of HPV vaccination on the incidence of high-grade cervical intraepithelial neoplasia (CIN2+) in women aged 20–25 in the northern part of Norway: a 15-year study. *NATO Adv Sci Inst Se.* 2024;12(4):421. doi: 10.3390/vaccines12040421.
28. Giuliano AR, Lee JH, Fulp W, Villa LL, Lazcano E, Papenfuss MR, Abrahamsen M, Salmeron J, Anic GM, Rollison DE, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet.* 2011;377(9769):932–940. doi: 10.1016/s0140-6736(10)62342-2.
29. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Liu B, Bateson D, McNamee K, Garefalakis M, Phillips S, Cummins E, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis.* 2014;14 (10):958–966. doi: 10.1016/s1473-3099(14)70841-2.
30. Patel C, Brotherton JM, Pillsbury A, Jayasinghe S, Donovan B, Macartney K, Marshall H. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? *Euro Surveill.* 2018;23(41). doi: 10.2807/1560-7917.Es.2018.23.41.1700737.
31. Nygård S, Nygård M, Orumaa M, Hansen BT. Quadrivalent HPV vaccine effectiveness against anogenital warts: a registry-based study of 2,2 million individuals. *Vaccine.* 2023;41(37):5469–5476. doi:10.1016/j.vaccine.2023.07.031.
32. Flagg EW, Torrone EA. Declines in anogenital warts among age groups most likely to be impacted by human papillomavirus vaccination, United States, 2006–2014. *Am J Public Health.* 2018;108(1):112–119. doi: 10.2105/ajph.2017.304119.
33. Cocchio S, Baldovin T, Bertonecello C, Buja A, Furlan P, Saia M, Baldo V. Decline in hospitalization for genital warts in the Veneto region after an HPV vaccination program: an observational study. *BMC Infect Dis.* 2017;17(1):249. doi: 10.1186/s12879-017-2361-5.
34. Hofstetter AM, Ompad DC, Stockwell MS, Rosenthal SL, Soren K. Human papillomavirus vaccination and cervical cytology outcomes among urban low-income minority females. *JAMA Pediatrics.* 2016;170(5):445–452. doi:10.1001/jamapediatrics.2015.3926.
35. Ellingson MK, Sheikh H, Nyhan K, Oliveira CR, Nicolai LM. Human papillomavirus vaccine effectiveness by age at vaccination: a systematic review. *Hum Vaccin Immunother.* 2023;19 (2):2239085. doi: 10.1080/21645515.2023.2239085.
36. World Health Organization. WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in Situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization 2014. <https://www.who.int/publications/i/item/9789241506779>.
37. Madeiro A, Rufino A. Cobertura e fatores associados à não realização do exame citopatológico do colo do útero entre mulheres brasileiras de 18 a 39 anos. *J Health Psychol & Biological Sciences.* 2022;10(1):1. doi: 10.12662/2317-3076/jhbs.v10i1.3521.p1-9.2022.
38. Lorenzi AT, Syrjänen KJ, Longatto-Filho A. Human papillomavirus (HPV) screening and cervical cancer burden. A Brazilian perspective. *Virol J.* 2015;12(1):112. doi: 10.1186/s12985-015-0342-0.
39. Corrêa FM, Migowski A, de Almeida LM, Soares MA. Cervical cancer screening, treatment and prophylaxis in Brazil: current and future perspectives for cervical cancer elimination. *Front Med (Lausanne).* 2022;9:945621. doi: 10.3389/fmed.2022.945621.
40. Bruni L, Serrano B, Roura E, Alemany L, Cowan M, Herrero R, Poljak M, Murillo R, Broutet N, Riley LM, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Glob Health.* 2022;10(8):e1115–e1127. doi: 10.1016/s2214-109x(22)00241-8.
41. Brown DR, Weaver B. Human papillomavirus in older women: new infection or reactivation? *The J Infect Dis.* 2013;207 (2):211–212. doi:10.1093/infdis/jis662.
42. Bogani G, Sopracordevole F, Ciavattini A, Vizza E, Vercellini P, Giannini A, Ghezzi F, Scambia G, Raspagliesi F, Di Donato V.

- Duration of human papillomavirus persistence and its relationship with recurrent cervical dysplasia. *Eur J Cancer Prev.* **2023**;32(6):525–532. doi: [10.1097/CEJ.0000000000000822](https://doi.org/10.1097/CEJ.0000000000000822).
43. Jentschke M, Kampers J, Becker J, Sibbertsen P, Hillemanns P. Prophylactic HPV vaccination after conization: a systematic review and meta-analysis. *Vaccine.* **2020**;38(41):6402–6409. doi:[10.1016/j.vaccine.2020.07.055](https://doi.org/10.1016/j.vaccine.2020.07.055).
 44. Bogani G, Supracordevole F, Ciavattini A, Ghelardi A, Vizza E, Vercellini P, Casarin J, Pinelli C, Ghezzi F, De Vincenzo R, et al. HPV-related lesions after hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer: a focus on the potential role of vaccination. *Tumori J.* **2024**;110(2):139–145. doi: [10.1177/03008916231208344](https://doi.org/10.1177/03008916231208344).
 45. Suchońska BE, Gajewska ME, Blok JM. To cut or not to cut - that is the question: a comparative analysis of long-term follow-up after complete and incomplete electroconization of the cervix due to high-grade squamous intraepithelial lesion. *Front Oncol.* **2024**;14:1421738. doi: [10.3389/fonc.2024.1421738](https://doi.org/10.3389/fonc.2024.1421738).
 46. Bogani G, Pinelli C, Chiappa V, Martinelli F, Lopez S, Ditto A, Raspagliesi F. Age-specific predictors of cervical dysplasia recurrence after primary conization: analysis of 3,212 women. *J Gynecol Oncol.* **2020**;31(5):e60. doi: [10.3802/jgo.2020.31.e60](https://doi.org/10.3802/jgo.2020.31.e60).
 47. Pan American Health Organization. Evaluating the impact of the human papillomavirus vaccine in Latin America and the Caribbean. Washington (DC): PAHO; **2023**. <https://iris.paho.org/Handle/10665.2/58377>.