

Human papillomavirus (HPV) vaccination coverage in Brazil: spatial and age cohort heterogeneity

Cobertura da vacina papilomavírus humano (HPV) no Brasil: heterogeneidade espacial e entre coortes etárias

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ABSTRACT: *Objective:* To estimate the coverage of the first and second dose of the human papillomavirus (HPV) vaccine in Brazil according to microregion, comparing cohorts of girls aged 14, 15, and 16 years in 2017, and investigate the association between spatial heterogeneity in vaccination coverage and sociodemographic variables. *Methods:* Information about the doses administered from 2013 to 2017 by age was gathered from the National Immunization Program. The number of girls aged seven, eight, and nine years living in each microregion in 2010 was obtained from the 2010 Brazilian Census. For the analysis, the cumulated vaccination coverage per microregion ($n = 558$) was categorized as low ($< 80\%$) and adequate ($\geq 80\%$), and a random intercept logistic model was adjusted, with adequate vaccination coverage as the outcome. The random effect (federative unit) was included to identify the correlation between microregions that belong to the same state. *Results:* The percentage of microregions with adequate vaccination coverage was significantly higher in the first dose (between 91.8 and 159.2%), regardless of the cohort. The coverage of the second dose was lower (between 7 and 79.9%), with heterogeneity associated with the degree of urbanization and households with private bathrooms in the municipality. The random effect showed a strong explanatory power, suggesting important differences among Brazilian states as to the outreach of vaccination coverage. *Conclusion:* Although the HPV vaccine is available through the Immunization Program, the findings of the present study point to a difficulty in achieving adequate vaccination coverage.

Keywords: Immunization. Vaccination coverage. Papillomaviridae. Ecological studies.

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Conflict of interests: nothing to declare – **Financial support:** National Council for Scientific and Technological Development (*Conselho Nacional de Desenvolvimento Científico e Tecnológico* — CNPq) and Rio de Janeiro Research Foundation.

RESUMO: *Objetivo:* Estimar a cobertura da primeira e da segunda dose da vacina papilomavírus humano (HPV) no Brasil, conforme a microrregião, comparando-se as coortes de meninas com 14, 15 e 16 anos em 2017, e investigar a associação da heterogeneidade espacial na cobertura vacinal com variáveis sociodemográficas. *Métodos:* A informação sobre doses aplicadas nos anos de 2013 a 2017 por idade foi obtida do Programa Nacional de Imunizações. O número de meninas residentes com sete, oito e nove anos em 2010, em cada microrregião, é oriundo do censo brasileiro de 2010. Para a análise, a cobertura vacinal acumulada por microrregião (n = 558) foi categorizada em baixa (< 80%) e adequada (≥ 80%), e um modelo logístico com intercepto aleatório foi ajustado, tendo cobertura vacinal adequada como desfecho. O efeito aleatório (unidade da federação) foi incluído para captar a correlação entre microrregiões que pertencem ao mesmo estado. *Resultados:* O percentual de microrregiões que alcançou a cobertura vacinal adequada foi significativamente maior para a primeira dose (entre 91,8 e 159,2%), independentemente da coorte. Observou-se menor cobertura da segunda dose (entre 7 e 79,9%), com heterogeneidade associada ao grau de urbanização e à presença de domicílios com banheiro de uso próprio no município. O efeito aleatório mostrou forte poder explicativo, sugerindo importantes diferenças entre os estados brasileiros no alcance da cobertura vacinal. *Conclusão:* Apesar de a vacina HPV estar disponível no Programa de Imunização, os achados do presente estudo apontam para uma dificuldade do alcance da cobertura vacinal adequada.

Palavras-chave: Imunização. Cobertura de vacinação. Papillomaviridae. Estudos ecológicos.

INTRODUCTION

The human papillomavirus (HPV) is one of the most common sexually transmitted infections in the world. Estimates indicate that, in 2015, 291 million women were carriers of the virus worldwide^{1,2}. The persistence of some types of HPV infection can progress to cervical cancer, a disease that has 530 thousand new cases per year^{1,3}. One of the main strategies for controlling this type of cancer is vaccination.

In the Americas, the HPV vaccine was introduced in 2006 in the United States, and, by mid-2019, it was present in the schedules of 40 countries and territories⁴. The quadrivalent vaccine has been the most used in 2020. It protects against infections caused by HPV types 6, 11, 16, and 18 and is recommended for girls and women aged 9 to 45 years and boys and men aged 9 to 26 years⁵.

In Brazil, the quadrivalent HPV vaccine was incorporated into the National Immunization Program (NIP) for free in 2014⁶. The inclusion of target populations in the vaccination schedule was gradual. It consisted of girls aged 11 to 13 years in 2014, was extended to the age group of 9 to 11 years in 2015, and to girls aged 14 years in 2017. This year, the program targeted girls aged 9 to 14 years and boys aged 11 to 14 years⁷.

The objective of the NIP is to achieve at least 80% of vaccination coverage in the first and second doses⁷. In 2014, 87% of Brazilian municipalities reached the recommended target for the first dose, but only 32% reached the recommended target for the second dose. The explanations listed for the low coverage were the difficulty of access, failures in recording the doses of vaccines administered, typing errors, and inaccuracies in the demographic data used to estimate the number of individuals in the target age group^{8,9}.

At the individual level, several factors have been analyzed and reported as associated with low HPV vaccination coverage, especially low schooling, low income, living in a rural area, low access to information and health services, and barriers imposed by religious dogmas¹⁰⁻¹⁴. Meanwhile, population analyses, with aggregated data, contribute to understanding social or structural determinants connected to the vaccination coverage achieved in a geographic area. For instance, household conditions (such as having a private bathroom) and access to public services (such as waste collection and running water) are *proxies* of the socioeconomic status of a location. Thus, we can infer that the higher the socioeconomic status of the municipality, the more likely it is to reach the recommended vaccination coverage. Similarly, more urban municipalities have a higher chance of achieving the desired coverage because they have broader dissemination of information on vaccination campaigns and offer health services with a supply of vaccines.

The present study aimed at analyzing the estimates of HPV vaccination coverage in Brazil in 2017, comparing cohorts of girls aged 14, 15, and 16 years in that year. We also sought to identify geographic heterogeneities in the coverage and test the association of municipal indicators with the vaccination coverage.

METHODS

We calculated the HPV vaccination coverage in three age cohorts of girls living in Brazil in 2017, stratified by microregions ($n = 558$ microregions). The cohorts were selected according to the start of vaccine availability. Thus, cohort 1 consisted of girls aged 10 years in 2013 who turned 14 in 2017; cohort 2 included girls aged 11 years in 2013 who turned 15 in 2017; and cohort 3 comprised girls aged 12 years in 2013 who turned 16 in 2017. Each of these cohorts had different opportunities to be vaccinated according to schedule changes.

DATA

Vaccination data were collected from the Immunization Program Evaluation System (*Sistema de Avaliação do Programa de Imunizações – API*), which is administered by the National Immunization Program General Coordination (*Coordenação Geral do Programa Nacional de Imunizações – CGPNI*) of the Ministry of Health¹⁵. We obtained the numbers of doses administered by age from 2013 to 2017, considering the first and second doses separately. The number of girls aged seven, eight, and nine years living in each microregion in 2010 was gathered from the 2010 Demographic Census. These girls comprised the target population of the three vaccination cohorts that started in 2013. We used the definition and spatial profile of microregions established by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística – IBGE*)¹⁶.

The following variables were used to investigate whether the spatial heterogeneity of the vaccination coverage was associated with the sociodemographic characteristics of the microregions: proportion of the urban population; proportion of households with waste collection; proportion of households with access to running water; proportion of households with private bathroom; proportion of the population with private health insurance; and proportion of the population with income lower than one minimum wage. These data were calculated based on the 2010 IBGE census records. The random variable federative unit (categorical) was included to identify the structure of dependence between microregions that belong to the same state since they share public policies. Confidence intervals of random effects were obtained assuming a normal distribution. Maps were constructed with shapefiles provided by IBGE.

VACCINATION COVERAGE

We calculated the vaccination coverage using the method of cumulated coverage per cohort recommended by the NIP⁷. This methodology consists in identifying age cohorts, defined as the set of girls who turned the same age in the same calendar year. The numerator was the cumulative sum of vaccine doses administered to each cohort since the first year they became eligible. The denominator was the number of girls aged seven, eight, and nine years residing in each Brazilian microregion in 2010. The present study defined three cohorts: girls aged 14 years in 2017 who were eligible for vaccination from 2014–2017 (aged 11, 12, 13, and 14 years), girls aged 15 years in 2017 who were eligible for vaccination from 2013–2015 (aged 11, 12, and 13 years), and girls aged 16 years in 2017 who were eligible for vaccination from 2013–2014 (aged 12 and 13 years) (Chart 1).

ANALYSIS

The cumulated vaccination coverage per microregion was categorized as low (< 80%) and adequate (\geq 80%), following the classification established by the NIP⁶, and calculated

Chart 1. Age-period-cohort that specifies the population used to calculate HPV vaccination coverage in Brazil in 2017 (c1, c2, c3 = cohort of girls aged 14, 15, 16 years, respectively, in 2017)*.

| | 9 years | 10 years | 11 years | 12 years | 13 years | 14 years | 15 years | 16 years |
|--------|---------|----------|----------|----------|----------|----------|----------|----------|
| 2013** | | c1 | c2 | c3 | | | | |
| 2014 | | | c1 | c2 | c3 | | | |
| 2015 | | | | c1 | c2 | c3 | | |
| 2016 | | | | | c1 | c2 | c3 | |
| 2017 | | | | | | c1 | c2 | c3 |

*In gray: opportunities for vaccination; **in 2013, the vaccination only occurred in the state of Amazonas and the Federal District; HPV: human papillomavirus.

separately for the first and second doses. A random intercept logistic model was adjusted, with adequate vaccination coverage as the outcome¹⁷. The fixed effect explanatory variables were: proportion of urban population, proportion of households with waste collection, access to running water, private bathroom, and income lower than one minimum wage. The models were adjusted using the lme4 library of the R environment, version 3.4.4¹⁶, and the results were displayed with the sjPlot library. Maps were constructed using the maptools library.

The secondary data used in the present study are anonymized and of public domain; thus, the research did not need to be submitted to and approved by a Research Ethics Committee.

RESULTS

The percentage of microregions with adequate vaccination coverage was significantly higher in the first dose, regardless of the cohort (cohort 1: 98%, cohort 2: 95%, cohort 3: 92.5%). However, a concentration of microregions with low coverage was identified in Northern Brazil, particularly in Amazonas (Table 1 and Figure 1) and some areas of Pará. We underline that the Federal District also presented inadequate coverage in the first dose (Table 1). The second dose showed lower coverage in general, reaching only 37% in cohort 1, 61% in cohort 2, and 37% in cohort 3. The distribution of vaccination coverage was spatially heterogeneous, as seen in Figure 1.

The logistic model best adjusted for the coverage of the first dose had only the cohorts as a significant fixed effect. For this dose, the youngest cohort was more likely to achieve the goal than the older cohorts 2 and 3 (cohort 2: odds ratio — OR = 0.09, confidence interval — 95%CI 0.02 – 0.35; cohort 3: 0.04, 95%CI 0.01 – 0.17). As for the second dose, the cohort effect was reversed, with cohort 2 having a greater chance of being vaccinated (cohort 2: OR = 4.48, 95%CI 3.3 – 6.09). In addition to the cohort effect, the percentage of urban population and of households with private bathroom showed a significant effect in the coverage of the second dose. Microregions with a higher urban population had a lower chance of achieving adequate coverage, but the effect was small (OR = 0.98, 95%CI 0.96 – 0.99).

Figure 2 shows the random effects estimated for each state. Values above 1 indicated greater “relative ease” to achieve adequate coverage, while lower values pointed to greater “relative difficulty”. Regarding the first dose, Amazonas (AM) had the highest random effect, with a large difference compared to other states. As to the second dose, the differences between states were smaller. Nevertheless, some states, such as Pará (PA), Tocantins (TO), Piauí (PI), Paraíba (PB), Bahia (BA), Goiás (GO), and Paraná (PR), showed relatively greater difficulties in reaching the coverage in comparison with others, such as Maranhão (MA), Ceará (EC), Espírito Santo (ES), and Roraima (RR). The variable federative unit represented an important source of variation between the coverages reached, both in the first (variance = 5) and second (variance = 2.54) doses.

Table 1. HPV vaccination coverage in Brazilian states in cohorts of girls aged 14 (cohort 1), 15 (cohort 2), and 16 years (cohort 3). Brazil, 2017.

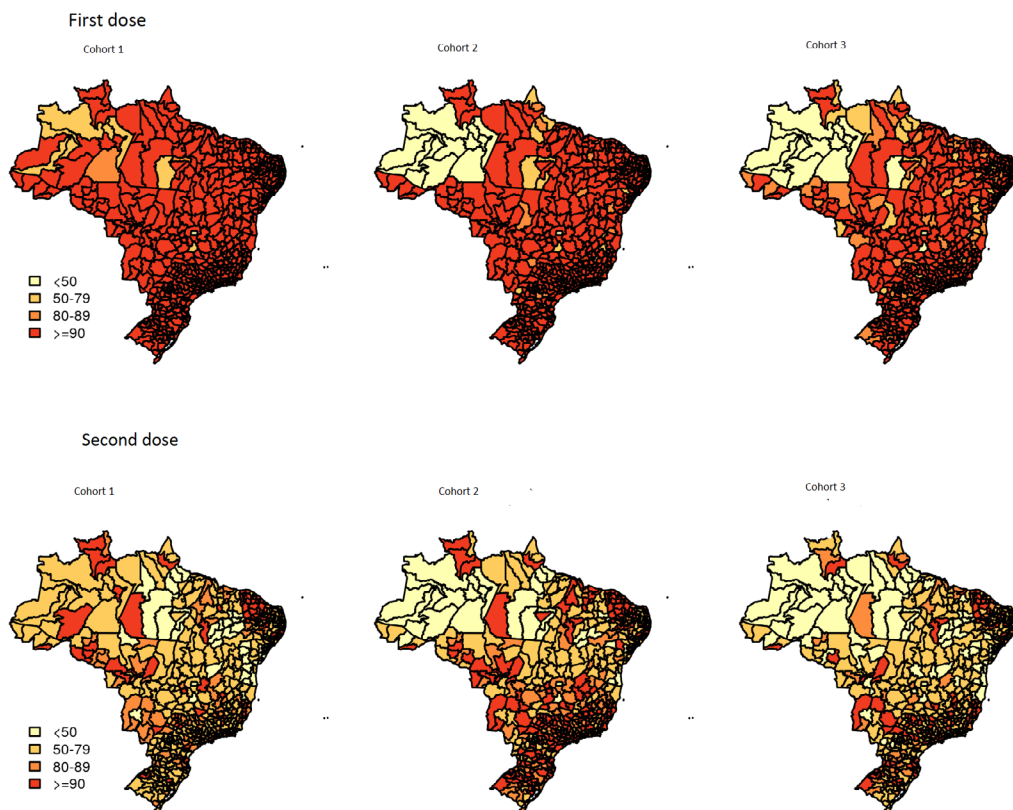
| Region/FU | First dose (%) | | | Second dose (%) | | |
|---------------------|----------------|----------|----------|-----------------|----------|----------|
| | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 1 | Cohort 2 | Cohort 3 |
| North | 111.7 | 84.2 | 72.5 | 68.1 | 61.5 | 48.2 |
| Acre | 131.4 | 113.4 | 101.2 | 66.4 | 71.5 | 60.2 |
| Amapá | 146.5 | 111.1 | 105.8 | 92.6 | 101.0 | 83.7 |
| Amazonas | 92.2 | 21.5 | 11.3 | 73.3 | 18.6 | 8.9 |
| Pará | 124.5 | 109.8 | 97.5 | 51.8 | 57.3 | 46.8 |
| Rondônia | 130.1 | 110.8 | 95.2 | 95.2 | 81.4 | 60.0 |
| Roraima | 151.9 | 126.1 | 95.1 | 102.4 | 101.5 | 78.9 |
| Tocantins | 137.0 | 110.1 | 103.2 | 62.0 | 70.7 | 59.3 |
| Northeast | 134.2 | 112.3 | 102.6 | 75.6 | 81.0 | 69.0 |
| Alagoas | 139.0 | 113.0 | 100.0 | 88.9 | 88.9 | 81.7 |
| Bahia | 123.6 | 106.1 | 99.2 | 54.2 | 62.2 | 51.5 |
| Ceará | 162.7 | 131.8 | 120.2 | 103.1 | 105.7 | 90.2 |
| Maranhão | 127.6 | 109.4 | 97.9 | 78.3 | 89.0 | 72.1 |
| Paraíba | 130.0 | 107.3 | 91.8 | 74.2 | 74.5 | 70.8 |
| Pernambuco | 134.7 | 115.7 | 106.7 | 87.0 | 88.5 | 72.9 |
| Piauí | 121.0 | 107.2 | 96.1 | 54.0 | 62.7 | 50.0 |
| Rio Grande do Norte | 127.4 | 105.5 | 105.3 | 70.8 | 78.5 | 61.9 |
| Sergipe | 142.5 | 115.4 | 106.2 | 70.6 | 79.4 | 70.5 |
| Midwest | 123.7 | 98.3 | 84.8 | 69.9 | 67.3 | 49.0 |
| Goiás | 151.8 | 135.2 | 105.9 | 79.4 | 92.6 | 60.6 |
| Mato Grosso | 135.7 | 110.5 | 100.1 | 74.4 | 79.9 | 58.8 |
| Mato Grosso do Sul | 159.2 | 133.6 | 122.7 | 83.2 | 86.4 | 69.7 |
| Federal District | 48.2 | 14.0 | 10.7 | 42.6 | 10.6 | 7.0 |
| Southeast | 144.6 | 118.3 | 107.0 | 84.1 | 96.3 | 82.7 |
| Espírito Santo | 141.6 | 114.4 | 100.8 | 95.1 | 105.5 | 96.6 |
| Minas Gerais | 142.1 | 114.7 | 104.3 | 77.5 | 100.0 | 79.9 |
| São Paulo | 152.0 | 122.9 | 112.1 | 81.9 | 93.9 | 85.9 |
| Rio de Janeiro | 143.0 | 121.5 | 110.9 | 81.9 | 86.1 | 68.5 |
| South | 131.6 | 111.2 | 104.3 | 72.1 | 88.5 | 77.8 |
| Paraná | 132.1 | 105.6 | 98.0 | 64.9 | 79.0 | 61.8 |
| Santa Catarina | 137.0 | 115.7 | 110.4 | 80.4 | 99.8 | 90.6 |
| Rio Grande do Sul | 125.8 | 112.4 | 104.7 | 71.0 | 86.8 | 81.0 |
| Brazil | 133.0 | 107.9 | 96.8 | 75.6 | 79.7 | 65.9 |

HPV: human papillomavirus; FU: federative unit.

DISCUSSION

The first dose had the highest percentage of microregions with adequate vaccination coverage, regardless of the cohort, compared to the second dose. The logistic model revealed that cohort 1 was more likely to reach the goal in the first dose, while for the second dose, cohort 2 had a greater chance of reaching the goal.

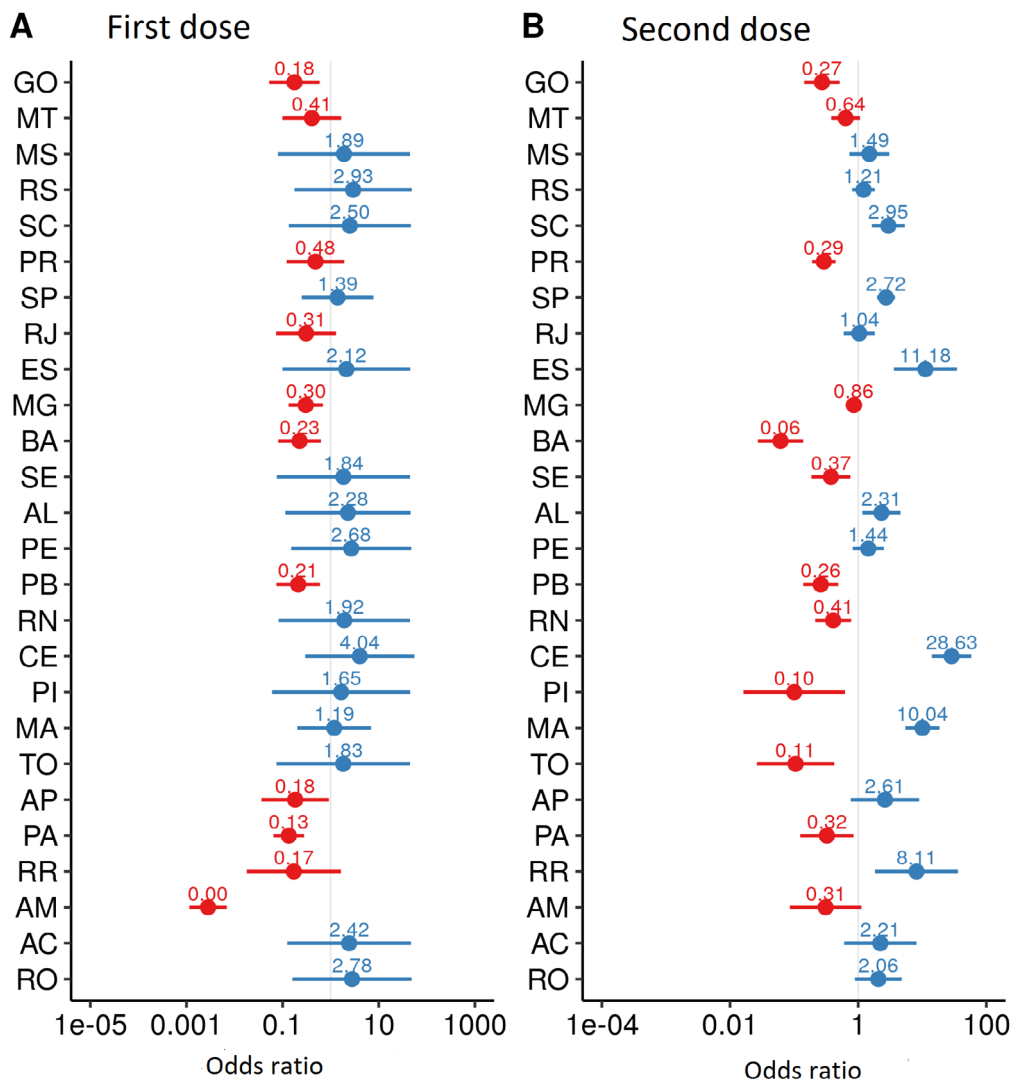
In Brazil, although the NIP stands out for its successful experiences in Brazilian public health, it is challenged by the complexity of the national epidemiological context, the socio-demographic indicators, and the inclusion of new vaccines in the schedule^{17,18}. The inclusion of the HPV vaccine for a target population different from that of routinely vaccinated children became a great challenge, and, to face it, several countries have created strategies for implementing vaccination in schools¹⁹. Vaccination in Brazil was freely provided in schools, which are important learning places²⁰, and in basic health units, contributing to the vaccination coverage outreach in 2014.



HPV: human papillomavirus.

Figure 1. Spatial distribution of vaccination coverage of the first and second doses of the HPV vaccine in cohorts of girls aged 14 (cohort 1), 15 (cohort 2), and 16 years (cohort 3). Brazilian microregions, 2017.

The HPV vaccine has faced challenges, such as changes in the target population and vaccination regimen, over time²¹. Despite the regional heterogeneity and specificities, the country had great success in the vaccination coverage of the first dose. This success is identified in the cohort of girls aged 14 years in 2017. This cohort had a higher chance of receiving the first dose of the vaccine, considering the inclusion of the HPV vaccine in the schedule and the gradual incorporation of the target population (of different ages along the years). National data indicate that cohorts of girls aged 13 and 14 years from 2013 to 2016 had a vaccination coverage above the recommended target (132.6 and 121.3%) in the first dose.



HPV: human papillomavirus.

Figure 2. Odds ratio (95% confidence interval) of reaching the goal of HPV vaccination coverage compared to not reaching the target, per Brazilian state, in 2017, after controlling for covariates.

Concerning the second dose, the vaccination coverage was below the recommended target in the cohort of girls aged 13 years (69%) and above the recommended goal (89.7%) in the cohort of girls aged 14 years²². The results of the present study regarding the vaccination coverage of cohorts 1 and 2 per microregions corroborate the Brazilian data for the first dose but disagree with those related to the second dose.

Comparing the cohorts, the coverage achieved in the first dose indicated a greater chance of younger cohorts being vaccinated, which possibly suggests an improvement in the vaccination program over the years. However, in the second dose, older cohorts were more likely to achieve the goal, which possibly points to a worsening of the program in maintaining high coverage for the second dose.

When we assessed the chances of a state achieving vaccination coverage after controlling for variations among cohorts, Amazonas stood out, as it had “relative difficulty” in reaching the coverage despite being the first state of the Northern region to offer the HPV vaccine in the public health system (*Sistema Único de Saúde – SUS*).

The analysis presented herein suggests an association between success in vaccination coverage and the proportion of households with bathrooms. This indicator measures both the situation of more than one household sharing a bathroom (more common in poorer urban households) and the use of septic tanks (more common in rural areas). In this context, microregions with higher values for this indicator can represent either more rural areas or poorer urban areas. This information corroborates findings of national adolescent immunization surveys, which identified that the coverage of the first dose of the HPV vaccine was significantly lower among adolescents from suburban and, particularly, rural areas than among those living in mostly urban areas²³.

Vaccination coverage also showed great heterogeneity between states, a finding not explained by the variables of urbanity and income used in the present study. These heterogeneities might be associated with different state public policies that affect the availability of vaccines for the population.

The present study highlights several challenges respecting the HPV vaccination coverage in Brazil. The estimated vaccination coverage of the first dose of the HPV vaccine in Brazil suggests high outreach, despite some locations not following the pattern (Federal District and Amazonas). In contrast, the second dose showed low cumulated vaccination coverage in all cohorts, with cohort 1 having the worst performance. This result implies that, despite the greater opportunity to receive the first dose, vaccination might be disrupted, a situation also called delayed vaccination. Delayed vaccination is recognized by the NIP as a recurring factor in other vaccines, hindering the protection against vaccine-preventable diseases in the population²⁴.

The reduction in vaccination coverage and, consequently, the resurgence of some diseases that had been eradicated in Brazil are worrying²⁵. The drop in vaccination coverage might be related to the hesitancy toward vaccination, defined as the delayed acceptance or refusal of the vaccines recommended, despite their availability in health services^{26,27}. A study showed that the main reasons for the hesitancy toward vaccination are the lack of trust in the efficacy/safety of the vaccine and concerns with adverse events²⁸.

Social media has an important role in spreading information and is one way to disseminate health recommendations. Nonetheless, we stress that the lack of information and/or fake information about the HPV vaccine can increase the issues related to adherence to vaccination^{21,29,30,31,32}.

The vaccination coverage of the second dose showed spatial heterogeneity. The variables associated with this coverage were: urban population and percentage of households with private bathrooms. This result suggests that variables related to social inequality, such as the percentage of households with private bathroom, influence the vaccination coverage, indicating that regions with better living conditions have a greater capacity to achieve coverage above the recommended target, perhaps by their greater access to health care³³.

The limitations of this study mainly involve inaccuracies in the calculation of vaccination coverage, which stem from uncertainties in the estimates of numerators and denominators. The numerator (number of doses administered) might not have properly measured the number of people vaccinated due to vaccine losses (vaccine wastage). Another bias could be the misclassification of first or second doses in information systems. On the other hand, the study advances when it compares the cumulated vaccination coverage in multiple cohorts and per microregion of the country. The results point to a successful vaccination coverage in the first dose and the need for greater attention to the second dose.

Although the HPV vaccine is available through the NIP, the findings of this research indicate the difficulty in maintaining the coverage outreach for the second dose, as well as the role of social inequality, which contributes to the spatial heterogeneity of vaccination coverage. This result shows the need for state managers to plan specific strategies for each area.

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Received on: 02/07/2020

Final version presented on: 07/16/2020

Accepted on: 07/17/2020

Author's contributions: Lívia de Lima Moura: data collection from the secondary databases cited in the text, participation in the study design, analysis, interpretation of results, and writing of the manuscript. Claudia Torres Codeço: participation in the study design, analysis, interpretation of results, and writing of the manuscript. Paula Mendes Luz: participation in the study design, analysis, interpretation of results, and writing of the manuscript.

