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HIGHLIGHT

Measles vaccination in Brazil: where have we been and where are we headed?

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Abstract *The re-emergence of vaccine-preventable diseases due to the decline in vaccine coverage (VC) has been documented in several countries. The objective was to analyze the VC, the homogeneity of VC, and measles cases in Brazil from 2011 to 2021, focusing on the period of the COVID-19 pandemic, its temporal trend, space-time distribution, and factors associated with clusters of lower VC. This is an ecological study on measles VC (dose 1), with methods of interrupted time series and evaluation of spatio-temporal disposition, through the sweep test to identify clusters of VC. Starting in 2015, we observe a progressive decline in VC and homogeneity, with an accentuation after 2020, in all regions, particularly in the North and Northeast. Low VC clusters were associated with worse human development indicators, social inequality, and less access to the Family Health Strategy. In Brazil, the pandemic intensified health inequalities with low VC of measles in socially more vulnerable and unequal municipalities. There is a risk of virus circulation, however, the challenge of strengthening primary care, improving health communication and guaranteeing access to the vaccine, reducing missed opportunities for vaccination and vaccine hesitancy, is highlighted.*

Key-words *Measles, Vaccination, Vaccination coverage, Time series studies, Spatial analysis*

Introduction

Globally, there was a substantial decrease in measles incidence and mortality during 2000-2016 and its resurgence from 2017 onwards, marking a setback in eradicating this disease[1]. In the context of falling vaccination coverage (VC), the re-emergence of some diseases, particularly vaccine-preventable ones, has been documented in several countries, and the problem has been exacerbated in the COVID-19 pandemic[2].

This setting is no different in Brazil. In 2016, the country received the certificate of measles eradication. However, in 2019, it lost this certification due to the registered cases for more than 12 months in the national territory[3]. As measles is highly infectious, its circulation and outbreaks are an important marker of inadequate coverage and gaps in the health system, especially in primary care. Measles eradication requires a robust immunization and surveillance system to maintain adequate VC levels and investigate suspected cases[2].

A drop in routine childhood immunization associated with the COVID-19 pandemic was observed globally. In 2020, the VC for the first dose of measles vaccine was 78.9% (95%CI 74.8-81.9), a relative reduction of 7.9% (95%CI 5.2-11.7) compared to doses expected in the absence of the COVID-19 pandemic. This situation means that approximately 27.2 million children missed the first dose of the vaccine between January and December 2020, resulting in 8.9 million children not routinely vaccinated against measles due to the pandemic[4]. In Brazil, a progressive drop in the VC of the MMR vaccine was identified from 2006 to 2016, with an annual reduction of 2.7% for the MMR vaccine, besides observing susceptible clusters in the states of Acre, Amazonas, Pará, Amapá, and Maranhão[5]. The declining number of MMR vaccine applied doses was also recorded when comparing the median number of doses before the COVID-19 pandemic mitigation measures (April 2019 to March 2020) and after the implementation of restrictive measures (April 2020 to September 2020). This reduction was observed in the North, Northeast, and South, particularly significant in the states of Acre, Amazonas, Roraima, Paraíba, Sergipe, Rio de Janeiro, and Santa Catarina when social distancing recommendations were established in Brazil[6].

In this context, the present paper aims to analyze the VC, its homogeneity rates, and measles cases in Brazil from 2011 to 2021, focusing on the COVID-19 pandemic period, its spatial distribution, and factors associated with lower VC clusters.

Methods

This is an ecological study on the VC of the first dose (D1) of the MMR vaccine (measles, mumps, and rubella) in children under one year of age using temporal and spatial analysis techniques, where the years 2011 to 2021 were considered the temporal analysis unit, and the Brazilian municipalities and federated units (UF) as the spatial analysis unit.

VC data recorded by the National Immunization Program Information System (SI-PNI) were obtained on November 11, 2022, and made available by the Department of Informatics of the SUS (DATASUS). VC was calculated by dividing the number of doses applied by the target population, multiplied by 100[7]. Measles cases per year, states, and regions were obtained from the Ministry of Health website[8]. The coordinates corresponding to the centroids of each municipality as decimal measurements of latitude and longitude were obtained from the website of the Brazilian Institute of Geography and Statistics (IBGE) (https://www.ibge.gov.br).

First, we performed a graphic description of the time series of measles VCs from D1 from 2011 to 2021 and the number of measles cases in the same period for Brazil, significant regions, and each of the 27 UFs. The predicted (expected) VC values for the pandemic years (2020 and 2021) were estimated from segmented linear regression, including the pre-pandemic period (2011 to 2019) as exposure and VC as the outcome.

The interrupted time series (ITS)[9] method was used to assess the impact of the COVID-19 pandemic on the VC. This quasi-experimental approach estimates changes in level and trend after an intervention (COVID-19 pandemic) when multiple observations are sorted sequentially[10]. Models for each UF were adjusted in STATA 16.0 software (Stata Corp., College Station, TX, USA), using a single-group design with a lag of a Newey-West variance estimator[11]. The coefficients are based on ordinary least squares (OLS) regression, as follows:

$y = \beta_0 + \beta_1$*time + β_2*level + β_3* (time*intervention); where:

$\beta 1$ = slope of the trend curve before the intervention (between January 2011 and December 2019); $\beta 2$ = change in the VC level when the

COVID-19 pandemic started (2020) (comparison with counterfactual); β3 = slope of the VC trend curve after the first year of the pandemic (December 2020 to December 2021); Global trend = difference between the trend of the period before the intervention and the trend after.

The measles VC homogeneity indicators of the UFs were built for each year of study considering the number of municipalities that reached a target of 95% or more coverage over the number of municipalities in the UF. The UF is considered homogeneous when 70% or more of its municipalities reach 95% of VC[12]. The municipality's temporal homogeneity indicator is presented based on the same homogeneity concept, considering the ratio between the number of times the municipality met the VC target of 95% and over and the number of study years.

The Kulldorff scanning method or Scan[13] statistics performed by the SatScan 10.1 software were used to analyze space-time and identify low and high VC area clusters. A cylindrical window defines the space-time scan statistic with a circular geographic base and height corresponding to time. The base is set to purely spatial scan statistics, while the height reflects the period of potential temporal clusters. The cylindrical window is then moved in space and time so that every possible period is scanned for every possible location and geographic size.

A retrospective analysis was performed to detect active clusters at the end of the study period and those that were active for some time. The design followed the Poisson discrete probability model with the number of doses per municipality for each year from 2011 to 2021 with the respective target population.

Initially, we calculated the optimal maximum Gini coefficient, representing the most accurate percentage value for adequate statistical inferences on the analyzed population, from a circular spatial window with 50% of the population exposed at risk. Then, we analyzed space-time considering 50% of the exposure time and 1% of the exposed population according to the scanning percentage adjusted by the Gini coefficient. A significance level of 5% was considered for p-values estimated by the Monte Carlo simulations with 999 permutations to assess the statistical significance of each cluster.

We also performed a purely spatial analysis with the SatScan scanning technique, as described above, from 2020 to 2021. Finally, the spatial clusters estimated in this period were categorized with high coverage in municipalities with a relative risk (RR) > 1 (observed VC higher than expected) and low coverage municipalities with RR < 1 (observed VC lower than expected) and used in simple and multiple models of logistic regression to verify the existence of an association between being in a low cluster VC in 2020-2021 and geographic region, population[14], Gini Index (2010)[15], Human Development Index (HDI) (2010)[15], the Family Health Strategy coverage (FHS) (median of 2020)[16], and the number of vaccination rooms per 100,000 inhabitants (2022)[17].

The study did not require approval from the Research Ethics Committee as it used only secondary, anonymized, and publicly accessible data per Article 1 of Resolution N° 510/2016 of the National Research Ethics Committee.

Results

Until 2014, all Brazilian regions had measles D1 VC above 95%. Coverage started to decline from 2015 onwards, and after 2016, no region reached a VC above 95%. In 2020 and 2021, the highest VC values recorded were 86.2% and 84.2%, respectively, in the South, and the lowest, 68.8% and 68.0%, respectively, in the North (Figure 1; Supplementary Table 1, available at: https://doi.org/10.48331/scielodata.5FY8G0).

The North had the lowest VC values from 2015 to 2021. In 2018, the first measles outbreak was observed in this region, with 9,237 confirmed cases. The two most significant measles outbreaks in the Northeast were in 2014 (866 confirmed cases) and 2019 (572 confirmed cases). In 2019, a more significant number of confirmed cases was observed in the Southeast (18,426), South (1,468), and Midwest (25). The Midwest had a VC above 90% from 2011 to 2019 (except in 2017, when coverage fell to 83.4%) and was the region with the lowest number of confirmed cases throughout the period. However, in 2020 and 2021, VC in the Midwest was below 80% (79.6% and 79.9%, respectively) (Figure 1; Supplementary Table 1, available at: https://doi.org/10.48331/scielodata.5FY8G0).

In the analyzed period, we observed a decrease in VC in all UFs and some peaks in measles cases, especially in Amazonas, Pará, Ceará, Pernambuco, and São Paulo. Acre was the only UF without any case of measles in the period (Supplementary Table 1, available at: https://doi.org/10.48331/scielodata.5FY8G0). Statistically significant global differences in trends before and

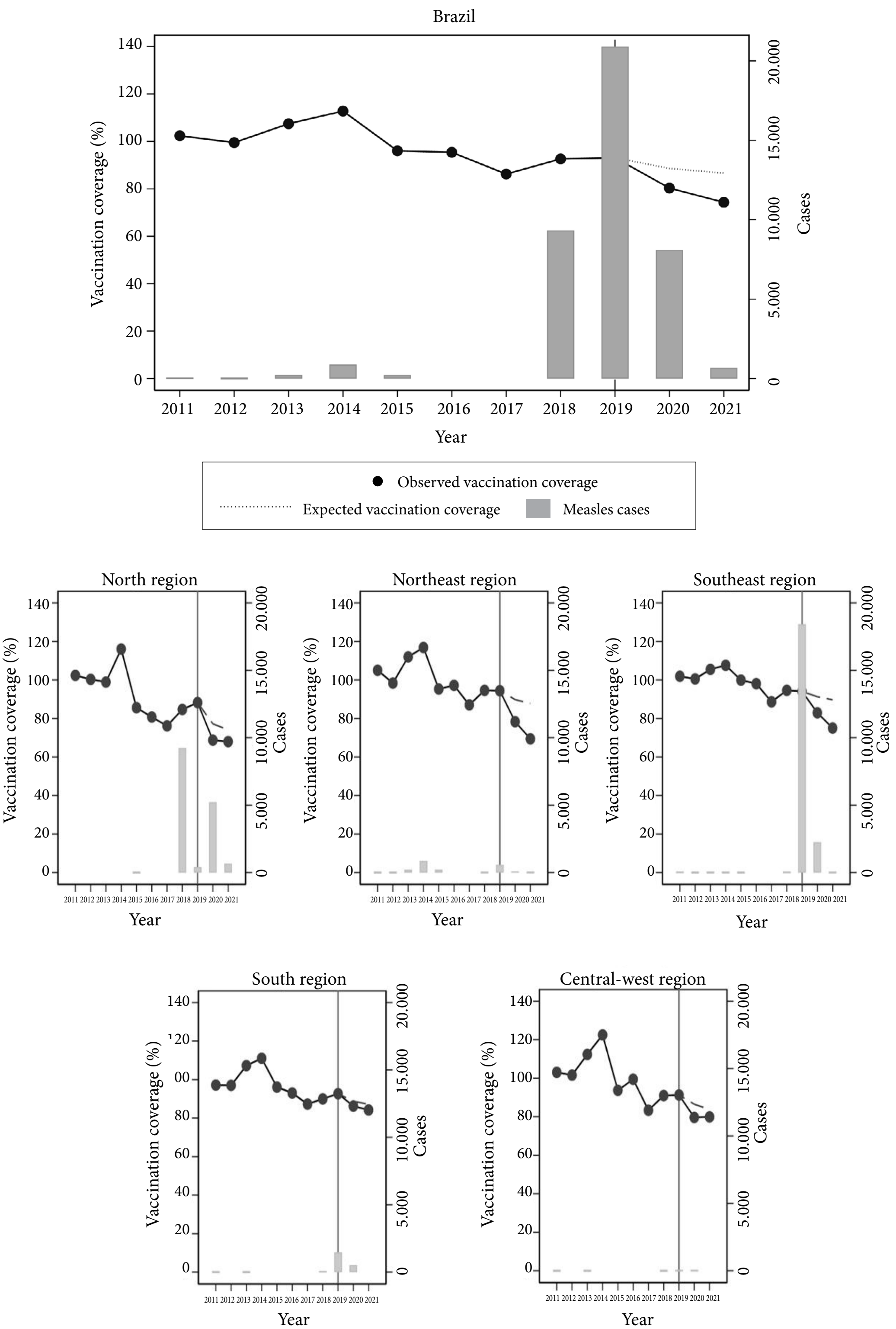

Figure 1. Time series of vaccine coverage for triple viral D1 and measles cases in Brazil and by region. Brazil, 2011-2021.

The vertical line delimits the last value (2019) before the start of the COVID-19 pandemic. The dashed line indicates the expected vaccination coverage based on previous years (2011-2019). Gray bars indicate measles cases.

Source: Source: Authors, based on data from MS\DATSUS\PNI.

after the pandemic were observed for almost all UFs, except for Amapá, Goiás, and the Federal District (Supplemental Table 2). The UF with the most significant drop in VC was Rio de Janeiro (b = -19.32; 95%CI: -31.14; -7.50) and the smallest, Paraná (b = -2.86; 95%CI: -5.05; -0.67). Some UFs in the Northeast also showed significant global differences, such as Ceará, Paraíba, Pernambuco, and Alagoas (Supplementary Table 2, available at: https://doi.org/10.48331/scielodata.5FY8G0).

Regarding the temporal homogeneity of VC for measles, we observed that municipalities in the North of the country reached the VC target (95% or more) in half or less of the 2011-2021 period. We also found a progressive decline in the number of municipalities that reached this goal in the country. In 2021, a few municipalities had VCs of 95% or more (Figure 2). The same pattern is observed in the homogeneity by UF so that in 2021, no UF reached the goal of 70% homogeneity; that is, 70% of municipalities with VC ≥ 95% (Supplementary Figure 1, available at: https://doi.org/10.48331/scielodata.5FY8G0).

In the space-time analysis, high and low VC clusters were presented with their temporal locations. Twelve active clusters were identified for low coverage (Figure 3, Map B), highlighting five among those active since 2017. Eight high-coverage clusters are identified, highlighting four with greater spatial magnitude, in force from 2013 to 2016 (Figure 3, Map A).

A total of 191 clusters of low and high VC of measles were identified in the specific spatial analysis for the 2020-2021 period, comprising 3,351 municipalities, 2,774 in high VC clusters (RR > 1) and 577 in low VC clusters (RR < 1) (Figure 3, Map C). In the multiple logistic analysis, the following were positively associated with belonging to the low VC cluster: municipalities in the North, Northeast, and Midwest geographic regions, against the Southeast; more populous; with the highest Gini Index (social inequality); lower HDI and FHS coverage lower than 75% (Table 1).

Discussion

After 2016, no Brazilian geographic region reached the VC target of 95% for measles. Moreover, a significant VC heterogeneity was observed, chronically lower in the North of the country. Measles cases occurred more frequently in the North and Northeast from 2014 to 2018, and in the Southeast, South, and North, from 2019 onwards, as several studies also point out[18,19]. The drop was aggravated after the start of the pandemic, more pronounced in municipalities in the North and Northeast, which are more populous, more unequal, less developed, and with less FHS coverage, expressing substantial health inequality.

The National Plan for the Eradication of Measles was implemented in 1992, with extensive vaccination and intensified epidemiological surveillance. It culminated in the interruption of autochthonous cases in the country in 2000. One hundred eighty cases were imported in the following decade, and measles outbreaks were recorded from 2013 to 2015 in Ceará and Pernambuco, with more than a thousand autochthonous cases. In 2016, the Americas region was designated an area free of endemic measles transmission. In 2018, several countries reported a significant number of cases of the disease, including Brazil, with the reintroduction of the virus in the country's northern region, due to the intense migratory flow in the border area in Roraima and low VC. In 2019, Brazil again lost the measles eradication certificate, with an incidence of 20.3/100,000 inhabitants-year. In 2020, the number of cases was still high until March, the onset of the COVID-19 pandemic, with a significant decline afterwards[12]. This drop could be explained by the cyclical behavior of the disease, the decreasing circulation of people, and the problematic diagnosis and notification of the disease after concentrating efforts to combat the pandemic[20]. Data from the Ministry of Health indicate that Brazil reached the target of three (investigation, submission, and timely result) of the nine quality indicators of surveillance of exanthematous diseases after the pandemic's start, with the loss of the indicator target referring to the notification rate since 2021. Likewise, we observe the impact of the pandemic on measles laboratory surveillance, with a declining number of tests requested and positivity in April 2020[12]. Even so, the significant drop in VC aggravated by the pandemic[21] overly challenges the eradication of measles and its maintenance.

In Brazil, the vertical actions of the PNI in the 1980s contributed to reducing the social gradient of VC and guaranteeing universal access to vaccination in the country. The first national VC surveys indicated worse coverage in the most deprived segments of the population. This difference disappeared in the late 1990s and was reversed in 2007, indicating equal access to vac-

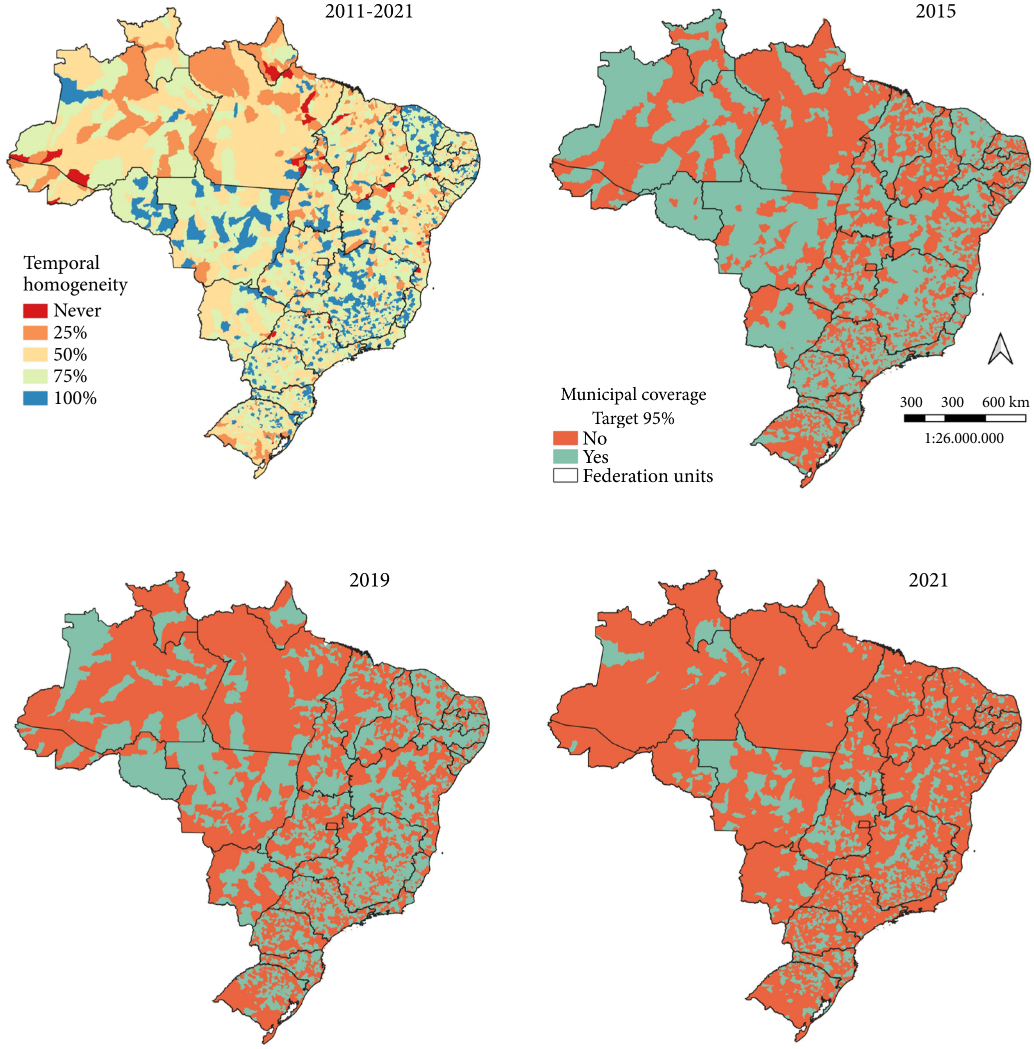

Figure 2. Temporal homogeneity of measles vaccination coverage (D1) according to municipalities, 2011-2021 and vaccination coverage (≥ 95%) in the years 2015, 2019 and 2021, Brazil.

Source: Source: Authors, based on data from MS\DATSUS\PNI.

cination in different socioeconomic strata of the Brazilian population[22]. High measles VC clusters were found in the Midwest and Northeast of the country but disappeared after 2017. The VC drop has been related to several factors, including the increasing complexity of the vaccination schedule of the Brazilian Unified Health System (SUS), changes in the PNI information system, and the strengthening of vaccine hesitancy[23-25].

This study found lower VC of measles in the North of the country, in a chronic form during the studied period. Other studies reported low VC of measles in this region before the pandemic[5,26]. The low VC homogeneity (< 70%) and the significant decline in the number of municipalities that reached a VC ≥ 95% should also be highlighted as essential indicators in the identification of areas of greater risk for measles transmission and, therefore, require intensifying vaccination, particularly in the most socially vulnerable areas[27].

This already troubling context is exacerbated by the challenging COVID-19 pandemic, direct-

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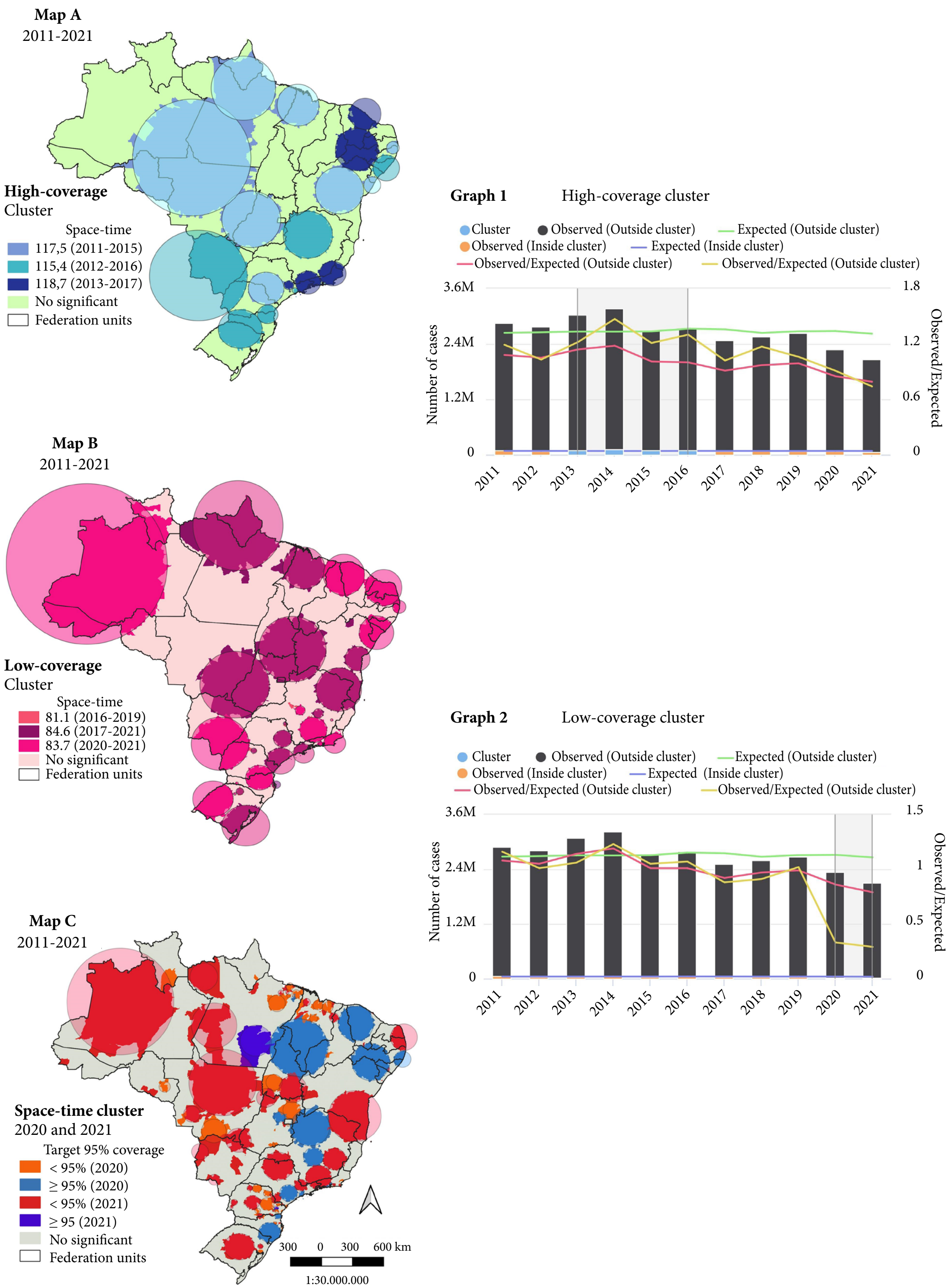

Figure 3. Space-time analysis of measles vaccination coverage (D1). Brazil, 2011-2021.

Source: Source: Authors, based on data from MS\DATSUS\PNI.

Table 1. Crude and adjusted odds ratio estimators between municipalities in clusters with low and high measles vaccination coverage, according to population, economic and primary care variables. Brazil, 2020-2021.

Variables	Number of municipalities		Crude OR	95%CI	Adjusted OR	95%CI
	Low VC cluster	High VC cluster				
Region						
North	136	117	20.6	14.3-29.6	11.8	7.3-19.2
Northeast	326	697	8.3	6.1-11.1	4.5	2.9-7.0
Southeast	57	1009	1.0	-	1.0	-
South	27	723	0.7	0.4-1.1	1.0	0.6-1.6
Midwest	31	228	2.4	1.5-3.8	2.7	1.6-4.5
Population						
Quintile 1	16	655	1.0	-	1.0	-
Quintile 2	54	616	3.6	2.0-6.3	3.0	1.6-5.4
Quintile 3	105	565	7.6	4.4-13.0	5.6	3.2-9.9
Quintile 4	136	507	13.2	7.8-22.3	8.3	4.8-14.5
Quintile 5	239	431	22.7	13.5-38.2	18.7	10.7-32.6
Gini Index*						
Quintile 1	30	761	1.0	-	1.0	-
Quintile 2	59	497	3.0	1.9-4.7	1.8	1.1-2.9
Quintile 3	121	713	4.3	2.8-6.5	1.7	1.1-2.7
Quintile 4	117	393	7.6	5.0-11.5	2.2	1.4-3.5
Quintile 5	250	406	15.6	10.5-23.2	3.0	1.9-4.8
HDI*						
Quintile 1	276	397	11.5	8.0-16.5	2.6	1.6-4.4
Quintile 2	145	532	4.5	3.1-6.6	1.3	0.8-2.1
Quintile 3	76	592	2.1	1.4-3.2	1.2	0.8-2.0
Quintile 4	42	620	1.2	0.7-1.8	1.0	0.6-1.6
Quintile 5	38	629	1.0	-	1.0	-
FHS coverage						
≥ 75	472	2470	1.0	-	1.0	-
50-l 75	73	202	1.9	1.4-2.5	1.8	1.2-2.6
< 50	32	102	1.6	1.1-2.5	1.9	1.1-3.3
Number of vaccination rooms per 100,000 inhabitants**						
Quintile 1	104	333	1.5	1.1-2.2		
Quintile 2	63	374	0.8	0.6-1.2		
Quintile 3	73	363	1.0	0.7-1.4		
Quintile 4	84	353	1.2	0.8-1.7		
Quintile 5	73	363	1.0	-		

* 4 municipalities without information; **1.168 municipalities without information; VC – Vaccination coverage; HDI – Human Development Index; FHS – Family Health Strategy coverage.

Source: Authors, based on data from MS\DATSUS\PNI.

ly affecting routine vaccination services and measles epidemiological surveillance[20,28]. Aligned with other studies[6,21], low VC clusters were found in 2020 and 2021 in all regions, emphasizing the country's North and Northeast. An ecological study indicated that these regions were at greater risk of exceeding the healthcare capacity due to the flow of patients infected with SARS-CoV-2[29], showing greater fragility of the health system.

The present study allowed a better understanding of the association between low VC and worse indicators of inequality, human develop-

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ment, and primary health care aggravated by the COVID-19 pandemic. Previous studies investigated the association between VC and contextual indicators. They found similar results, with worse measles VC in municipalities with lower HDI and more significant social inequality expressed by the Gini Index[27,30].

The FHS promotes increased vaccination coverage[27,31], as it expands the gateway to the health system and access, provides more significant opportunities for vaccination, and facilitates the uptake of individuals with incomplete vaccination schedules, besides establishing more effective communication and a relationship of trust between the community and health professionals. Thus, the need to strengthen the SUS is emphasized as an instrument for inducing health equity with the principle of "health as a right for all", essential for achieving and preserving high, homogeneous vaccination coverage.

In September 2022, the Ministry of Health launched the Action Plan to stop the circulation of the measles virus, aligned with the Action Plan for the Sustainability of the Eradication of Measles, Rubella and Congenital Rubella Syndrome in the Americas, 2018-2023, approved at the 29th Pan American Health Conference. The plan aims to operationalize the interruption of endemic transmission of measles within 12 weeks, starting from the date of the rash of the last confirmed case in 2022, and maintain its eradication to document evidence and subsequently subsidize re-verification for Measles-Free Country certification. Strategies include strengthening epidemiological and laboratory surveillance, vaccination, and health care, besides social communication, in all management spheres, with increased responsiveness and data analysis for decision-making[12]. Health communication is a challenge[32] in infodemic times, with the spread of misinformation, news, and false scientific claims, which needs to be addressed more forcefully in a country where infodemics are added to an ideological political posture.

Measles eradication requires global commitments, both within and outside the health sector, as part of a coordinated effort to strengthen health systems infrastructure, especially primary health care, and innovations to overcome barriers to access and increase trust in vaccines. Since 2001, the global partnership Measles & Rubella Initiative (M&RI) has coordinated actions to achieve a world free of measles and rubella. The Measles and Rubella Strategic Plan 2012-2020, endorsed by M&RI, was launched in 2012. It aimed to eliminate measles in at least five of the six WHO regions, with VC ≥ 95% in all countries, and establish a target date for measles eradication. Considerable advances have been observed in measles control, but no target has been reached[20]. In 2020, the 2030 Immunization Agenda endorsed by the World Health Assembly was presented by WHO and its partners. It considers vaccination and measles incidence performance markers of immunization programs to boost efforts to strengthen immunization and primary care[33]. Moreover, vaccination plays a crucial role in achieving the Sustainable Development Goals, especially Goal 3 (SDG 3) – ensuring healthy lives and promoting well-being for all at all ages[34].

The present study has limitations inherent to using secondary data on VC, calculated from data on applied doses reported by municipalities, which may have heterogeneous quality, and population estimates based on the 2010 Census, underestimating or overestimating VC and allowing VC above 100%. Only the doses applied in the routine strategy were considered, without considering the vaccination campaigns in the period[12]. In 2013, some changes occurred in the PNI information system. The system started to record individual vaccination data, negatively impacting VC estimates unevenly in the country[35]. However, these are the official PNI data used in the management and evaluation of the program. While the drop started in 2015, it highlighted a more significant decline from the year of the pandemic onset. The Gini Index and HDI adopted in the study were based on the 2010 Census, which, even with a 10-year interval, are the most current data available for Brazilian municipalities. Possibly other important explanatory variables were not considered in the model. Furthermore, the associations were analyzed at an ecological level, which is not a limitation but requires care in its interpretation.

Conclusion

Achieving and keeping high and homogeneous VCs is crucial for measles eradication and requires global efforts and commitments. In Brazil, the COVID-19 pandemic has escalated health inequalities with low VC of measles in socially more vulnerable and unequal municipalities. On the other hand, this challenge can be addressed by implementing strategies that strengthen primary health care and ensure vaccine access, reducing missed opportunities for vaccination and vaccine hesitancy.

Collaborations

APS Sato, AC Boing, RLF Almeida, MO Xavier, RS Moreira, EZ Martinez, AM Matijasevich and MR Donalisio contributed to the conception and design of the study, data analysis and interpretation, writing and critical review of the manuscript's content. All authors approved the final version of the manuscript and are responsible for all its aspects, including the guarantee its accuracy and integrity.

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