MEASLES-CONTAINING VACCINES IN BRAZIL: COVERAGE, HOMOGENEITY OF COVERAGE AND ASSOCIATIONS WITH CONTEXTUAL FACTORS AT MUNICIPAL LEVEL

1. Introduction

Since 1977, measles-containing vaccines (MCV) have been the main public health strategy to prevent measles outbreaks and to avoid the spread of the measles virus by reaching and maintaining a high vaccination coverage [1]. Recent epidemiological evidence has shown that, despite the success of the Brazilian National Immunization Program (NIP), the 95% coverage target for MCV, as recommended by the World Health Organization (WHO) and adopted by the Brazilian Ministry of Health (MoH), has not been achieved [2, 3].

During the period 2016-2017, no confirmed measles case has been reported in Brazil, where the last autochthonous case was registered in 2000. The last measles outbreak occurred in 2013-2015, in Pernambuco and Ceará states, Northeast region, leading to the mobilization of health services to identify suspect measles cases and monitoring of vaccine coverage in each region.

However, recent studies showed that the coverage of the first dose of MCV has decreased substantially in Brazil from 106.8% to 85%. A similar scenario has been observed for the levels of homogeneity for MCV coverage across municipalities [4, 5]. This may have enabled the occurrence of a measles outbreak in 2018. It started in February 2018 in the North region of the country, likely due to the intense migration from Venezuela, the presence of individuals susceptible to the virus and multiple measles virus importations, resulting in 5,346 confirmed cases reaching twenty one federal units by September 2019 [5- 7]. The reintroduction of measles in Brazil and the presence of endemic transmission of the virus resulted in Brazil losing its measles-elimination certificate issued by the WHO in 2016 [8]. This fact could jeopardize the certification of the Region of the Americas, as Brazil would be the second country to confirm the reestablishment of endemic transmission in the post-certification period [9].

Therefore, we aimed to describe both the coverage and the homogeneity of coverage of the first and second doses of MCV in Brazil in 2017. In addition, we investigated the potential influence of important contextual factors at municipal level.

2. Materials and Methods

This is an ecological study with data on the coverage of the first and second doses of MCV and associated contextual factors at municipal level. All 5,570 Brazilian municipalities were included in this study. Data on vaccination coverage was obtained from the information system of the Brazilian National Immunization Program (NIP). Coverage was calculated through an administrative method based on the number of doses administered in routine vaccination and the target population [10].

Routine vaccination follows the schedule established by the Brazilian MoH, i.e. one dose of measles-mumps-rubella (MMR) vaccine administered at 12 months of age; one dose of vaccine against measles, mumps, rubella, varicella (MMRV) at 15 months; two doses of MMR between 2–29 years of age, and one dose of MMR from 30–49 years of age. We considered the dose of MMR at 12 months and the dose of MMRV at 15 months as first and second doses of MCV, respectively. The coverages of both doses in 2017 were the primary outcomes of this study. We also estimated the homogeneity of coverage at state level by dividing the number of municipalities that reached the 95% target by the total number of municipalities in the same state [11]. In Brazil, the target set by The Unified Health System for the homogeneity of MCV coverage was 70% i.e. 70% of the municipalities should reach ≥ 95% for the MCV coverage administered at 12 months of age.

Data on contextual factors were obtained from the following data sources:

- Brazilian Institute of Geography and Statistics and the Atlas of Human Development in Brazil: average per capita income; Gini index; illiteracy rate of the population aged 18+ years; infant mortality; municipal Human Development Index (HDI); number of vaccination room per 100,000 inhabitants; percentage of the population living in

households with a density of more than 2 persons per dormitory; percentage of the population living in households with electricity; percentage of the population living in urban households with a garbage collection; percentage of women 10 to 14 years of age who had children; percentage of women 15 to 17 years of age who had children; proportion of extremely poor children; proportion of people in households vulnerable to poverty and who spend more than an hour to get to work; total fertility rate; population size;

- Information System of Primary Health Care (Sisab): Family Health Strategy (FHS) coverage;
- NIP: number of vaccination room per 100,000 inhabitants.

Most indicators are from the 2010 Census; the definition of each indicator and detailed information on its calculation are available elsewhere [12]. Data on coverage of FHS and number of vaccination room were from 2016, and were obtained through the Citizens Information System (SIC) of the Brazilian MoH. Selected indicators are available from public and official repositories of the Brazilian government.

We initially described the coverage levels and their homogeneity for the first and second doses of MCV at national, regional and state levels. Linear regression models were used to investigate the associations in the bivariate analysis. Most variables were divided into quintiles, except the coverage of FHS (<50%; 50-75%, >75%), population size (<25,000; 25,000-100,000; and >100,000 inhabitants), the percentage of women 10 to 14 years of age who had children (tertiles), and number of vaccination room per 100,000 inhabitants (tertiles). Adjusted multivariate linear regression models were performed using the stepwise backward selection approach. All indicators were initially included, and a significance level of 5% was considered to keep the indicator in the adjusted model. All analyses were conducted in Stata version 13 (StataCorp).

3. Results

Table 1 shows the coverage and homogeneity of coverage of the first and second doses of MCV by regions and Federal Units in 2017. At national level, the 95% coverage target was not reached for both doses of MCV. The homogeneity of coverage of the first and second doses of MCV did not reach the 70% target i.e. 54.9% and 35% for the first and second doses respectively. Regional differences were also observed. The North and Center-West regions presented the lowest coverages of the first and second doses of MCV, respectively. The North region also presented the lowest estimate of homogeneity of coverage for the first dose of MCV (46.4%); the Northeast region had the lowest homogeneity of coverage of the second dose of MCV. The federal units of Pará, Amapá and Acre, located in the North region, stood out because of their low coverage and high heterogeneity for both doses of MCV **(Figure 1)**.

All 16 selected indicators were associated with both first and second doses of MCV ($p<0.001$) (**Table 2**). Half of them showed clear inverse associations with both doses, and stronger associations were found with the population size, Gini index, teenage pregnancy, extreme poverty and high density per dormitory. Some indicators, such as the population size, and the Gini index, were strongly associated with the second dose of MCV in comparison with the first dose. Municipalities with coverage of FHS over 75% were more likely to present higher coverage of both first and second doses of MCV in relation to those with coverage below 50%. In addition, the number of vaccination room per 100,000 inhabitants showed a direct positive association with MCV coverage.

In the multivariate analysis, seven and nine indicators remained significantly associated with the coverage of the first and second doses of MCV, respectively (Figure 2). The municipal HDI, the proportion of people in households vulnerable to poverty and who spend more than an hour to get to work, the coverage of FHS, the percentage of women aged 15-17 years who had children and the population size were significantly associated with the coverage of both first and second doses of MCV after adjustments.

Regarding the first dose, the population size presented a strong inverse association with the coverage, showing substantially lower coverage for municipalities with more than 100,000 inhabitants in relation to those with less than 25,000 inhabitants. An inverse association were also found with the percentage of women aged 15-17 years who had children. The percentage of the population living in households with electricity, a proxy for living conditions, and the number of vaccination room per 100,000 inhabitants showed positive associations with the coverage. In addition, a U-shaped association was found with the municipal HDI.

Similarly to the first dose, the population size was the indicator that showed the strongest association with the coverage of the second dose of MCV. The association with the coverage of FHS was also similar for both doses of MCV, and the percentage of urban households with garbage collection, another proxy for living conditions, also showed a positive association with the coverage. In addition, a strong inverse association was found for the dormitory density and for infant mortality. A different pattern was observed for the association of the municipal HDI with the coverage of the second dose of MCV in relation to the first dose, more similar to a J-shaped association.

4. Discussion

Our findings from a large middle-income country in the Region of the Americas highlight the importance of monitoring the homogeneity of MCV coverage at national, regional and state levels, as it allows for the identification of areas at higher risk of measles spread that should be targeted for vaccination. In 2017, the Northern region had the lowest estimates of coverage and homogeneity of coverage for the first dose of MCV in Brazil, as a result of considerable reductions since 2007 [3, 4]. This evidence might help explain the fast spread of the measles virus in the Northern region after its reintroduction due to migration from Venezuela, especially in the federal units of Roraima, Amazonas and Pará [5]. Our analyzes also showed significant associations of both first and second doses of MCV with population size, coverage of FHS and other indicators of living conditions and inequalities.

Previous research has reported on individual factors associated with non-vaccination and vaccination hesitancy [2,12- 16]. In addition, we found studies that have applied multilevel analysis to investigate simultaneously individual and contextual factors at regional, household and village levels [17- 19]. Although this approach seems to be more appropriate to assess immunization differentials, in a large country such as Brazil it is complex and expensive to conduct nationally representative studies to collect individual and contextual data.

In this scenario, administrative data may provide crucial information that could help design public health interventions aimed at increasing vaccination coverage by taking into account regional and local differences. For example, our findings portray the importance of considering the population size, as larger municipalities tend to have substantially lower vaccination coverage. Additionally, the FHS, a very successful strategy in primary health care in Brazil [20], and the number of vaccination rooms seem to contribute positively to the coverage of MCV. Therefore, municipalities with low coverage of FHS and with fewer vaccination rooms per 100,000 inhabitants need to implement complementary strategies to reach higher vaccination coverages, as they are restricted to few areas and cover only part of the population. We also highlight the importance of targeting individuals living in poorer neighborhoods, with limited access to health services, especially in municipalities with high indicators of inequalities.

There are some limitations that should be acknowledged. Firstly, this is an ecological study that considered as units of analysis all the Brazilian municipalities and, therefore, our findings should not be interpreted as individual-level estimates. Secondly, the indicators included in our analytical models were selected from a panel of more than forty indicators extracted from the 2010 Census. Although the selected indicators were based on their likelihood to explain the relationship between contextual factors and MCV coverage in Brazil, some relevant indicators may have potentially been excluded. Thirdly, as most of the selected indicators are from the 2010 Census, with a time lag of nineyears in relation to the outcomes, these estimates may have changed over time. However, this is the best data available at municipal level in Brazil.

Finally, we used administrative data available on the official webpage of the Brazilian Ministry of Health. It is based on data from routine vaccination and does not include data on vaccination campaigns. In addition, issues related to coverage of the information system, completeness and consistency of the data cannot be ruled out. It is important to note that a coverage higher than 100% indicates that the number of administered doses in a municipality is higher than the number of residents of an age group for a specific period.

This is the first study, to the authors' knowledge, to investigate contextual factors associated with MCV coverage at national level in Brazil, including all Brazilian municipalities. Our findings provide evidence that could support public health strategies aiming at increasing MCV coverage and, consequently, preventing the spread of the measles virus to other Brazilian federal units. Targeting large cities i.e. 100,000 or more inhabitants, especially poor neighborhoods and areas with low FHS coverage, could lead to improvements in coverage homogeneity. Studies investigating indicators at both individual and contextual levels are needed to help understand the reasons for lower MCV coverage levels, as well as the determinants of its substantial decrease since 2016 in Brazil.

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