**TRENDS AND SPATIAL DISTRIBUTION OF MMR VACCINE COVERAGE IN BRAZIL DURING 2007-2017**

Measles is a highly contagious and vaccine-preventable viral disease that usually manifests with high fever, rash and cough or conjunctivitis or coryza, and can lead to complications such as blindness, encephalitis or death [1]. In 2016, the Region of the Americas was declared as free of the endemic transmission of the measles virus [2]. However, as the measles virus has been circulating worldwide, it is imperative that countries reach the target of 95% coverage of measles-containing vaccine [3].

In February 2018, the last outbreak of measles in Brazil began~~an outbreak has started in Brazil~~, where the last autochthonous cases had been registered in 2000. As of 24~~8~~ January~~October~~ 2019~~8~~, 10,302~~2,044~~ cases of the disease were confirmed, of which 9,803~~1,629~~ were registered in the state of Amazonas, 355~~330~~ in Roraima, 62 in Pará, 46~~36~~ in Rio Grande do Sul, 19~~18~~ in Rio de Janeiro,~~ 17 in Pará~~, 4 in Pernambuco~~,~~, 4 in Sergipe, 3 in São Paulo, 3 Bahia, 2 in Rondônia and 1 in Distrito Federal [4]. In the states of Amazonas, which comprises 95% of the confirmed cases, the incidence was higher among children under 1 year of age (2,189.3 per 100.000 inhabitants), followed by the age groups 15-29 years (427.2 per 100.000 inhabitants) and 1-4 years (354.1 per 100.000

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inhabitants). Most cases have been registered in the North region (99.26,8%) and the D8 genotype has been identified among the confirmed cases, which is identical to the one that has been circulating in Venezuela since the epidemiological week 26 of 2017 [5].

**MMR coverage and measles outbreaks**

We used MMR coverage data available through the Information System of the National Immunization Program (SI-PNI) of the Brazilian Ministry of Health (MoH), from 1 January 2007 to 31 December 2017. In Brazil, vaccination coverage is obtained through an administrative method, based on the number of doses and the target population [6]; therefore, coverage can be above 100% when the number of doses administered in the municipality is greater than the number of residents in a specific age group and time period. According to the national immunization schedule, the first and second doses of the MMR must be offered to children aged 12 and 15 months, respectively. The ~~coverage~~ target for MMR coverage adopted by the MoH is 95% for the eligible age groups, in accordance with the World Health Organization recommendation.

During 2007-2016, the 95% target was achieved for the first dose of MMR among children aged 12 months; however, national coverage decreased to 85% in 2017. For the

second dose, at 15 months of age, the target was not achieved during 2013-2017. After two years with none confirmed cases, there was a marked increase in reported cases in 2018. As of 24~~8~~ January~~October~~ 2019~~8~~, 10,302~~2,044~~ measles cases were confirmed, most of them (~~95,8~~98,6%) in the states of Amazonas and Roraima, both in the North region. The D8 genotype has been identified among the confirmed cases [4], which is identical to the one that has been circulating in Venezuela since the epidemiological week 26 of 2017 [5] (Figure 1).

Nationally, the 95% target was achieved for the first dose of MMR from 2007 to 2016 among children under one year of age; however, national coverage decreased to 85% in 2017. For the second dose, the target was not achieved in the period under study. Applying the third order moving averages smoothing technique, a downward trend in the national coverage was identified from 2014 onwards, which can also be seen in the analyzes stratified by regions. A steeper decline was observed for the North region, where coverage has remained below the 95% target since 2015, reaching 77% in 2017. The Southeast, South and Center-West regions also did not reach the target in 2017 (Figure 2).

**Time trends**

We used linear multilevel regression models to calculate time trends at country, region and Federal Unit levels using the approach described by Victora et al [7]. ~~The contribution of poor and rural populations to national trends in reproductive, maternal, newborn, and child health coverage: analyses of cross-sectional surveys from 64 countries. The Lancet Global Health. 2017;5(4):PE402-E7.].~~ Aggregation at each level was done by pooling all municipalities with available data for the years under study, considering each years' estimate as level one units, and regions or Federal Units as level two units. We also estimated the annual percentage change (APC) of MMR coverage using the Prais-Winsten regression [8].

The multilevel approach indicated that all regions have significant downward trends, which can also be seen at the state level. Conversely, most trends were considered as stable using the Prais-Winsten procedure, although with high values of APC. Consistent with the results from the multilevel approach, the state of Ceará presented a significant positive APC. In addition, the North region presented a marked downward trend, especially in the states of Acre, Amazonas and Pará; the later had the steepest decrease in the period under study. Also, the states of Maranhão, Piauí, and Sergipe, all in the Northeast region, presented significant decreases over time (Table 1).

**Variations in spatial distribution**

In 2009, 26 out 27 Federal Units reached the 95% target; the Federal District presented the lowest coverage. By 2013, most states maintained MMR coverage above the recommended target; however, the states of Amapá and Roraima, both located in the North region, presented decreases in coverage. The scenario worsened markedly in 2017, when two states in the North (Acre and Pará) and one in the Northeast region (Piauí) presented coverage below 80%. Only 11 out 27 Federal Units met the 95% target in 2017. In the states of Pernambuco and Ceará, where measles outbreaks happened during 2013-2015 [3], actions were taken to intensify vaccination against measles during these outbreaks, which seem to have been maintained since then (Figure 3A).

We also analyzed the spatial point distributions of the MMR coverage of each of the 5,570 municipalities in Brazil to obtain the kernel density estimation [9]; the kernel bandwidth (search radius) was 100 km and the smoothing function chosen was quartic (biweight). A higher concentration of municipalities below the 95% target was found in the South, Southeast and Northeast regions throughout the study period. In 2017, the states of Goiás and Pará, located in the Center-West and North regions, respectively, also presented areas

with high concentration of municipalities with MMR coverage below the target (Figure 3B).

We investigated spatial autocorrelations using the global Moran's I, using 999 permutations and considering a 5% significance level [10]. Significant positive spatial autocorrelations were observed for the MMR vaccine coverage moving averages in 2009 (Moran's I = 0.108; p=0.001), 2013 (Moran's I = 0.095; p=0.001), and 2017 (Moran's I = 0.170; p=0.001), suggesting the existence of clusters in their spatial distribution.

**Discussion**

The ongoing measles outbreak in Brazil seems to be related to the decrease in MMR coverage among infants, especially in the states of the North region. Areas with high concentration of municipalities with coverage below the 95% target were ~~are more susceptible to the spread of the virus,~~ located mainly in the states of Pará, Maranhão, Piauí and Sergipe; these areas are more susceptible to the spread of the virus. Conversely, states such as Pernambuco and Ceará managed to keep MMR coverage above the target, even after the containment of the outbreaks that occurred during 2013-2015.

Global data point to a stagnation in the coverage of the first dose of measles-containing vaccines worldwide during 2000-2016; as a result, measles outbreaks continue to occur among unvaccinated individuals [11, 12]. In 2018, as of 1820 January~~uly~~ 2019~~98~~, 16,571~~2,472~~ confirmed cases of measles were reported by 12~~1~~ countries in the Region of the Americas; of these, most cases ~~(65%)~~ were registered in Brazil (61,9%) and Venezuela (34,1%) [5].

The ongoing outbreak in Brazil started in the state of Roraima, located in the North region, which shares borders with Venezuela. Roraima ~~and~~ has received a great number of migrants since 2015, following the economic crisis in the ~~neighboring~~neighbouring country. Since its introduction in Roraima, the genotype D8 measles virus, imported from Venezuela, has spread to six other states in Brazil~~, apparently due to high circulation of the virus and low levels of MMR coverage~~. Elidio et al. [13], analysing the measles outbreak in Manaus, capital of the Amazonas state, suggested that although the reintroduction of the virus in the municipality may be linked to the outbreak in Venezuela, the spread of the virus was made possible by the low levels of measles vaccine coverage. The Brazilian National Immunization Program (in Portuguese, Programa Nacional de Imunizações do Brasil – PNI) was implemented in 1975 and, since then, has promoted

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free-of-charge vaccination countrywide [6]. Despite the advances achieved by the program over its 45 years of existence, our findings indicate that, similar to the Amazonas state which presented favourable conditions for the spread of the ~~virus.~~virus; other Brazilian states are also at risk of facing measles outbreaks. This is ~~-~~due to the large number of susceptible individuals who have not been vaccinated over the years, especially in the ~~n~~Northern and ~~northeastern~~Northeastern regions. This finding may be related to several factors, including socioeconomic, political, and cultural aspects [14, 15].

A rapid monitoring of vaccination coverage was conducted in the state of Ceará, ~~n~~Northeast Brazil, which faced a measles outbreak in 2013-2015; the main reasons refereed by the parents/guardians for non-vaccination against measles in children were the lack of time, vaccine, or scheduling, and difficulty in getting to the place where vaccination was happening [16]. In addition, a literature review on the potential causes of vaccine hesitancy/refusal showed that personal factors could also play an important role, including doubts about the actual need for vaccines and its adverse events; also, health professionals who have rarely seen or cared for patients with vaccine-preventable diseases may be less inclined to strongly recommend vaccination and to provide reliable information to parents/guardians about these diseases [14].

Although analysing the coverage estimates at state level allows assessing the risk of spread of the measles virus to states with low coverage and with a decreasing pattern, we highlight the importance of monitoring the coverage at municipal level. The spatial analysis carried out in this study allowed identifying clusters of municipalities with coverage below the 95% target in different states, some of them with overall coverage above the target. This finding indicates that the likelihood of spread of the measles virus after introduction differ not only by state, but also by area and municipality. In addition, it is plausible ~~ossible to suppose~~ that the MMR vaccine coverage might not be uniform across neighbourhoods of a municipality. ~~;~~ eEstimates at neighbourhood level are not available at the national information system and, therefore, ~~ so that~~ we were not able to explore this further.

We acknowledge some limitations of our study. Firstly, our results are based on administrative data, which can be affected by issues related to the coverage, completeness and consistency. ~~;~~ iIn addition, it only includes doses applied in routine vaccination, as official information on the coverage of vaccination campaigns are not publicly available.~~;~~ ~~h~~However, this is the best data available at the national and regional levels, which has been used for public health decision-making.

Secondly, we only analyzed the coverages of the first and second doses of MMR at 12 and 15 months of age, respectively, as these indicators are periodically calculated by the MoH; data on coverage of the second dose were available for a restrict period (2013-2017) and no information was obtained for other age groups. Finally, data on the ongoing outbreak are being updated weekly by the MoH; we highlight the high number of cases still under investigation, as well as the substantial number of new suspected cases that have been reported weekly, indicating the rapid spread of the disease.

In Brazil, the MMR vaccine is available in more than 36,000 vaccination ~~rooms~~ sites located throughout the country. ~~As one of the additional actions to interrupt the ongoing outbreak, t~~The MoH sent 13,504,000 supplementary doses of the MMR vaccine to the states presenting confirmed cases as one of the additional actions to interrupt the ongoing outbreak. The main objectives are ~~, to be used for~~ blocking and intensification actions as well as ~~, and~~ vaccination campaigns. Moreover, the MoH has supported states and municipalities to achieve the 95% coverage target by ensuring free supply of the MMR vaccine according to the national immunization schedule [4].

Our findings may contribute to target vaccination strategies in priority areas, where the coverages of the first and second doses of the MMR are below the 95% target, as well as

in areas showing a marked decrease in coverage. Strategic actions should be undertaken immediately to effectively stop the transmission of the measles, avoiding the spread of the virus to areas with low coverages of MMR. Moreover, it is essential to extend these ~~pand~~ actions to ~~for travelers~~travellers, migrants and refugees.

## Conflict of interest

None declared

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