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Longitudinal profiling of the vaccination coverage in Brazil reveals a recent change in the patterns hallmarked by differential reduction across regions

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ABSTRACT

Objective: Vaccination coverage is decreasing worldwide, favoring the potential reemergence of vaccine-preventable diseases. In this study, we performed a longitudinal characterization of vaccination coverage in Brazil and compared the profiles between the distinct regions in the country to test whether there has been a substantial change over the last 5 years.
Methods: De-identified publicly available data were retrieved from the repository of the Brazilian Ministry of Health, comprising detailed information on vaccination coverage in all age groups between 1994 and 2019. The vaccination coverage for the whole country and for each Brazilian region, by year, was examined, and a time-series pattern analysis was performed.
Results: A significant decrease in overall vaccination coverage across the country regions was observed between 2017 and 2019, especially in childhood immunization. A reduction in BCG, hepatitis B, influenza, and rotavirus vaccine coverage was observed. Conversely, vaccines against measles, mumps, rubella, varicella, and meningococcus showed an increase in coverage. Region-specific changes in vaccination patterns within the study period were observed.
Conclusions: A substantial reduction in vaccination coverage was detected in Brazil, a country already highly susceptible to the emergence of epidemic infectious diseases. Continuing evaluation of the immunization program actions may help to improve vaccination coverage and prevent new epidemics.
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Introduction

Over recent decades, humanity has seen the control or eradication of several diseases due to the development of vaccines (Hotez et al., 2020). Some generations have never experienced an epidemic situation of certain diseases such as measles and polio (Greenlee and Newton, 2018). Recently, however, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been affecting countries worldwide, and the current absence of an effective vaccination against the virus has had a devastating impact on public health, with millions of casualties (Luan et al., 2020; Velavan and Meyer, 2020), reinforcing the importance of vaccines. Unfortunately, vaccination coverage has been decreasing worldwide. This reduction could lead to the potential reemergence of vaccine-preventable diseases (VPDs) (Siani, 2019).

The Brazilian National Immunization Program (Programa Nacional de Imunizações, PNI) and the Unified Health System (Sistema Único de Saúde, SUS) have been providing free vaccines against several diseases to people of all age groups, reaching a national coverage higher than 90% (Sato, 2018). Nevertheless,

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despite government efforts with vaccination campaigns, vaccine coverage in Brazil has been falling since 2013 and an increased level of vaccine refusal has been demonstrated in the country (Brown et al., 2018). These phenomena have been strongly associated with the ‘scientific proven disadvantages of vaccines’ that have spread rapidly via social media. Such misinformation campaigns have led to population hesitancy to be vaccinated and have become a big challenge for the PNI in recent years (Aps et al., 2018). Despite regular challenges to vaccinate the population, all of these new issues have had a harmful impact on coverage, with a potential increase in the number of preventable deaths (Sato, 2018).

The dynamics of vaccination coverage in Brazil can be assessed using PNI vaccination data. Using this approach, it may be possible to identify the behavior of the population and the potential risk of the reintroduction of VPDs in the country.

This study was performed to evaluate PNI vaccination data from the whole country and the dynamics of coverage over the years in different regions, in order to understand the vaccine coverage profiles and potentially identify which vaccinations have decreased in Brazil.

Methods

This study used secondary data that are publicly available from the Department of Informatics of the Brazilian Ministry of Health (DATASUS: http://tabnet.datasus.gov.br/cgi/dhdat.exe?bd_pni/dpnibr.def). The data include all of the information regarding vaccination coverage, in all age groups. All data available for the years 1994–2019 were retrieved and de-identified, following the regulations of Resolution No. 466/12 on Research Ethics of the National Health Council, Brazil. The information regarding all vaccinations in Brazil was retrieved from the Brazilian National Immunization Program (Programa Nacional de Imunizações, PNI) databank and stratified by region, as described previously (Silva and Autran, 2019).

The differences in vaccination coverage for the whole country and for each region, by year, were compared with the Pearson Chi-square test. In addition, time-series analyses were performed using a native *stats* (V.3.6.2) package available in R software (R Development Core Team, 2003). The smooth line to exploratory trends of vaccination in Brazil along the selected periods was performed and represented using the ggplot2 package developed in R 3.6.2 (http://www.R-project.org). A Venn diagram was generated to check the common vaccine changes by region using the *venndiagram* package for R. Comparisons of time-series patterns and the prediction algorithm using the auto regressive integrated moving average (ARIMA) were performed using the exponential smoothing state space model in *forecast* and *aTSA* package, available in R 3.6.2. These packages analyzed the patterns and extracted the information of random, trend, and seasonal patterns from the time-series with the *decompose* function. This modeling is used to forecast future values in the time series by identifying the best-suited model for specified time-series data. The lag plot was performed using the *gglagplot* function in R, to measure the auto-dependence, autocorrelation, and seasonality during the indicated months of the years between 2004 and 2019. This plot allows it to be determined whether the values in a time-series are random. Differences with p-values <0.05 were considered statistically significant.

Results

During the time period evaluated, the lowest number of vaccination doses applied was in the year 1994, with 19 513 606 doses. Conversely, the highest numbers of vaccinations were seen in 2014 (125 357 642 immunizations), 2001 (123 428 150 immunizations), and 2017 (118 590 603 immunizations). The peak in 2017 was followed by a decrease over the next 2 years, resulting in 102 469 969 vaccinations in 2019 (a reduction of 13.6%). The smooth line in vaccination data shown in Figure 1Adepicts a fluctuation of the immunization coverage over the last 8 years. Although there was a decrease in absolute number of vaccination doses, the PNI had increased the variety of vaccines offered during the same timeframe: it offered 11 vaccines in 1994, which had

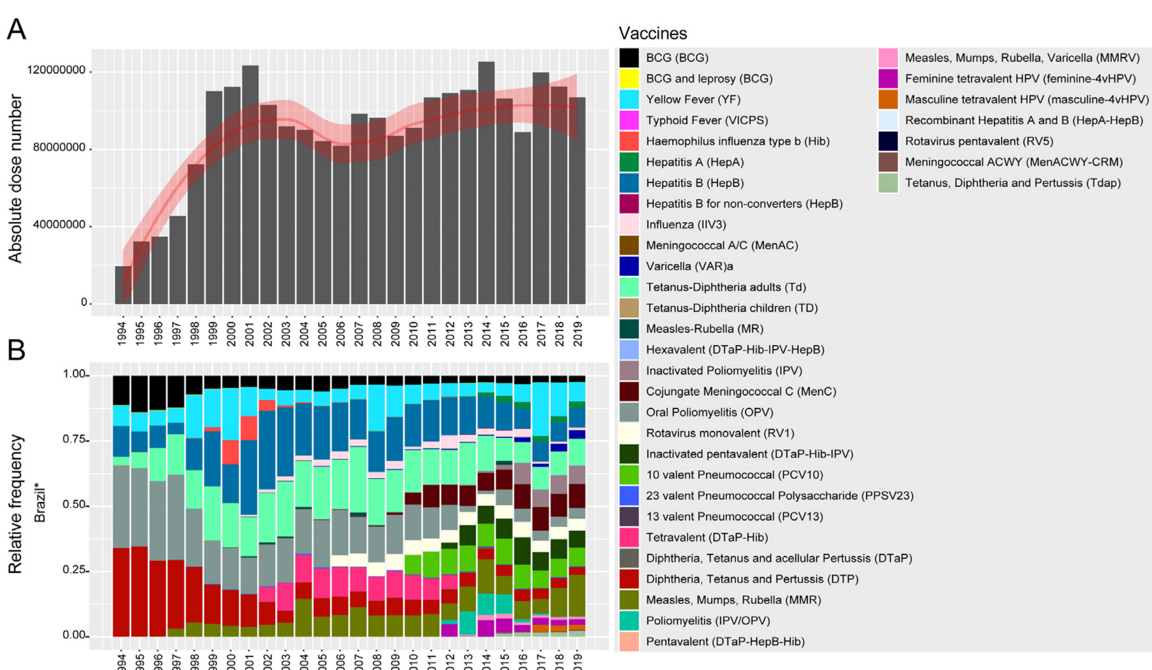

Figure 1. Distribution of vaccinations in Brazil between 1994 and 2019. (A) Bar chart of vaccinations by year and smooth line representing the trends with 95% confidence intervals. (B) Relative abundance of each vaccine shot given in Brazil by year. Colors represent different vaccines tested; Pearson Chi-square test. The asterisk (*) represents a statistically significant difference ($p < 0.05$).

increased to 36 vaccines in 2019 (Supplementary Material File S1). On closer inspection, examining the profiles of each specific vaccine offered in 2019 revealed that 44.44% ($n = 16$) showed a decrease in the number of applied doses, whereas 22.22% ($n = 8$) exhibited increases in the number of doses in comparison with the last 2 years (2017 and 2018). The differences in proportions of vaccinations across these years was significant, as evaluated with the Chi-square test ($p < 0.001$) (Figure 1B).

We next examined the vaccination coverage among the different regions of the country (Figure 2A). A reduction in the absolute numbers of vaccination doses occurring in all regions in the last 3 years was detected, mirroring the overall reduction observed in the whole country (Figure 1), except the South region, which presented an increase in the number of vaccinations during the last 3 years (Figure 2A). Although there was a reduction in absolute number, linear regression analysis revealed only a slight decline in the North, Northeast, and Midwest regions over the last 3 years (Figure 2B). The region presenting a more significant reduction in vaccination coverage was the Northeast, which exhibited a decrease of 1 162 122 vaccines in 2018 in comparison with 2017, and 1 344 017 in 2019 in comparison with 2018 (representing reductions of 4.05% and 4.68%, respectively, in the number of vaccinations). The variety of vaccines offered in all regions increased in 2019, as revealed by the Chi-square test ($p < 0.001$; Figure 2C).

After describing the overall changes in vaccination coverage observed in Brazil during the period studied, we investigated the coverage of each specific vaccine in 2019. Using the Venn diagram approach, it was observed that seven vaccines displayed a reduction in the number of doses in all Brazilian regions in 2019 when compared with 2018 (Figure 3A). Interestingly, all of the seven vaccines identified were those given to babies and children and are recommended by the Brazilian Society of Pediatrics. Several vaccines presented a specific reduction in coverage in some regions, such as oral poliovirus (OPV) in the South; Tdap (acellular triple vaccine; pertussis, tetanus, and diphtheria), Hib

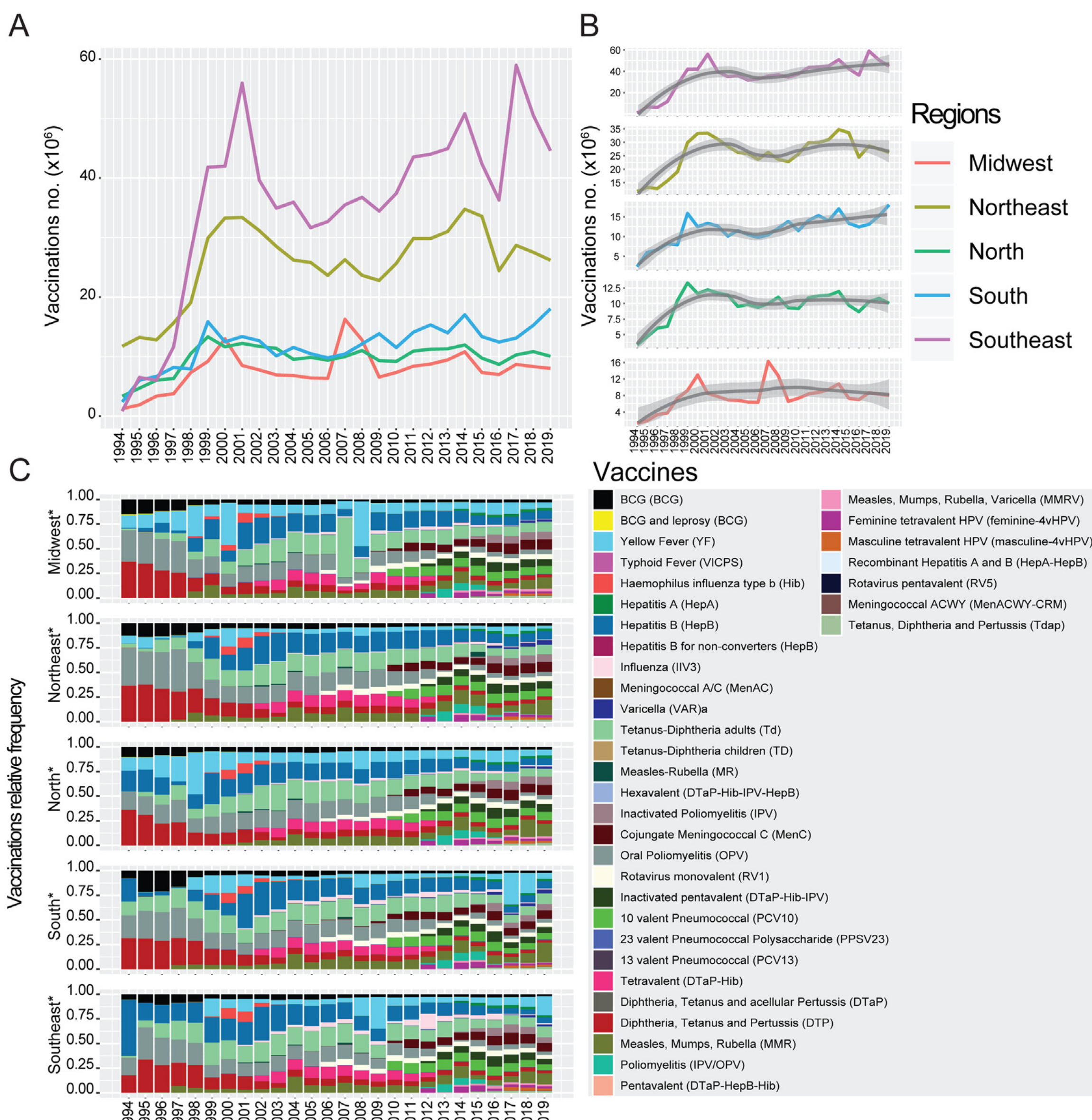

Figure 2. Number of vaccine doses given in each Brazilian socio-economic region by year. (A) Line chart of the absolute numbers of vaccinations by year in each region. (B) Line chart with a smooth line (with 95% confidence interval) of the absolute number of vaccinations by year in each region. (C) Relative abundance of each vaccine shot given in each Brazilian socio-economic region by year. Colors represent different vaccines tested; Pearson Chi-square test. The asterisk (*) in the label represents a statistically significant difference ($p < 0.05$).

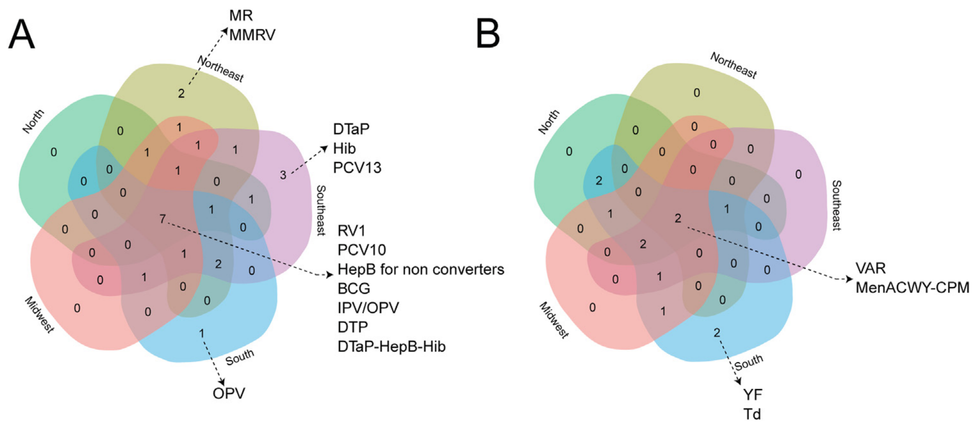

Figure 3. Dynamics of vaccination profiles in Brazil. Venn diagram of vaccines that decreased (A) and increased (B) in the number of shots given in 2019 compared to 2018, stratified by the different Brazilian regions.

(*Haemophilus influenzae* type b), and PCV13 (13-valent pneumococcal conjugate vaccine) in the Southeast; and measles–rubella and MMRV (measles, mumps, rubella, and varicella) vaccines in the Northeast. On the other hand, only two vaccines, meningococcal ACYW and varicella vaccines, showed an increase in immunization doses in 2019 for all regions (Figure 3B). Yellow fever and Td (diphtheria and tetanus for adults) vaccines showed an increase in immunization doses only in the South region.

To investigate the evidence for the reduction in number of vaccinations in Brazil, a time-series analysis was performed using data from 2004 to 2019. The number of vaccines applied in Brazil was higher in June, August, and May, with lower vaccination doses being applied in December and November (Figure 4A). The time-series pattern was extracted from the data using a decomposing technique (described in the Methods section), using forecast modeling. In the analysis of the whole country, a seasonal pattern was observed starting in 2004; this pattern was lost in 2011 (Figure 4B). In order to confirm the seasonal pattern, a lag plot analysis was performed. The lag plots showed an absence of autocorrelation within the time-series, suggesting a random structure across the data by the months (Figure 4C). To predict the vaccination coverage pattern for the next 5 years, the exponential smoothing state space model was employed using ARIMA (see Methods for details). The prediction model revealed a maintenance of the random pattern in vaccination coverage for the next 5 years (Figure 4D). The same approach was performed in each Brazilian region and revealed that the change from seasonal to random, as well as the

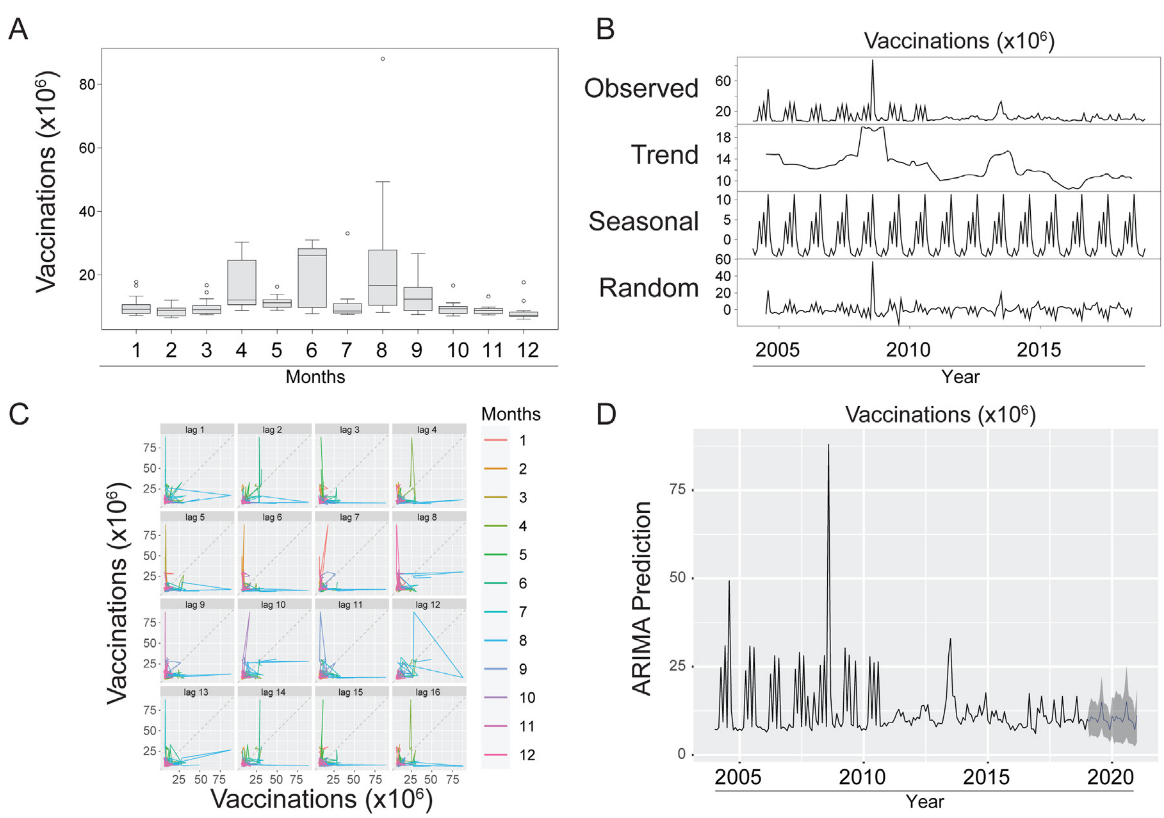

Figure 4. Time-series pattern analysis of vaccination coverage in Brazil. (A) Boxplot chart of vaccines applied in Brazil across the months between 2004 and 2019. (B) Decomposition of the time-series in random, trend, and seasonal patterns of vaccinations applied in Brazil between 2005 and 2019. (C) Lag plot of administered vaccines per month between 2004 and 2019. (D) Forecast prediction for the next 5 years of vaccinations in Brazil, based on data from the last 16 years.

prediction for the next 5 years, were reproduced in all regions (Supplementary Material Figure S1).

Discussion

Due to the current rapid flow of information, misleading false 'scientific information facts' spread by anti-vaccination groups throughout the world have impacted vaccination coverage. This phenomenon has shown a strong association with measles, mumps, and pertussis outbreaks in the United States (Ventola, 2016; Goldani, 2017; Smith, 2017; Paniz-Mondolfi et al., 2019). Recently, measles outbreaks have also occurred in South American countries including Venezuela, Colombia, and Brazil (Dias Leite and Naaman Berezin, 2015). These outbreaks have highlighted the importance of the need for improvements in vaccination surveillance and control strategies by the public health systems of these countries (Silveira et al., 2020). According to the study results, seven vaccines showed a reduction in doses applied in Brazil in 2019 when compared with the previous year, all of these being used for the immunization of children. The study findings from Brazil are in direct agreement with the impression that there has been a recent decrease in vaccination coverage in other countries.

This observation is of extreme concern, because of the increased susceptibility to new infections in this age group due to their less mature immune system. Furthermore, successfully controlled VPDs would be ready to return, potentially causing new epidemics, raising challenges for new physicians without experience in these diseases (Greenlee and Newton, 2018). Since 2016, vaccination coverage has fallen by about 10–20% in children under 10 years of age in Brazil (Hussain et al., 2018). This reduction has been associated with a reduction in funding dedicated to the SUS, aside from increasing public distrust in vaccines and vaccination hesitancy (Sato, 2018). However, in the present study, we observed a peak in overall immunization in 2017; this was due to yellow fever vaccine shots, especially in the Southeast region, which was the epicenter of a yellow fever outbreak in that year (Goldani, 2017). This peak was followed by a continuous decrease in the absolute number of vaccinations in the following 2 years. The ARIMA time-series model was used here to predict the vaccination coverage profile for the next 5 years in the whole country and in each region. This model has been used to predict the mortality incidence of pneumonia and influenza (Choi and Thacker, 1981) and infectious diseases (Allard, 1998), and to investigate the changes in pattern of immunizations during a mass vaccination program in Canada (Trottier et al., 2006). These modeling approaches are based on the mathematical properties of the time series and do not consider other aspects related with the event, in our case the population behavior or socio-economic factors.

Socio-economic inequities may have played an important role in the reduction of vaccination uptake reported here. A study evaluating four birth cohorts between 1982 and 2015 conducted in Pelotas, Rio Grande do Sul, demonstrated that there was a shift in vaccination coverage through those years (Dias Leite and Naaman Berezin, 2015). The authors showed that vaccination coverage in the 1980s was higher in wealthy families and that this socio-economic inequality had reduced in the 1990s and 2000s. In 2015, the vaccination coverage profile was reversed, with children from better-off families presenting lower coverage. Misleading ideas on the side effects of vaccinations could have made them feel able to criticize medical science regarding vaccines, leading them to believe in alternative non-scientific facts found on the internet (Dias Leite and Naaman Berezin, 2015).

Vaccination hesitancy is not the only factor responsible for lower vaccination coverage. Political conflicts, socio-economic collapse, and difficulties bringing vaccines to remote areas, such as indigenous and rural communities, have been pointed out as challenges for the Brazilian national immunization program (Hotez et al., 2020). A study conducted in São Paulo highlighted the psychological element as an important factor in delaying vaccination schedules due to parent anxiety, worrying about their children receiving vaccine shots (Silveira et al., 2020). Such aspects combined with anti-vaccination group activism on social media and distrust in medical science have exposed the complexity of contending the reduction in vaccination coverage (Smith, 2017; Silveira et al., 2020). Therefore, a multifaceted strategy is necessary to avert the recurrence of VPDs and to once again eradicate such diseases.

Although the study findings led us to speculate that there is a relationship between the anti-vaccination movement and immunization coverage in Brazil, additional prospective investigations with the systematic collection of primary data on both the anti-vaccination movement and vaccination hesitancy are still warranted to directly test this hypothesis.

People tend to avoid vaccination when they perceive it to be unnecessary due to the lack of perception of an illness threat. They pay more attention to minor vaccine side-effects such as mild fever, muscle and joint aches, headache, and pain at the injection site (Nour, 2019). This behavior is reinforced by anti-vaccination propaganda, spread on social media, which highlights these side effects together with unproven 'facts' (e.g., the MMR vaccine is associated with autism (Kolff et al., 2018)) over the individual and community benefits of vaccines. Therefore, to counteract this bad propaganda against vaccines, physicians, the scientific community, and health agencies should be more active on the internet and social media, reminding people of how dangerous these VPDs are and guiding people to maintain better health behaviors (Smith, 2017). A social-ecological model could suggest where vaccination campaigns should be targeted to promote increased coverage, taking into account strategies on the individual, interpersonal, organizational, community, and society levels (Kolff et al., 2018). As well as counteracting messages on social media, the use of blogs and apps delivering surveillance data and health education material may also contribute to stimulating healthy behaviors. It is important to note that to battle such a complex health problem, all strategies should be performed together, and for a long-term solution it is essential to educate future generations about scientific methodology and evidence-based medicine and health, so that they can critically evaluate the veracity of the information they obtain from social media (Hopf et al., 2019).

In conclusion, the findings from this study corroborate the idea that there has been a tendency of lower vaccination coverage in recent years in Brazil, especially for vaccines indicated for childhood immunization. Thus, it is extremely important for physicians, the scientific community, and health agencies to take countermeasures and avoid the recurrence of once eradicated VPDs. The reduction in the last 3 years and the random pattern of vaccination coverage detected and predicted in the analyses presented here are an alert to the Brazilian authorities, and strategies must be developed to improve vaccine coverage and reduce vaccine hesitancy, primarily for the pediatric vaccines.

Author contributions

K.F.F. conceived and designed the study. N.C., T.F.M., K.F.F., F.F.L. L., and A.C.M.L. performed the data extraction and curation. B.B.A., A.T.L.Q., and K.F.F. performed the data analysis and visualization. R. L., L.F.Q., and K.F.F. helped interpreting the study findings. N.C., T.F. M., and K.F.F. wrote the first version of the manuscript. B.B.A., A.T.L. Q., and K.F.F. wrote the final version of the manuscript. All authors have read and approved the final version of the manuscript.

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Ethical approval

This study used de-identified publicly available data and did not require approval by the Institutional Review Board.

Data availability statement

The datasets generated during and/or analyzed during the current study are available in the public data repository of the Department of Informatics of the Brazilian Ministry of Health (DATASUS) and can be accessed at http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/cpniuf.def.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.06.092.

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