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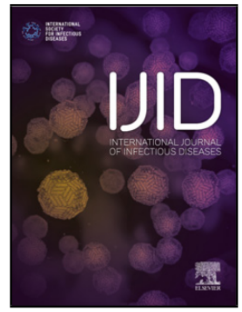

Longitudinal Profiling of the Vaccination Coverage in Brazil Reveals a Recent Change in the Patterns Hallmarked by Differential Reduction Across Regions

Náthaly Césare, Tiago F. Mota, Fernanda F.L. Lopes, Ana Claudia M. Lima, Ricardo Luzardo, Luiz Fernando Quintanilha, Bruno B. Andrade, Artur T.L. Queiroz, Kiyoshi F. Fukutani

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Title: Longitudinal Profiling of the Vaccination Coverage in Brazil Reveals a Recent Change in the Patterns Hallmarked by Differential Reduction Across Regions

Authors: Náthaly Césare[1*], Tiago F. Mota[2*], Fernanda F. L. Lopes[1], Ana Claudia M. Lima[1], Ricardo Luzardo[1], Luiz Fernando Quintanilha[1], Bruno B. Andrade[1,2,3,4,5†], Artur T. L. Queiroz[2,5†], Kiyoshi F. Fukutani[1,2,5†]

Affiliations

[1] Curso de Medicina, Faculdade de Tecnologia e Ciências (UniFTC), Salvador, Bahia, Brazil

[2] Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Bahia, Brazil

[3] Universidade Salvador (UNIFACS), Laureate Universities, Salvador, Bahia, Brazil

[4] Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, Bahia, Brazil

[5] Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER), Salvador, Bahia, Brasil.

[*] N.C. and T.F.M. equally contributed to this work.

[†] B.B.A., A.T.L.Q. and K.F.F. equally contributed to this work.

Running Head: Recent reduction in vaccination coverage in Brazil

Address for correspondence: Bruno B. Andrade, MD, PhD. Laboratório de Inflamação e Biomarcadores, Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão, no. 121, Candeal, Salvador, Bahia 40296-710, Brazil. Tel: +55 71 3176-2264. E-mail: Bruno.andrade@fiocruz.br.

Highlights

- There has been a recent reduction in vaccination coverage in Brazilian regions
- Most relevant reduction in vaccination coverage occurred in childhood immunization
- Increases web searches of anti-vaccine relate to reduction in immunization coverage

Abstract

Objective: Vaccination coverage is decreasing worldwide, favoring potential reemergence of vaccine-preventable disease. Here, we performed a longitudinal characterization of the 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 five years.

Methods: We retrieved de-identified data publicly available from the repository of the Brazilian Ministry of Health, comprising detailed information on vaccination coverage, in all age groups, between 1994 and 2019. We examined the vaccination coverage from the whole country and each Brazilian region, by year, and performed a time-series pattern analysis.

Results: A significant decrease in overall vaccination coverage across the country regions was observed between 2017 and 2019, especially in childhood immunization. BCG, Hepatitis B, influenza and rotavirus vaccines displayed a reduction in coverage. Conversely, vaccines against measles, mumps, rubella, varicella, and meningococcus had an increase in coverage. Region-specific changes in vaccination patterns within the study period were observed.

Conclusions: Substantial reduction in vaccination coverage was detected in Brazil, a country already highly susceptible to emergency of epidemic infectious diseases. Recursively evaluation of the immunization program actions may help to improve vaccination coverage and prevent new epidemics.

Keywords: Vaccination; Immunization Programs; Immunization Coverage.

Introduction

In the last decades, humanity has experienced control and eradication of several diseases due to the development of vaccines (Hotez et al. 2020). Some generations have never experienced an epidemic situation of some diseases such as measles and polio (Greenlee and Newton 2018). Recently, nevertheless, the world has been through the SARS-Cov-2 pandemic, and the absence of an effective vaccination against such virus has caused so far 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 and this reduction could be a potential risk of reemergence of vaccine-preventable disease (VPDs), jeopardizing the overall population health (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 for several diseases to people from all age groups, reaching a national coverage higher than 90% (Sato 2018). Notwithstanding, the government efforts with the vaccination campaigns, Brazil's vaccination coverage has been dropping since 2013 and an increased level of vaccine refusal has been detected in the country (Brown et al. 2018). These phenomena have been strongly associated with the “scientific proofed disadvantages of vaccines” rapidly spread through social media. This misinformation campaign leads the population hesitancy to be vaccinated and has become a big challenge for the PNI in recent years (Aps et al. 2018). Despite the regular challenges to vaccinate the population, all these new issues have a harmful impact on the coverage with a potential increase in the number of preventable deaths (Sato 2018). The comprehension of the dynamics of the vaccination coverage in Brazil can be accessed using the PNI’s vaccination data. This approach helps to identify the behavior of the population and potential risks for reintroduction of VPDs in the country.

The present study was aimed at evaluating the PNI’s vaccination data from the whole country and its dynamics over the years in different regions, to understand the vaccination coverage profiles and potentially identify which vaccines have been decreased in Brazil.

Methods

The present study used secondary data publicly available on the Department of Informatics from the Brazilian Ministry of Health (DATASUS: http://tabnet.datasus.gov.br/cgi/dhdat.exe?bd_pni/dpnibr.def), comprising all the information regarding vaccination coverage, in all age groups. All the retrieved data available between 1994 and 2019 were de-identified, following the regulations of the Resolution no. 466/12 on Research Ethics from the National Health Council, Brazil. The information regarding all the vaccinations in Brazil were retrieved from the Brazilian National Immunization Program (Programa Nacional de Imunizações, PNI) databank and stratified by region according to previously described (Silva and Autran 2019). The differences in vaccination coverage from the whole country and each region, by year, were compared with the Pearson's chi-Square test. In addition, time-series analyses were performed using a native *stats (*V.3.6.2) package available in the 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). The Venn diagram to check the common vaccines changes by region was performed with the *venndiagram* package for R. The comparisons of time-series patterns and the prediction algorithm using Auto Regressive Integrated Moving Average (ARIMA) were performed by using the exponential smoothing state space model performed with *forecast* and *aTSA* package, available in R 3.6.2. These packages analyzed the patterns and extracted the information of random, trends and seasonal patterns from the time-series by the *decompose* function. This modelling 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 us to identificate whether the values in a time series are random. Differences with p-values <0.05 were considered statistically significant.

Results

Among the evaluated period, the year of 1994 presented the lowest number of vaccination shots applied, with 19,513,606 doses. On the converse, 2014, 2001 and 2017 exhibited the highest number of vaccinations, with 125,357,642, 123,428,150 and 118,590,603 immunizations, respectively. This peak in 2017 was followed by a decrease in the next two years, resulting in 102,469.969 vaccinations in 2019 (a reduction of 13.6%). The smooth line in vaccination data depicts a fluctuation of the immunization coverage in the last 8 years in Figure 1A. Although there was a decrease in absolute number of vaccination shots, the PNI had increased the variety of vaccines offered during the same timeframe: it offered 11 vaccines in 1994 and increased to 36 vaccines in 2019 (Supplementary File 1). A closer, look at the profiles of each specific vaccine offered in 2019 revealed that 44.44% (n=16) of those had 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 substantially different, with $p<0.001$ evaluated by the chi-square test (Figure 1B).

We next profiled the vaccination coverage among the different country regions (Figure 2A). We detected a reduction in the absolute numbers of vaccination shots occurring in all regions in the last three years, mirroring the overall reduction observed in the whole country (Figure 1), except the South region which presented an increase in the number of vaccination in the last three years (Figure 2A). Although the reduction in the absolute number, the linear regression analysis revealed just a slight decline in the North, Northeast and Midwest regions in the last three years (Figure 2B). The region presenting with 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 4.05% and 4,68% reduction respectively in the number of vaccinations). The variety of vaccines offered in all regions increased in 2019, tested by chi-square test ($p<0.001$; Figure 2C).

After describing the overall changes in vaccination coverage observed in Brazil during the studied period, we investigated the of coverage of each specific vaccine in 2019. Using the Venn diagram approach, we observed that 7 vaccines were identified as displaying a reduction in the number of shots in all Brazilian regions in 2019 when compared with 2018 (Figure 3A). Interestingly, all of the 7 vaccines identified were doses 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 OPV (Oral Poliovirus) in the South; Tdap (acellular triple vaccine - Pertussis, Tetanus, and Diphtheria), Hib (*Haemophilus influenzae* type b) and PCV13 (Pneumococcal 13-valent conjugate) in the Southeast; and Measles-Rubella and MMRV (Measles, Mumps, Rubella, and Varicella) vaccines in the Northeast. On the other hand, only 2 vaccines, meningococcal ACYW, and varicella vaccines had an increase in immunization doses in 2019 for all regions (Fig 3B). Only in the South region, yellow fever and Td (diphtheria and tetanus for adults) vaccines have shown an increase in immunization doses.

To investigate the evidence of reduction in the number of vaccinations in Brazil, a time-series analysis was performed using data from 2004 to 2019. The number of applied vaccines 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 by a decomposing technique (described in Methods), using the forecast modelling. In the analysis of the whole country, a seasonal pattern was observed starting in 2004; such 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 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 prediction for the next 5 years were reproduced in all regions (Supplementary Figure 1).

Discussion

Due to the current rapid information flow, misleading false "scientific information facts" spread out by anti-vaccination groups throughout the globe have impacted vaccination coverage. This phenomenon had 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 such as Venezuela, Colombia, and Brazil (Dias Leite and Naaman Berezin 2015). These outbreaks have brought attention to the public health systems of such countries about the importance of improvements in their vaccination surveillance and control strategies (Silveira et al. 2020). According to our results, in 2019 seven vaccines showed a reduction in doses applied in Brazil when compared with the previous year, all of these being used for the immunization of children. Our study findings from Brazil are in direct agreement with the idea that there has been a recent decrease in vaccination coverage in other countries.

This observation is of extreme concern, because of this age group's increased susceptibility to new infections due to less mature immune system. Furthermore, successfully controlled VPDs would be ready to return, potentially causing new epidemics, raising challenges for new physicians without experience with these diseases (Greenlee and Newton 2018). Since 2016, the vaccination coverage has been dropping in children under 10 years about 10% to 20% in Brazil (Hussain et al. 2018). This reduction was associated with reduction in funding dedicated to the SUS, aside from the increasing people's distrust in vaccines and vaccination hesitancy (Sato 2018). However, in the present study, we observed a peak of overall immunization in 2017, due to yellow fever vaccine shots especially in the southeastern 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 two 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 mortality incidence of pneumonia and influenza (Choi and Thacker 1981), infectious diseases (Allard 1998) and to investigate the pattern changes during a mass vaccination 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 socioeconomic.

The socioeconomic inequities may have played an important role in this reduction reported here. A study evaluating four birth cohorts between 1982 - 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 have shown that vaccination coverage in the 1980s was higher in wealthy families and such socioeconomic 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. This misleading assumption could make them feel able to criticize medical science regarding vaccines, tending them to believe in alternative non-scientific facts found in the internet (Dias Leite and Naaman Berezin 2015). Vaccination hesitancy is not the only factor responsible for lower vaccination coverage. Political conflicts, socioeconomic collapse, and difficulties to bring 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 has highlighted the psychological element as an important factor in delaying vaccination schedules due to parents' anxiety, pitying their children from getting vaccine shots (Silveira et al. 2020). Such aspects combined with anti-vaccination groups activism in social media and distrust in medical science expose the complexity of contending the reduction of vaccination coverage (Smith 2017; Silveira et al. 2020). Therefore, a multifaceted strategy is necessary to avert recurrence of VPDs and to eradicate once again such diseases. Although our findings led us to speculate that there is a relation between anti-vaccination movement and immunization coverage in Brazil, additional prospective investigations systematically collecting primary data on both anti-vaccination movement and vaccination hesitancy are still warranted to directly test hypotheses.

People tend to avoid vaccination when they perceive it as unnecessary due to the lack of illness threat perceptions. They pay more attention to vaccine minor side effects such as mild fever, muscle, and joint aches, headache and pain where the shot was given (Nour 2019). This behavior is reinforced by anti-vaccination propaganda, spread in social media, which highlights those side effects together with unproven "facts" (e.g. MMR vaccine associated with autism (Kolff et al. 2018)) over the individual and community benefits of vaccines. Therefore, to counteract this bad propaganda against vaccines, the physicians, scientific community and health agencies should be more active in the internet and social media remembering how dangerous these VPDs are and guiding people to maintain better health behaviors (Smith 2017). A social-ecological model can suggest where vaccination campaigns should go to promote increased coverage taking into account strategies in individual, interpersonal, organizational, community and society levels (Kolff et al. 2018). Not only social media should be aimed at, but 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, leading them to critically evaluate the veracity of the information they get from social media (Hopf et al. 2019).

Conclusion

The findings from the present study corroborate with the idea that there is a tendency of lower vaccination coverage in the last years in Brazil, especially in 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 by the analyses presented here are an alert to Brazilian authorities and strategies must be developed to improve the vaccine coverage and reduce the vaccine hesitancy, primarily in the pediatric vaccines.

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

Potential conflicts of interest: The authors declare that they have no conflicts of interest.

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.

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 assesses at http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/cpniuf.def.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure Legends

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 CI 95%. (B) Relative abundance of each vaccine shot given in Brazil by year. Colors represent different vaccines tested by the Pearson's chi-square test. The "*" in label represents a statistically significant difference (p<0.05).

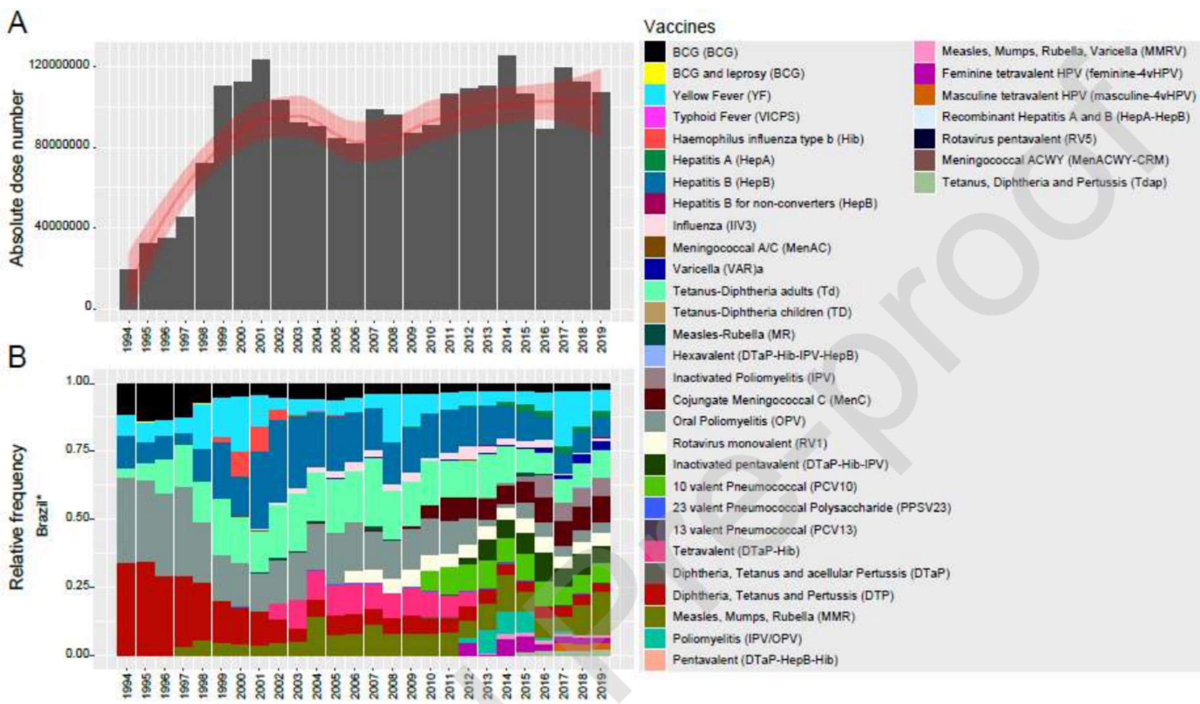

Figure 2. Number of vaccine doses given in each Brazilian socio-economic region by year. (A) Line chart of each region's absolute vaccination numbers by year. (B) Line chart with smooth line (with CI95%) in each region of absolute vaccination number by year. (C) Relative abundance of each vaccine shot given in each Brazilian socio-economic region by year. Colors represent different vaccines tested using the Pearson's chi-square test. The "*" in the label represents a statistically significant difference (p<0.05).

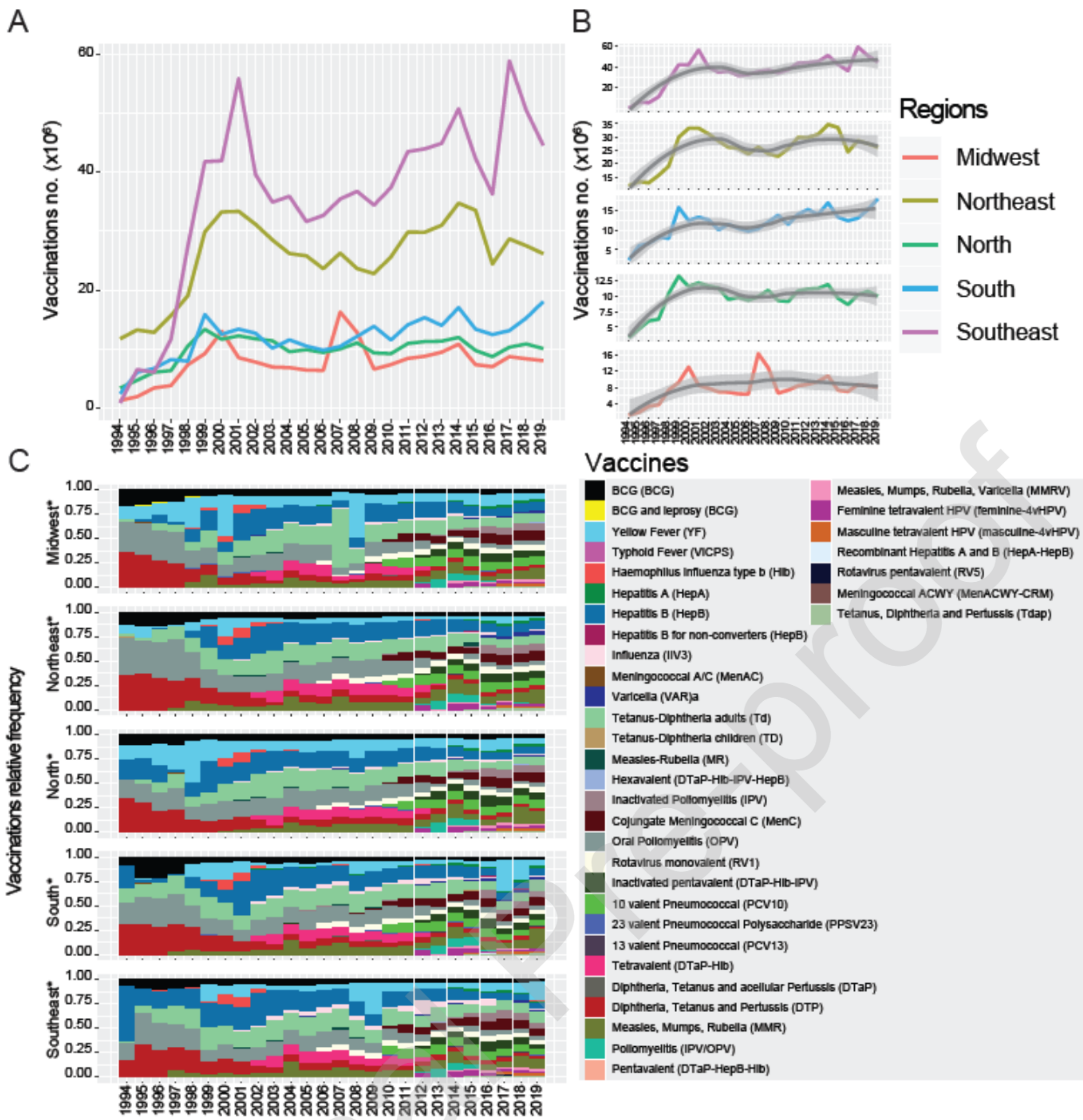

Figure 3. Dynamics of vaccination profiles in Brazil. Venn diagram of vaccines that decreased (A) or increased (B) in the number of shots given in 2019 compared to 2018 stratified by the different Brazilian regions.

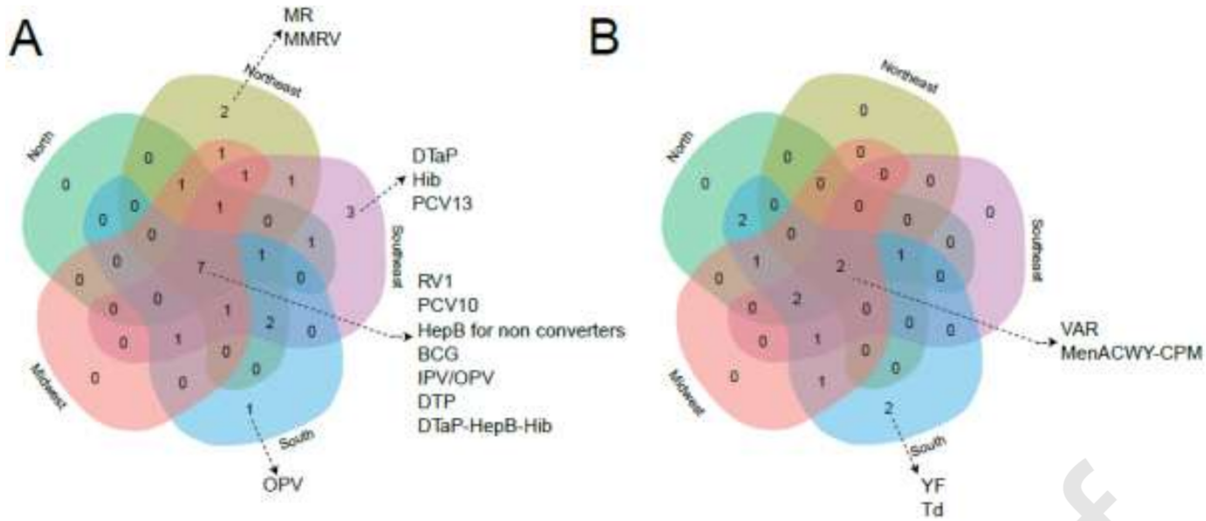

Figure 4. Time-series pattern analysis of vaccination coverage in Brazil. (A) Boxplot chart of applied vaccines in Brazil across the months between 2004 to 2019. (B) Decomposition of time-series in random, trends and seasonal patterns of applied vaccinations in Brazil between 2005 to 2019. (C) Lag plot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