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Original Article

Severe Varicella in Children Under Five Years of Age in the Context of Herd Immunity, Vaccine Hesitancy, and the COVID-19 Pandemic in Brazil, 2008-2023

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Abstract

Objective: Varicella (chickenpox) is a highly contagious disease, and its vaccine was incorporated into the Brazilian National Immunization Program in 2013. Objectives: (i) To analyze trends in hospitalization rates for severe chickenpox by age; (ii) To assess the impact of the interventions "anti-vaccine movement/vaccine hesitancy" and "COVID-19 pandemic" on hospitalization rates.

Materials and methods: Classical Time Series (CTS) and Interrupted Time Series (ITS) methods were applied to estimate the impact of the anti-vaccine movement/vaccine hesitancy (intervention-1) that occurred in 2016 and the COVID-19 pandemic (intervention-2) that began in 2020 on hospitalization rates among children under 5 years old, stratified by groups based on vaccine-ineligible (< 1 year old) and vaccine-eligible (1-4 years old) children.

Results: CTS results supported the potential for herd immunity effects, showing an annual decline of -17% and -14% in hospitalization rates for vaccine-eligible (1-4 years) and vaccine-ineligible (< 1 year) groups, respectively. The ITS model for vaccine-ineligible children showed an upward trend (coefficient 0.35) after intervention-1(isolate) (p=0.001), as well as after intervention-1 (coefficient 0.42; p 0.011) adjusting for intervention-2 (p=0.135). For vaccine-eligible children, the ITS model revealed an upward trend (coefficient 0.14) only after intervention-1 (isolate) (p=0.006).

Conclusion: The decline in varicella hospitalizations indicates a herd immunity effect among vaccine-ineligible children. ITS analysis reveals that the anti-vaccine movement/vaccine hesitancy contributed to increased hospitalizations in both vaccine-eligible (1-4 years) and vaccine-ineligible (<1 year) groups, while the COVID-19 pandemic had no discernible impact.

Keywords: Varicella; Vaccination; Notification; Hospitalization; COVID-19; Vaccination Hesitancy; Interrupted Time Series Analysis

Introduction

Chickenpox, also known as varicella-zoster, is a highly contagious disease caused by the *Varicella-zoster virus* (VZV), commonly affecting children. The disease spreads easily through droplets, aerosols, or direct contact with respiratory secretions due to its high person-to-person transmissibility, which can

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occur even before the appearance of skin lesions (1).

The main preventive mechanism is the attenuated chickenpox vaccine, developed from the modified Oka VZV strain, remaining safe, well tolerated, and effective against herpesvirus infections (2). In 2013, this vaccine was officially incorporated into the Brazilian National Immunization Program (PNI), with administration recommended for children aged 13 months and older. A new recommendation issued in 2018 mandated a second dose (3).

Since the vaccine is not recommended for use during the infant's first year of life, infants rely for protection solely on passive immunity from maternal antibodies, which largely disappear between 6 and 12 months after birth (4). Although chickenpox is considered a self-limiting disease with a benign course mainly in children under 15 years of age, newborns face a higher risk of developing severe chickenpox, with a fatality rate reaching up to 30% (5).

A Danish study based on data from 2015 to 2023 indicates that moderate to severe infections are more prevalent in children less than one year of age, with this age group remaining an important independent risk factor for hospitalization even after adjusting for other variables (6). Regarding the COVID-19 pandemic, while chickenpox cases nearly disappeared from early 2020 to late 2021, the country again experienced outbreaks with resurgence of moderate to severe cases in 2022 and 2023 (6).

Regarding the vaccination coverage recommended by the Brazilian Ministry of Health, target values (≥95%) were achieved in 2015 but experienced repeated fluctuations in subsequent years, likely due to the resurgence of the anti-vaccine movement in the country in 2016 (7). A literature search retrieved 137 publicly accessible publications posted on websites promoting arguments in line with the anti-vaccine movement (7).

The introduction of the chickenpox vaccine into the Brazilian immunization program coincided temporally with the resurgence of behaviors associated with the anti-vaccine movement observed within the country (7) and worldwide (8), as well as the onset of the COVID-19 pandemic, with these events potentially influencing the occurrence of vaccine-preventable diseases. This presents an adverse and potentially dangerous scenario for the occurrence of highly transmissible diseases such as chickenpox, particularly considering populations of children who are not eligible for vaccination.

Given that the reporting of chickenpox in Brazil is mandatory only for severe cases requiring hospitalization or resulting in death or outbreaks, this study, based on hospitalized cases, aims to assess the magnitude and temporal patterns of severe chickenpox among children <5 years old. Therefore, this study aims to (i) analyze trends in hospitalization rates for severe chickenpox stratified by age (children < 1 year and 1-4 years) and (ii) assess the impact of interventions related to Brazil's "anti-vaccine movement/vaccine hesitancy" and the "COVID-19 pandemic" on hospitalization rate patterns.

Materials and methods

Study design: This study is an ecological, quasi-experimental design that used secondary, aggregated data to estimate Classical Time Series (CTS) and Interrupted Time Series (ITS) models for assessing the impact of population interventions on the temporal trends of public health indicators (9). The data used in the study were coordinated and provided by the Department of Informatics of the Unified Health System (DATASUS) under the Brazilian Ministry of Health. These data were accessed online at: https://datasus.saude.gov.br/ (10). The study adheres to recommendations for research development in Brazil and received approval from the Research Ethics Committee of the institution where the research was conducted, with register CAAE 84135624.4.0000.5243.

Study context: Brazil is a geographically vast country, with most of its territory located in the tropics. The country is geographically divided into five macro-regions, each exhibiting a wide range of socioeconomic and cultural diversity. Over a 16-year period (2008 to 2023), Brazil's population aged 0 to 4 years decreased by approximately 12%, from 15,329,999 in 2008 to 13,421,242 in 2023. In the control of infectious and vaccine-preventable diseases, Brazil operates the National Immunization Program (PNI), established in 1973. Beyond vaccines developed to control COVID-19, the PNI offers 15 different childhood vaccines, 9 adolescent vaccines, and vaccines for adults and the elderly (3).

Variables of interest and data sources: Variables of interest included: year (2008 to 2023), age group (under 1 year and 1 to 4 years), and the absolute number of hospitalizations due to chickenpox (ICD-10: B01) recorded in hospital units from Unified Health System (SUS), nationwide.

The number of hospitalization cases was obtained through the Hospital Admission System of the Unified Health System (SIH-SUS), which serves as

an administrative platform for storing hospital admission data of SUS users and covers 80% of the Brazilian population (10). Hospitalization cases were selected based on ICD-10 (B01) coding and stratified by age group (under 1 year and 1 to 4 years), while also accounting for the study period (2008 to 2023).

Child population data were obtained from population projection figures by the Brazilian Institute of Geography and Statistics (IBGE) and were disaggregated by age group into (i) under 1 year and (ii) 1 to 4 years (11).

Data analysis

Indicator calculation (hospitalization rates): The annual hospitalization rates from 2008 to 2023 were calculated and disaggregated by age group (<1 year and 1-4 years), considering the number of hospitalizations (numerator) and population size (denominator), with results expressed per 10,000 person-years.

Analysis of hospitalization rate trends using Classical Time Series (CTS): CTS analysis was performed using generalized linear regression to verify the trend estimates of the adjusted hospitalized rates in Brazil. After logarithmic transformation of the observed coefficients, the autoregressive model proposed by Prais-Winsten (suitable for dealing with serial autocorrelation issues) (12) was employed to reduce the heterogeneity of residuals (9). The annual percentage changes (APC) and their respective 95% confidence intervals (95% CI) were calculated using the following equations, with β representing the value of the angular coefficient provided by the generalized linear regression.

Equation 1 for calculating APC: $([-1+10^{\beta 1}]*100)$

Equation 2 for calculating the 95% confidence interval (95% CI) of APC:

Lower limit of 95% CI: $([-1+10^{\beta 1 min}]*100)$

Upper limit of 95% CI: $([-1+10^{\beta 1 max}]*100)$

Results are interpreted based on trends: increasing, decreasing, or stationary.

Assessing the impact of multiple interventions on hospitalization rates using Interrupted Time Series Analysis (ITS): ITS analysis was employed to examine the effects of multiple interventions (anti-vaccine movement/vaccine hesitancy and the COVID-19 pandemic). To this end, segmented linear regression using the ordinary least squares statistical technique was applied, adjusting the linear models with autoregressive terms and accounting for *n* lags (13). The study period was segmented into distinct time points determined by the interventions as follows:

a) Pre-intervention period (2008 to 2015): From the initial year of the series (2008) to the year when vaccination coverage peaked at 95% (2015).

b) Period marking the beginning of intervention-1, namely the "anti-vaccine movement/vaccine hesitancy," which reemerged in 2016. From 2016 onward, Brazil experienced a decline in vaccination coverage (3). This situation supports the interpretation of a potential resurgence of anti-vaccine movement and vaccine hesitancy, with the latter referring to a 'delay in accepting vaccination or refusal to be vaccinated' (14).

c) Period marking the beginning of intervention-2, namely the 'COVID-19 pandemic', spanning from 2020 to 2023. In Brazil, the first COVID-19 case was reported in the city of São Paulo on February 26, 2020. The disease subsequently spread rapidly nationwide, prompting the government's decision to impose various restrictions on access to and use of healthcare services, which were reserved exclusively for COVID-19 patients (15).

Parameter estimation: First, as mentioned above, the observed parameters were calculated for each year within the period (2008 to 2023). Next, models were specified to obtain β0 (intercept: baseline rate value), β1 (slope coefficient specifying the progressive change trends in rates during the period before intervention-1), β2 (coefficient representing the abrupt change in rates occurring immediately after intervention-1), β3 (slope coefficient specifying the progressive change trends in rates during the period after intervention-1), β4 (coefficient representing the abrupt change in rates occurring immediately after intervention-2), and β5 (slope coefficient specifying the progressive change trends in rates during the period after intervention-2).

The observed, estimated, and predicted (counterfactual) parameter values were plotted to facilitate visualization of the isolated effects of the 'anti-vaccine movement/vaccine hesitancy' intervention on hospitalization rates for children under 1 year old and those aged 1 to 4 years, as well as to demonstrate the effects of the 'anti-vaccine movement/vaccine hesitancy + COVID-19 pandemic' interventions on the same age groups.

The specification of serial autocorrelation terms was conducted based on the Durbin-Watson statistics method, with a significance level set at 5% (16), combined with visual inspection of the autocorrelation function (ACF) and partial autocorrelation function (PACF) graphs. Statistical analysis was performed

using the 'car' and 'nlme' packages within R statistical program version 4.3.2 (17).

Results

In Brazil, from 2008 to 2023, the number of severe chickenpox cases requiring hospitalization among children under five years of age reached 36,326, with nearly 36% occurring in children under one year of age (n=12,742).

Herd immunity: Comparing the initial year (2008) to the final year (2023), hospital admission rates fell by 88% and 84% among children eligible (aged 1 to 4 years) and ineligible (under 1 year) for vaccination, respectively. However, the magnitude of this decline also indicates that hospitalization rates for severe chickenpox remained consistently higher among children < 1 year old than among those aged 1 to 4 years. The annual comparison highlights that the smallest difference between groups occurred in 2012, with the incidence rate among younger children (3.29 per 10,000pt) being 1.54 times that of older children (2.13 per 10,000pt). Conversely, the largest recorded difference was in 2020, with the incidence rate among younger children (0.56 per 10,000pt) being 3.91 times that of older children (0.14 per 10,000pt) (Table 1).

Classical Time Series Analysis: The Prais-Winsten modeling framework supports the potential effect of herd immunity, with results indicating a consistent decline in varicella hospitalization rates regardless of vaccination eligibility. However, the Annual Percent Change reveals a more pronounced decrease in hospital admissions among children aged 1 to 4 years (-17%) compared to those under 1 year (-14%) (Table 2).

Estimated Parameters and the effects of the anti-vaccine movement/vaccine hesitancy and the COVID-19 pandemic

a) Children < 1 year: Considering the onset of the anti-vaccine movement in 2016, the implementation of ITS captured an abrupt change: the level of hospitalization rate dropped immediately after intervention-1, though not statistically significant (p 0.841), followed by a change in trends with progressively increasing coefficients (p <0.001). When adjusting for the ITS incorporating multiple interventions (anti-vaccine movement + COVID-19 pandemic), the drop in hospitalization rate was observed immediately after intervention-1 (anti-vaccine movement; not statistically significant: 0.488) and immediately after intervention-2 (COVID-19 pandemic; p 0.045). ITS also detected a change in the trend of hospitalization rates, showing a statistically significant gradual upward trend after the first intervention (p 0.011) but not after the second intervention (p 0.135) (Table 3).

Table 1: Hospitalizations due to severe varicella in population of the under-five-years old children, Brazil, 2008-2023

Year	Hospitalizations per agea group		Hospitalization ratesbper age group	
	< 1	1 a 4	< 1	1 a 4
2008	2031	3023	6.80	2.45
2009	1477	2520	4.97	2.07
2010	1641	3789	5.62	3.16
2011	1119	2537	3.83	2.15
2012	967	2490	3.29	2.13
2013	1273	2900	4.36	2.49
2014	814	1796	2.76	1.55
2015	610	973	2.02	0.83
2016	587	813	1.99	0.69
2017	574	716	1.99	0.61
2018	426	555	1.46	0.47
2019	460	495	1.59	0.42
2020	155	165	0.56	0.14
2021	138	227	0.51	0.20
2022	216	267	0.83	0.24
2023	254	318	1.01	0.29

b) Children aged 1 to 4 years: In the 1-4 age group, ITS captured statistically significant effects, indicating an immediate drop in hospitalization rates following the start of the anti-vaccine/vaccine hesitation movement (p 0.001), followed by a progressive upward trend in the indicator trend (p 0.006).

Table 2: Temporal trends of hospitalization rates due to severe varicella in population of the under-five-years old children, Brazil, 2008-2023

Year	Hospitalization Rates[a]		Temporal Trends		
	Initial Year	Final Year	APC[b] (%)	95% CI[c] (%)	Interpretation
Age Group	2008	2023			
< 1-year old	6.80	1.01	-14.44	-17.59; -11.17	Reduction
1 to 4 years old	2.45	0.29	-17.13	-22.08; -11.86	Reduction

[a]Hospitalization Rates. [b]Annual Percent Change. [c]Confidence Interval

Table 3: Effect of the anti-vaccine movement and COVID-19 pandemic on the hospitalizations due to severe varicella in under-one-year old child population, Brazil, 2008-2023

Parameter	Model with intervention-1[a]			Model with intervention-1[a] and intervention-2[b]		
	Beta	95% CI[c]	P Value[d]	Beta	95% CI	P Value
Intercept (β_0)	6.70	6.06; 7.33	<0.001	6.60	6.24; 6.96	<0.001
Time (β_1)	-0.55	-0.68; -0.43	<0.001	-0.53	-0.60; -0.46	<0.001
Change in level after intervention 1 (β_2)	-0.08	-0.93; 0.75	0.841	-0.31	-1.16; 0.53	0.488
Change in trends after Intervention 1 (β_3)	0.35	0.17; 0.52	0.001	0.42	0.15; 0.70	0.011
Change in level after Intervention 2 (β_4)	NA[e]	NA	NA	-1.28	-2.39; -0.17	0.045
Change in trends after Intervention 2 (β_5)	NA	NA	NA	0.28	-0.05; 0.62	0.135

[a]Anti-vaccine movement occurred in 2016. [b]COVID-19 pandemic started in 2020. [c]Confidence Intervals. [d]Statistical significance of 5%. [e]Not applicable.

ITS analysis of multiple interventions confirmed an abrupt drop in hospitalization rates following the start of the anti-vaccine/vaccine hesitation movement (p 0.012). The COVID-19 pandemic also led to a decline in hospitalization rates, though the difference was not statistically significant (p = 0.281). Simultaneously adjusting for both interventions revealed gradual upward trends (coefficient 0.01) in hospitalization rates, but the difference was not statistically significant (p = 0.920) (Table 4).

The summary of the ITS findings can be understood by examining the behavior of the observed (filled circles), estimated (solid line), and predicted/counterfactual (dashed line) hospitalization rates displayed in pictorial form (Figure 1). Among younger children, the direction of the predicted rates suggests that severe cases of chickenpox would have virtually disappeared without the reemergence of the anti-vaccine/vaccine hesitation movement (Figure 1-A), although the simultaneous adjustment for both interventions altered this trend (Figure 1-B). Regarding the older child population, both the isolated effect of the anti-vaccine/vaccine hesitation movement (Figure 1-C) and the effect after adjusting for both interventions (Figure 1-D) appear to indicate that these interventions had no impact on severe chickenpox hospitalizations.

Discussion

This study focused on the hospitalization rates for severe chickenpox recorded in the Brazilian Unified Health System (SUS) from 2008 to 2023, conducting a stratified analysis by subgroups of eligible (1 to 4 years old) and ineligible (under 1 year old) children for vaccination. This context enables the assessment of the potential effects arising from herd immunity, vaccine hesitancy, and the COVID-19 pandemic.

In Brazil, hospitalization rates declined by over 88% among children aged 1–4 years and by 84% among under-1-year-olds, highlighting the substantial impact of the vaccination program. A similar phenomenon occurred in Canada between 1990 and 2010, period where the ineligible population (under 1 year) was the second-largest beneficiary subgroup experiencing hospitalization reductions (18). Although interpreted cautiously due to limited vaccination coverage data, the temporal correlation between Canada's vaccine availability and declining hospitalizations suggests substantially reduced viral circulation; likely resulting from herd immunity, which conferred protective effects on the unvaccinated group (18).

Table 4: Effect of the anti-vaccine movement and covid-19 pandemic on the hospitalizations due to severe varicella in 1-4 years old child population, Brazil, 2008-2023

Parameter	Model with intervention-1[a]			Model with intervention-1[a] and intervention-2[b]		
	Beta	95% CI[c]	P Value[d]	Beta	95% CI	P Value
Intercept (β_0)	3.06	2.72; 3.40	<0.001	3.05	2.73; 3.38	<0.001
Time (β_1)	-0.19	-0.26; -0.12	<0.001	-0.19	-0.25; -0.12	<0.001
Change in level after intervention 1 (β_2)	-0.94	-1.40; -0.48	0.001	-1.24	-2.05; -0.43	0.012
Change in trend after Intervention 1 (β_3)	0.14	0.05; 0.23	0.006	0.26	0.00; 0.52	0.071
Change in level after Intervention 2 (β_4)	NA[e]	NA	NA	-0.61	-1.68; 0.44	0.281
Change in trend after Intervention 2 (β_5)	NA	NA	NA	0.01	-0.30; 0.33	0.920

[a]Anti-vaccine movement occurred in 2016. [b]COVID-19 pandemic started in 2020. [c]Confidence Intervals. [d]Statistical significance of 5%. [e]Not applicable.

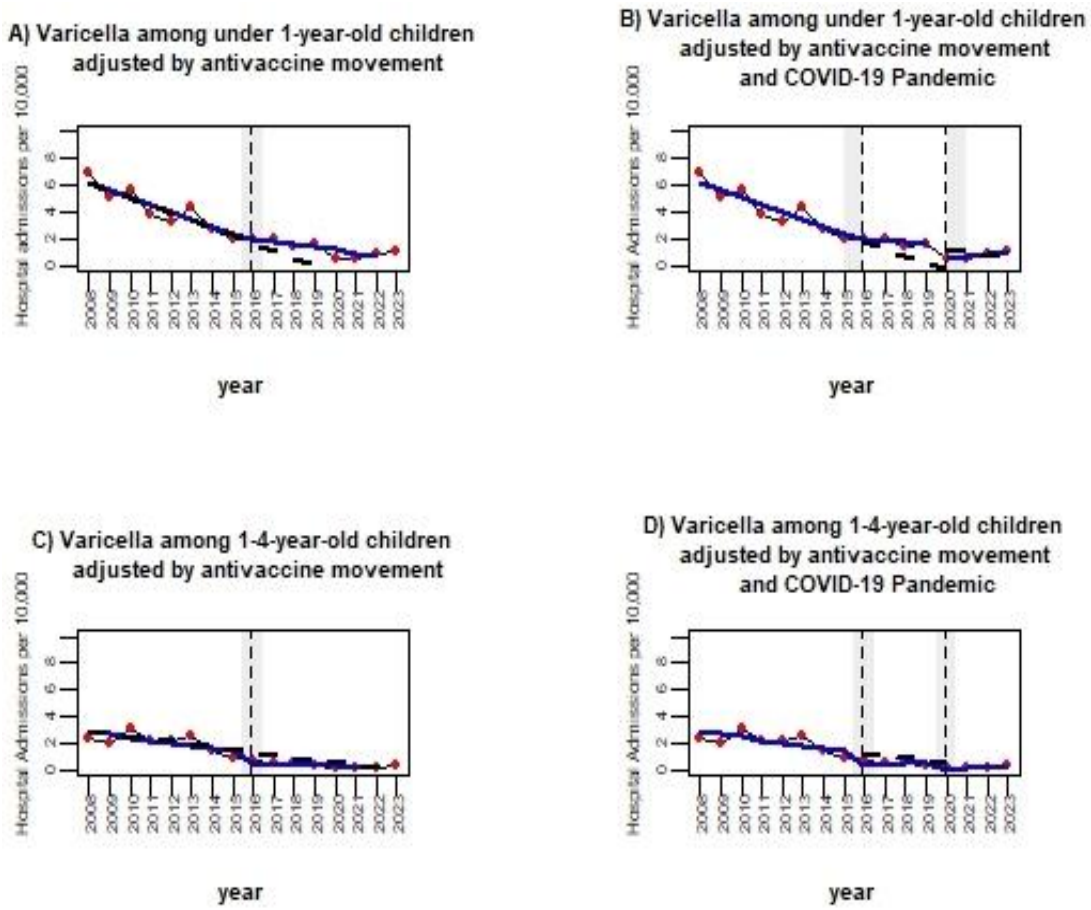

Figure 1: Observed (filled red circles), estimated (solid blue line), and predicted/counterfactual (dashed black line) hospitalization rates due to severe varicella in children, Brazil, from 2008 to 2023: A) Hospitalization rates in under-1-year-old children adjusted by antivaccine movement. B) Hospitalization rates in under-1-year-old children adjusted by antivaccine movement and COVID-19 pandemic. C) Hospitalization rates in 1-4-year-old children adjusted by antivaccine movement. D) Hospitalization rates in 1-4-year-old children adjusted by antivaccine movement and COVID-19 pandemic.

Herd immunity is a phenomenon determined by disease characteristics, population factors, environmental conditions, and vaccination program quality, including the availability of high-quality immunobiological products and vaccination coverage (19). In South Korea, the authors used the basic reproductive number (Ro) to calculate herd immunity thresholds and define critical vaccination coverage limits by integrating empirical data on vaccine seroprevalence (19). In that country, Ro for chickenpox was estimated at 5.67 (95% CI: 5.33; 6.33). Under the circumstances of a well-functioning vaccination program combined with perfect quality immunobiological products, the herd immunity threshold was established at 82.4% (95% CI: 81.2%, 84.2%), suggesting that this phenomenon can be achieved if vaccination coverage also reaches 82.4% (19).

Despite the downward trend in severe chickenpox cases, the findings of the present study indicated that hospitalization rates for children under 1 year of age consistently exceed those for children aged 1 to 4 years. Similar findings were derived from a comparison of the 2010-2012 and 2014-2016 triennia (20). The authors pointed out that the force of chickenpox hospitalizations among children under 1 year old (3.96 and 2.26 per 10,000) was higher than that among children aged 1-4 years (1.96 and 1.03 per 10,000), corroborating that younger children were more vulnerable to severe chickenpox infection due to their immature immune systems (20) and ineligibility for vaccination.

Under multiple population interventions, ITS also revealed a less favorable pattern among infants, indicating that the anti-vaccine/vaccine hesitation movement leads to an upward trend in hospitalization rates, independent of the COVID-19 pandemic. Counterfactual projections suggested that hospitalizations for severe cases among children under one year old could have declined to negligible levels prior to the COVID-19 pandemic.

Maintaining herd immunity induced by vaccination requires rigorous vaccination coverage (21). While safety remains the primary reason for vaccine hesitancy in developed countries, social, cultural, and religious factors also influence vaccination willingness in low- and middle-income countries, in addition to safety concerns (21). In the case of the COVID-19 vaccine, willingness to be vaccinated depended on a positive assessment of the vaccine's risks and benefits, with hesitancy being influenced by attitudes and beliefs (21).

Since 2018, the Brazilian National Immunization Program has included a two-dose vaccine schedule in its routine varicella vaccination program (5). The two-dose schedule has proven highly effective in preventing outbreaks and mitigating clinical manifestations in suspected cases (22), with an estimated effectiveness rate of up to 98.3% during the first 2.5 years following the introduction of the immunobiological agent into the vaccination program (22). Current results indicate that even amid the impact of the COVID-19 pandemic, the anti-vaccine/vaccine hesitation movement has redirected the trend of severe chickenpox.

Although herd immunity does not imply elimination (23), the reality of Brazil's severe chickenpox reflects the significant impact of the vaccination program. On the other hand, attitudes of denialism such as vaccine hesitancy/the anti-vaccine movement have influenced the magnitude and direction of hospitalizations. Considering the importance of herd immunity in protecting unvaccinated groups, Brazil urgently needs to increase investments to eliminate vaccine hesitancy behaviors.

Limitations: This study has some limitations. First, the data are secondary data obtained from administrative databases and were not collected for research purposes. Second, case statistics are based on the ICD-10 classification of diseases recorded in the DATASUS database, where chickenpox is grouped under the chickenpox/herpes zoster code (10). Additionally, insufficient time points limited the robustness of ITS analysis for COVID-19; however, this study meets methodological criteria for assessing the anti-vaccine movement/vaccine hesitancy effects initiated in 2016. Future studies covering a sufficient time period are needed to clarify the impact of the COVID-19 pandemic on hospitalizations among children diagnosed with chickenpox.

Conclusion

This study on severe chickenpox reveals an important role for herd immunity, with significant and sustained reductions in hospital admissions observed among both ineligible children (under 1 year old) for vaccination and eligible children (1 to 4 years old). Despite the benefits of herd immunity, indicators for ineligible children consistently remained worse than those for eligible children. Under multiple interventions, ITS analysis further revealed an unfavorable trend among children and provided evidence that the anti-vaccine/vaccine hesitancy movement redirected hospitalization trends upward, while the COVID-19 pandemic had no discernible impact. Protecting children who are ineligible for vaccination due to age presents a major public health challenge in real-world settings, requiring measures that address the multifactorial nature of the problem, including behaviors associated with vaccine hesitancy.

Conflict of Interests

Authors declare no conflict of interests.

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This study follows the Helsinki Declaration of 1975 and was developed in accordance to the Brazilian Ethical Recommendations for research involving human beings.

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