Indirect Impact of COVID-19 Vaccination on Weekly Trends in Morbidity and Mortality Indicators in Brazil, 2020 to 2021

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Research Article

Keywords: Time series analysis, Brazil, Vaccine coverage, COVID-19, Hospitalizations, Pandemic, Trends, Vaccination

Posted Date: December 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1146790/v1>

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Abstract

Background: With the outbreak of the COVID-19 pandemic, safe and efficacious vaccines were quickly developed and made available to reduce its morbidity and mortality. This study aimed to describe the trends and evaluate the association of COVID-19 vaccination with indicators of morbidity and mortality due to the disease in Brazil.

Methods: This was an ecological study whose unit of analysis was the time elapsed between February 16th, 2020, from the introduction of COVID-19 in Brazil and July 17th, 2021, six months after the start of vaccination in the country. From secondary databases, indicators of morbidity and mortality (incidence of hospitalization, proportion of severe cases, lethality and mortality) and vaccine coverage (doses 1, 2 or single dose) per epidemiological week (EW) and age groups were calculated (18 to 59 years and 60 years or older). Indicators of morbimortality were compared in the pre-vaccination (EW 8/2020 to EW 2/2021) and vaccination (EW 3/2021 to EW 28/2021) periods, analyzing the trends estimated using the JointPoint model and their associations using the Poisson model.

Results: For individuals aged 60 years and over, during the period of COVID-19 vaccination there was a weekly trend towards a reduction in the incidence of hospitalizations (PMSV: -4.7%), severity (PMSV: -0.3%, lethality (PMSV: -2.0%) and mortality (PMSV: -2.8%); the increase in COVID-19 vaccination coverage was inversely associated with the incidence of hospitalizations (IRR: 0.969), lethality (IRR: 0.993), and mortality (IRR: 0.981). For individuals aged 18 to 59 years of age, during the period of COVID-19 vaccination there was a weekly trend towards a reduction in the incidence of hospitalizations (PMSV: -2.6%) and lethality (PMSV: -2.0%), while there was an increase in mortality (PMSV: 3.8%); the increase in COVID-19 vaccination coverage was inversely associated with the incidence of hospitalizations (IRR: 0.975) and lethality (IRR: 0.939). Conversely, it was directly associated with mortality (IRR: 1.054).

Conclusions: it was demonstrated that COVID-19 vaccination had an indirect impact in reducing the morbidity and mortality trend from the disease in Brazil, especially in the elderly population, in which vaccination was prioritized and achieved greater coverage, when compared to individuals aged 18 to 59 years.

Background

Since 2020, the world has experienced the most significant public health emergency in recent decades, the pandemic caused by the new coronavirus, the SARS-CoV-2 virus, the agent responsible for the 2019 coronavirus disease (COVID-19). COVID-19 is an infectious disease transmitted mainly from person to person through exposure to respiratory droplets expelled by an infected person when talking, sneezing or coughing. Most individuals who contract the disease will have mild to moderate flu-like symptoms, however, some individuals will manifest a severe clinical condition, such as difficulty breathing, and these patients will need hospitalization, intensive care and invasive ventilatory support, and may even progress to death. Elderly individuals and patients with comorbidities, such as systemic arterial hypertension, diabetes mellitus, among others, are at greater risk for severity and death from COVID-19.(1)

According to the World Health Organization (WHO), globally, more than 209.2 million cases of COVID-19 had been confirmed, including more than 4.3 million reported deaths, as of August 19th, 2021. The Region of the Americas accounted for more than a third (36%) of cases and nearly half (47%) of confirmed deaths from COVID-19 worldwide. In this context, Brazil ranked third in number of cases and second in number of deaths from COVID-19 when compared to other reporting countries.(2)

Since the beginning of the pandemic, several efforts have been made to accelerate the development, production, and equitable access to COVID-19 vaccines, to reduce morbidity and mortality and help control the disease.(3) In December 2020, the first vaccines were approved for emergency use after rigorous safety and efficacy studies. As of August 18th, 2021, globally, more than 4.5 billion doses of vaccines had been administered.(2)

Initially, considering the limited amount of doses of vaccines and supplies worldwide, WHO published a guide with recommendations from the *Strategic Advisory Group of Experts on Immunization* (SAGE) to prioritize groups for the use of COVID-19 vaccines, including, first, health care workers and elderly individuals.(4)

In Brazil, COVID-19 vaccination started on January 18th, 2021, prioritizing health workers, elderly individuals living in long-term care facilities, individuals aged 18 years and over with institutionalized disabilities, and the indigenous population; other groups were included in the national plan to operationalize the COVID-19 vaccination, as the availability and acquisition of vaccines gradually increased.(5)

Preliminarily, according to the COVID-19 National Vaccination Plan, four vaccines developed on three different platforms were introduced in Brazil: i) non-replicating viral vector (AstraZeneca/Oxford University and Janssen Pharmaceutical), ii) inactivated virus (Sinopharm), and iii) messenger RNA-based (Pfizer/BioNTech) platforms.(5) The efficacy of these vaccines to prevent SARS-CoV-2 infection ranged from 54% to 95%, and to prevent moderate to critical COVID-19 cases ranged from 67% to 76%.(5–9)

The success of COVID-19 vaccination was observed in several countries that quickly managed to vaccinate a large portion of their population, such as Israel, the United States of America (USA), the United Kingdom, Chile, among others, which were successful in decreasing the number of reported cases and deaths. (10) However, with the emergence of new SARS-CoV-2 variants that invariably had greater virulence or transmission capacity, and could even escape the immunity already acquired (via vaccine or natural infection), which are called variants of concern (VOCs), a new increase in the number of confirmed cases of the disease was observed in these countries. The VOCs detected up to July 2021 are known as Alpha (formerly B.1.1.7, identified in the UK), Beta (formerly B.1.351, identified in South Africa), Gamma (formerly P.1, identified in Brazil), and Delta (formerly B.1.617.2, identified in India) variants.(11,12)

Considering the possible impact of the above factors on morbidity and mortality from COVID-19 in Brazil, after six months of vaccination against the disease in the country, from February 17th to July 17th, 2021, the objective of this study was to describe the time trend of epidemiological indicators related to morbidity and mortality from COVID-19 and to analyze their association with COVID-19 vaccine coverage, in individuals aged 18 to 59 years and in those aged 60 years and over.

Methods

Type of study

This was a time series study(13) whose unit of analysis was time, elapsed in epidemiological weeks (EW), in the period from February 16th, 2020 (EW 8/2020) to July 17th, 2021 (EW 28/2021). The choice of this period considered the introduction of the SARS-CoV-2 virus in Brazil in 2020 and the first six-month period after the start of COVID-19 vaccination, counted from January 18th, 2021 (EW 3/2021).

Selection criteria

Hospitalized COVID-19 cases, confirmed by laboratory criteria, reported to the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), and who had the onset of symptoms or progression to death between February 16, 2020 and July 17, 2021, were selected and divided into the following age groups: i) 18 to 59 years of age, and ii) 60 years or older.

Variable and data sources

The following variable and data sources were consulted and analyzed:

- SIVEP-Gripe: official system for recording hospitalized cases and deaths from Severe Acute Respiratory Syndrome (SRAG) in Brazil, whose database is available without case identification (anonymized data) in the link: <https://opendatasus.saude.gov.br/organization/ministerio-da-saude>. The databases used in the study (SRAG-2020 and SRAG-2021) were obtained on August 8th, 2021. Data such as date of symptom onset, age (18 to 59 years / 60 years or more), admission to the Intensive Care Unit (ICU), use of invasive ventilatory support, final classification (COVID-19), termination criteria (laboratory), progression (death), and date of progression were used for analysis.
- National COVID-19 Vaccination Campaign: COVID-19 vaccination records in Brazil were made available by the National Health Data Network (RNDS) which integrates different databases such as the Information System of the National Program for Immunizations (SI-PNI), e-SUS APS (Primary Health Care), and state and municipal systems. The database was obtained for analysis on August 8, 2021, using the link: <https://localizadas.saude.gov.br/>. Data such as date of vaccination, age (18 to 59 years / 60 years or older) and dose (D1, D2 or single dose) were used for analysis.
- Population estimate: population by age (18 to 59 years / 60 years or more) calculated by the Ministry of Health of Brazil based on census data from the Brazilian Institute of Geography and Statistics (IBGE) for the year 2020.

Indicators

- Incidence of hospitalizations from COVID-19 per 1,000,000 population: the numerator used was the number of cases hospitalized per EW of symptom onset and the denominator used was the number of individuals residing in the country according to the age group.

- Proportion of severity: the numerator used was the number of cases admitted to the ICU and/or who received invasive ventilatory support and the denominator applied was the number of hospitalized cases, disaggregated by age group and EW of symptom onset.
- Lethality: the numerator used was the number of deaths and the denominator used was the number of hospitalized cases, separated by age group and EW of symptom onset.
- Mortality from COVID-19 per 1,000,000 population: the numerator used was the number of deaths per EW of the date of progression and the denominator used was the number of individuals residing in the country according to the age group.
- Vaccination coverage: the numerator used was the number of individuals per age group with a complete vaccination schedule (2 doses or single dose) for any COVID-19 vaccine established in the National COVID-19 Vaccination Plan and the denominator used was the number of individuals residing in the country by the age group, calculated by EW of the vaccination date.

Data analysis

The following analyzes were performed:

1. Temporal trends were estimated for all indicators using the JointPoint model. To identify the EW (independent variable) in which there were statistically significant changes in the trend of epidemiological indicators and vaccine coverage (dependent variables), up to five inflection points in each time series were used. The weekly percentage of variation (PSV) was calculated for each segment in which there was an inflection in the time series and the average weekly percentage of variation (PMSV), for the pre-vaccination (EW 8/2020 to EW 2/2021) and vaccination (EW 3/2021 to 28/2021) periods, including their respective 95% confidence intervals (95% CI). The significance test used to select the best model was the traditional *Bayesian Information Criteria* (BIC3) method, considering a statistical significance level < 0.05 .
2. Association of epidemiological indicators with vaccination coverage: analyzed by simple Poisson models, whose dependent variables were the epidemiological indicators (incidence of hospitalizations, severity, lethality and mortality from COVID-19), analyzed separately, and the explanatory variable in all cases was the vaccination coverage with a complete vaccination schedule (D2 or single dose). Incidence-rate ratios (IRR) and their respective 95% CI were calculated, considering a significance level < 0.05 . Model fit was assessed using the pseudo R^2 statistical method, which measures the reduction in deviation due to the explanatory variable.

The statistical programs used were *JointPoint Trend Analysis* 4.9 and STATA v. 13. The databases obtained for analysis are publicly accessible and do not have personal identification variables, so the study was not submitted for appraisal by an ethics committee for research with human beings, according to the Resolution of the National Health Council number 510/ 2016 which provides rules applicable to methodological procedures involving the use of secondary data in Brazil.

Results

There were 2,083,217 cases of SARS reported during the study period, of which 1,371,187 (65.8%) were confirmed for COVID-19. Of these, 1,215,314 (88.6%) cases were confirmed by laboratory criteria, of which 621,703 (51.2%) were between 18 and 59 years of age and 573,812 (47.2%) were aged 60 years or older. There were 263,408 deaths from COVID-19 in individuals aged 60 years and over, and for 692 (0.3%) there was no record of the date of death. There were also 120,271 deaths from COVID-19 in individuals between 18 and 59 years of age, and for 376 (0.3%) there was no record of the date of death.

Six months after the introduction of COVID-19 vaccination, first and second doses vaccination coverage reached, respectively, 47.7% and 35.0% in individuals aged 60 years and over, and 45.9% and 9.2% in individuals between 18 and 59 years of age.

Considering that individuals aged 60 years and over, for the most part, were prioritized to vaccination in Brazil, the results for this age group will be shown before the findings for individuals aged 18 to 59 years, which will be shown in sequence.

Progression of COVID-19 and vaccination in individuals aged 60 years and over

Figure 1 shows the distribution of observed and estimated weekly trends of epidemiological indicators of morbidity and mortality from COVID-19 and first and second doses vaccination coverage, in individuals aged 60 years and over. Table 1 shows the PSV that was calculated for each change in the time trend of indicators of morbidity and mortality and vaccine coverage, whereas Table 2 shows the PMSV of these indicators for the COVID-19 pre-vaccination and vaccination periods. Finally, Table 3 shows the result of the association between indicators of morbidity and mortality and COVID-19 vaccination coverage with a complete scheme (2nd dose or single dose).

The data show that the progression of vaccination coverage in individuals aged 60 years and over had three inflection points, and four trend segments for the first dose have been estimated: 1st from EW 3/2021 to EW 6/2021 with weekly increase (PSV: 112.2%), 2nd from EW 6/2021 to EW 13/2021 with new weekly increase (PSV: 37.8%), 3rd from EW 13/2021 to EW 18/2021 with the lowest weekly increase (PSV: 11.3%) and 4th from EW 18/2021 to EW 28/2021 with the greatest reduction in the weekly increase (PSV: 0.3%). As for the vaccination coverage of the second or single doses, there were also three inflection points, and four trend segments were estimated: 1st from EW 3/2021 to EW 5/2021 with weekly increase (PSV: 1st from EW 3/2021 to EW 5/2021 with weekly increase (PSV: 72.0%), 2nd from EW 5/2021 to EW 8/2021 with the highest weekly increase (PSV: 234.0%), 3rd from EW 8/2021 to EW 17/2021 with the lowest weekly increase (PSV: 42.4%) and 4th from EW 17/2021 to EW 28/2021 with the greatest decrease in the weekly increase (PSV: 4.0%). In the first six months of COVID-19 vaccination, there was a weekly increase trend in vaccination coverage, in individuals aged 60 years and over, for both the first dose (PMSV: 22.5%) and for second or single dose (PMSV: 39.5%).

The incidence of hospitalizations from COVID-19 in this population showed four inflection points, and five time trend segments have been estimated: 1st from EW 8/2020 to EW 12/2020 with intense weekly increase (PSV: 230.6%), 2nd from EW 12/2020 to EW 19/2020 with the lowest weekly increase (PSV: 35.4%), 3rd from EW 19/2020 to EW 42/2020 with weekly reduction (PSV: -3.7%), 4th from EW 42/2020 to EW 11/2021

with new weekly increase (PSV: 6.1%), and 5th from EW 11/2021 to EW 28/2021 with a new weekly reduction (PSV: -9.4%). Hospitalizations increased in the pre-vaccination period (PMSV: 15.6%) and declined in the vaccination period (PMSV: -4.7%). COVID-19 vaccination coverage was inversely associated with the weekly incidence of hospitalizations for the disease in individuals aged 60 years and over (IRR: 0.97).

On the other hand, the proportion of individuals aged 60 years or over who manifested a more severe clinical condition showed three inflection points with four time trend segments: 1st from EW 8/2020 to 10/2020 with weekly increase (PSV: 19.8%), 2nd from EW 10/2020 to EW 17/2020 with weekly reduction (PSV: -7.0%), 3rd from EW 17/2020 to EW 34/2020 with new weekly increase (PSV: 1.0%), and 4th from EW 34/2020 to EW 28/2021 with a new weekly reduction (PSV: -0.3%). Severity showed a decrease trend both in the pre-vaccination period (PMSV: -0.1%) and in the vaccination period (PMSV: -0.3%). Furthermore, COVID-19 vaccination coverage was not statistically associated with the proportion of severity in individuals aged 60 years and over (p-value: 0.762).

On the other hand, lethality in individuals hospitalized for COVID-19 in this population had five inflection points and six time trend segments: 1st from EW 8/2020 to EW 12/2020 with weekly reduction (PSV: -4.0%), 2nd from EW 12/2020 to EW 15/2020 with weekly increase (PSV: 8.5%), 3rd from EW 15/2020 to EW 43/2020 with new weekly reduction (PSV: -1.5%), 4th from EW 43/2020 to EW 10/2021 with new weekly increase (PSV: 1.5%), 5th from EW 10/2021 to EW 25/2021 with another weekly reduction (PSV: -1.2%), and 6th from EW 25/2021 to 28/2021 with the greatest weekly reduction (PSV: -13.4%). Lethality showed a slight decrease trend in the pre-vaccination period (PMSV: -0.3%) and to a greater decline in the vaccination period (PMSV: -2.0%). COVID-19 vaccination coverage was inversely associated with lethality in individuals hospitalized for COVID-19 who were 60 years of age or older (IRR: 0.99).

Mortality from COVID-19 in individuals aged 60 years and over also showed five inflection points and six time trend segments: 1st from EW 12/2020 to EW 14/2020 with intense weekly increase (PSV: 255.4%), 2nd from EW 14/2020 to EW 19/2020 with the lowest weekly increase (PSV: 48.6%), 3rd from EW 19/2020 to EW 32/2020 with weekly reduction (PSV: -0.4%), 4th from EW 32/2020 to EW 44/2020 with the greatest weekly reduction (PSV: -7.3%), 5th from EW 44/2020 to EW 13/2021 with new weekly increase (PSV: 7.8%), and 6th from EW 13/2021 to 28/2021 with a new weekly reduction (PSV: -9.2%). There was a mortality increase trend in the pre-vaccination period (PMSV: 10.7%) and declined in the vaccination period (PMSV: -2.8%). COVID-19 vaccination coverage was inversely associated with the weekly incidence of hospitalizations for COVID-19 in individuals aged 60 years and over (IRR: 0.98).

Table 1 – Weekly percentage of variation by trend segment according to hospitalizations, severity, lethality and mortality from COVID-19 in individuals aged 60 years and over, Brazil, epidemiological week 8/2020-28/2021

Indicators	Segments	Epidemiological Week / Year		Duration of segment (weeks)	PSV*	PSV 95% CI		P-Value
		Start	End			Min.	Max.	
Hospitalizations	1	8/2020	12/2020	4	230.6	179.1	291.6	<0.001
	2	12/2020	19/2020	7	35.4	23.6	48.2	<0.001
	3	19/2020	42/2020	23	-3.7	-4.9	-2.5	<0.001
	4	42/2020	11/2021	22	6.1	4.6	7.5	<0.001
	5	11/2021	28/2021	17	-9.4	-11.1	-7.7	<0.001
Severity	1	8/2020	10/2020	2	19.8	8.6	32.2	0.001
	2	10/2020	17/2020	7	-7	-8.5	-5.4	<0.001
	3	17/2020	34/2020	17	1	0.6	1.4	<0.001
	4	34/2020	28/2021	47	-0.3	-0.4	-0.2	<0.001
Lethality	1	8/2020	12/2020	4	-4.0	-7.5	-0.4	0.030
	2	12/2020	15/2020	3	8.5	-3.4	21.8	0.166
	3	15/2020	43/2020	28	-1.5	-1.7	-1.3	<0.001
	4	43/2020	10/2021	20	1.5	1.1	1.8	<0.001
	5	10/2021	25/2021	15	-1.2	-1.8	-0.7	<0.001
	6	25/2021	28/2021	3	-13.4	-18.3	-8.2	<0.001
Mortality	1	12/2020	14/2020	2	255.4	141.8	422.2	<0.001
	2	14/2020	19/2020	5	48.6	31.6	67.9	<0.001
	3	19/2020	32/2020	13	-0.4	-2.7	1.9	0.707
	4	32/2020	44/2020	12	-7.3	-9.7	-4.9	<0.001
	5	44/2020	13/2021	22	7.8	6.7	8.8	<0.001
	6	13/2021	28/2021	15	-9.2	-10.7	-7.7	<0.001
Vaccination coverage - Dose 1	1	3/2021	6/2021	3	112.1	99.8	125.1	<0.001
	2	6/2021	13/2021	7	37.8	35	40.6	<0.001
	3	13/2021	18/2021	5	11.3	7.2	15.6	<0.001
	4	18/2021	28/2021	10	0.3	-0.6	1.3	0.472
Vaccination coverage - Dose 2 or single dose	1	3/2021	5/2021	2	72.0	37.4	115.5	<0.001
	2	5/2021	8/2021	3	234.0	166.7	318.3	<0.001

3	8/2021	17/2021	9	42.4	38.9	45.9	<0.001
4	17/2021	28/2021	11	4.0	2.5	5.6	<0.001

*Weekly Percentage of Variation

Table 2 – Average weekly percentage of variation for the COVID-19 pre-vaccination and vaccination periods according to indicators of hospitalizations, severity, lethality and mortality from the disease in individuals aged 60 years and over, Brazil, epidemiological week 8/2020-28/2021

Indicators	Pre-vaccination period*			Vaccination period**		
	PMSV	PMSV** CI 95%		PMSV	PMSV 95% CI	
		Min.	Max.		Min.	Max.
Hospitalizations	15.6	13.2	18.0	-4.7	-6.0	-3.5
Severity	-0.1	-0.6	0.4	-0.3	-0.4	-0.2
Lethality	-0.3	-1.1	0.5	-2.0	-2.8	-1.3
Mortality	10.7	8.0	13.5	-2.8	-3.8	-1.8
Vaccination coverage – dose 1	-	-	-	22.5	21.1	23.9
Vaccination coverage – dose 2 or single dose	-	-	-	39.5	35.1	43.9

*EW 8/2020 to EW 2/2021; **EW 3/2021 to EW 28/2021

**Average weekly percentage of variation

Table 3 – Association of COVID-19 vaccination coverage (2nd or single dose) and indicators of hospitalizations, severity, lethality and mortality from the disease in individuals aged 60 years and over, Brazil, epidemiological week 3/2021-28/ 2021

Dependent variables	IRR	IRR IC 95%		P-value	Pseudo R2 (%)
		Min.	Max.		
Hospitalizations per 1 million population	0.969	0.967	0.971	<0.001	54.3
Severity (%)	0.999	0.994	1.004	0.762	0.1
Lethality (%)	0.993	0.988	0.997	0.001	6.3
Mortality per 1 million population	0.981	0.978	0.983	<0.001	23.6

Progression of COVID-19 and vaccination in individuals aged 18 to 59 years

Figure 2 shows the distribution of observed and estimated weekly trends of epidemiological indicators of morbidity and mortality and vaccination coverage, for the first and second doses, for COVID-19 in individuals aged 18 to 59 years. Table 4 shows the PSV that was calculated for each change in the time trend of indicators of morbidity and mortality and vaccine coverage, whereas Table 5 shows the PMSV of these indicators for the COVID-19 pre-vaccination and vaccination periods. Finally, Table 6 shows the result of the association between indicators of morbidity and mortality and COVID-19 vaccination coverage with a complete scheme (dose 2 or single) in this population group.

The data show that the progression of vaccination coverage in individuals aged 18 to 59 years showed four inflection points and five trend segments for the first dose: 1st from EW 3/2021 to EW 5/2021 with weekly increase (PSV: 66.4%), 2nd from EW 5/2021 to EW 12/2021 with the lowest weekly increase (PSV: 4.8%), 3rd from EW 12/2021 to EW 17/2021 again with weekly increase (PSV: 8.2%), 4th from EW 17/2021 to EW 25/2021 with the highest weekly increase (PSV: 23.5%) and 5th from EW 25/2021 to EW 28/2021 with a reduction in the weekly increase (PSV: 10.2%). As for the second dose or single dose, the vaccination coverage trend had an inflection point and two trend segments: 1st from EW 3/2021 to EW 7/2021 with intense weekly increase (PSV: 241.1%) and 2nd from EW 7/2021 to EW 28/2021 with the lowest weekly increase (PSV: 8.6%). In the first six months of COVID-19 vaccination, there was a weekly increase trend in vaccine coverage, in individuals aged 18 to 59 years, for both the first dose (PMSV: 16.1%) and the second or single dose (PMSV: 30.5%).

The incidence of hospitalizations from COVID-19 in this population showed four inflection points and five time trend segments: 1st from EW 8/2020 to EW 12/2020 with intense weekly increase (PSV: 238.5%), 2nd from EW 12/2020 to EW 18/2020 with the lowest weekly increase (PSV: 37.6%), 3rd from EW 18/2020 to EW 41/2020 with weekly reduction (PSV: -4.5%), 4th from EW 41/2020 to EW 21/2021 with new weekly increase (PSV: 5.7%), and 5th from EW 21/2021 to EW 28/2021 with a new weekly reduction (PSV: -21.1%). Hospitalizations showed a trend towards an increase in the pre-vaccination period (PMSV: 14.9%) and declined in the vaccination period (PMSV: -2.6%). COVID-19 vaccination coverage was inversely associated with the weekly incidence of hospitalizations for the disease in individuals aged 18 to 59 years (IRR: 0.97).

The proportion of severity in individuals aged 18 to 59 years showed three inflection points and four time trend segments: 1st from EW 8/2020 to 10/2020 with weekly increase (PSV: 29.9%), 2nd from EW 10/2020 to EW 16/2020 with weekly reduction (PSV: -7.5%), 3rd from EW 16/2021 to EW 17/2020 with new weekly increase (PSV: 0.5%), and 4th from EW 17/2021 to EW 28/2021 with a new weekly reduction (PSV: -1.2%). Severity in this population showed a trend towards an increase in the pre-vaccination period (PMSV: 0.5%) and declined in the vaccination period (PMSV: -0.3%). COVID-19 vaccination coverage was not statistically associated with the proportion of individuals aged 18 to 59 years who manifested a more severe clinical condition (p-value: 0.498).

On the other hand, lethality in individuals hospitalized from COVID-19 who were between 18 and 59 years old had five inflection points and six time trend segments: 1st from EW 8/2020 to EW 10/2020 with weekly decrease (PSV: -28.0%), 2nd from EW 10/2020 to EW 15/2020 with weekly increase (PSV: 11.3%), 3rd from

EW 15/2020 to EW 44/2020 with new weekly reduction (PSV: -1.7%), 4th from EW 44/2020 to EW 12/2021 with new weekly increase (PSV: 3.6%), 5th from EW 12/2021 to EW 24/2021 again with weekly reduction (PSV: -2.4%), and 6th) from EW 24/2021 to 28/2021 with the greatest weekly reduction (PSV: -19.4%). Lethality in this population showed a decrease trend in the pre-vaccination period (PMSV: -0.5%) and towards a greater reduction in the vaccination period (PMSV: -3.3%). COVID-19 vaccination coverage was inversely associated with lethality in individuals hospitalized for the disease who were between 18 and 59 years of age (IRR: 0.94).

Finally, mortality from COVID-19 in this population showed five inflection points and six time trend segments: 1st from EW 11/2020 to 13/2020 with intense weekly increase (PSV: 707.6%), 2nd from EW 13/2020 to EW 18/2020 with the lowest weekly increase (PSV: 82.0%), 3rd from EW 18/2020 to EW 45/2020 with weekly reduction (PSV: -4.6%), 4th from EW 45/2020 to EW 7/2021 with new weekly increase (PSV: 6.8%), 5th from EW 7/2021 to EW 12/2021 with the highest weekly increase (PSV: 28.3%), and 6th from EW 12/2021 to 28/2021 with a new weekly reduction (PSV: -3.5%). Mortality showed a weekly trend towards an increase both in the pre-vaccination period (PMSV: 16.1% and in the vaccination period (PMSV: 3.8%). COVID-19 vaccination coverage was directly associated with mortality from COVID-19 in individuals aged 18 to 59 years (IRR: 1.05).

Table 4 – Weekly percentage of variation by trend segment according to hospitalizations, severity, lethality and mortality from COVID-19 in individuals aged 18 to 59 years, Brazil, epidemiological week 8/2020-28/2021

Indicators	Segments	Epidemiological Week / Year		Duration of segment (weeks)	PSV*	PSV* 95% CI		P-Value
		Start	End			Min.	Max.	
Hospitalizations	1	8/2020	12/2020	4	238.5	180.1	309.1	<0.001
	2	12/2020	18/2020	6	37.6	20.4	57.3	<0.001
	3	18/2020	41/2020	23	-4.5	-5.8	-3.1	<0.001
	4	41/2020	21/2021	33	5.7	4.8	6.5	<0.001
	5	21/2021	28/2021	7	-21.1	-27.2	-14.5	<0.001
Severity	1	8/2020	10/2020	2	29.9	15.5	46.2	<0.001
	2	10/2020	16/2020	6	-7.5	-9.9	-5.0	<0.001
	3	16/2020	17/2021	54	0.5	0.4	0.6	<0.001
	4	17/2021	28/2021	11	-1.2	-2.0	-0.4	0.003
Lethality	1	8/2020	10/2020	2	-28.0	-39.0	-14.9	<0.001
	2	10/2020	15/2020	5	11.3	5.6	17.3	<0.001
	3	15/2020	44/2020	29	-1.7	-2.0	-1.4	<0.001
	4	44/2020	12/2021	21	3.6	3.1	4.1	<0.001
	5	12/2021	24/2021	12	-2.4	-3.5	-1.3	<0.001
	6	24/2021	28/2021	4	-19.5	-23.6	-15.1	<0.001
Mortality	1	11/2020	13/2020	2	707.6	410.7	1177.0	<0.001
	2	13/2020	18/2020	5	82	57.4	110.3	<0.001
	3	18/2020	45/2020	27	-4.6	-5.4	-3.8	<0.001
	4	45/2020	7/2021	15	6.8	4.5	9.1	<0.001
	5	7/2021	12/2021	5	28.3	11.0	48.3	0.001
	6	12/2021	28/2021	16	-3.5	-5.2	-1.8	<0.001
Vaccination coverage - Dose 1	1	3/2021	5/2021	2	66.4	58.7	74.6	<0.001
	2	5/2021	12/2021	7	4.8	4.0	5.7	<0.001
	3	12/2021	17/2021	5	8.2	6.5	9.8	<0.001
	4	17/2021	25/2021	8	23.5	22.7	24.3	<0.001
	5	25/2021	28/2021	3	10.2	7.6	12.9	<0.001
Vaccination coverage - Dose	1	3/2021	7/2021	4	241.1	178.0	318.6	<0.001

2 or single dose	2	7/2021	28/2021	21	8.6	6.9	10.4	<0.001
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*Weekly Percentage of Variation

Table 5 - Average weekly percentage of variation for the COVID-19 pre-vaccination and vaccination periods according to indicators of hospitalizations, severity, lethality and mortality from the disease in individuals aged 18 to 59 years, Brazil, epidemiological week 8 /2020-28/2021

Indicators	Pre-vaccination period*			Vaccination period**		
	PMSV ¹	PMSV 95% CI		PMSV	PMSV 95% CI	
		Min.	Max.		Min.	Max.
Hospitalizations	14.9	12.1	17.7	-2.6	-4.8	-0.4
Severity	0.5	-0.1	1.1	-0.3	-0.6	0.1
Lethality	-0.5	-1.4	0.4	-3.3	-4.2	-2.3
Mortality	16.1	13.0	19.3	3.8	0.7	7.1
Vaccination coverage - dose 1	-	-	-	16.1	15.4	16.7
Vaccination coverage - Dose 2 or single dose	-	-	-	30.5	26.2	34.9

Notes: *EW 8/2020 to EW 2/2021; **EW 3/2021 to EW 28/2021

¹Average weekly percentage of variation

Table 6 - Association of COVID-19 vaccination coverage (2nd or single dose) and indicators of hospitalizations, severity, lethality and mortality from the disease in individuals aged 18 to 59 years, Brazil, epidemiological week 3/2021-28/ 2021

Dependent variables	IRR*	IRR 95% CI		P-value	Pseudo R2 (%)
		Min.	Max.		
Hospitalizations per 1 million population	0.975	0.958	0.991	0.003	1.5
Severity (%)	0.990	0.960	1.020	0.498	0.3
Lethality (%)	0.939	0.902	0.976	0.002	6.5
Mortality per 1 million population	1.054	1.019	1.090	0.002	3.9

*Incidence-rate ratios

Discussion

The present study described and analyzed the progression of COVID-19 vaccine coverage in relation to indicators of morbidity and mortality trends from the disease, both in individuals aged 18 to 59 years and in individuals aged 60 years and over, in the first six months of vaccination, in Brazil.

As far as is known, this was the first study published that analyzed the indicators of morbidity and mortality time trends from COVID-19, comparing the pre-vaccination and the vaccination periods, in Brazil. In this sense, this study adds up-to-date findings of interest not only to the national community, but also to the international community, as the control of the pandemic will depend on the efforts that each country has made/is making to face COVID-19, especially countries large and populous like Brazil, which have an intense migratory movement of individuals and strong international trade and economic relations.

The methods of this study have also been used to assess the indirect impact of vaccination on morbidity and mortality trends of other vaccine-preventable diseases, such as pneumococcal disease and chickenpox, both of which are infectious and transmitted mainly from person to person by respiratory route, as well as COVID-19.(14,15)

The main findings of this study show that there were important changes in indicators of morbidity and mortality trends from COVID-19 over time in both populations evaluated, especially after the start of vaccination against the disease, with the exception of the proportion of hospitalized severe cases that remained. practically stable in the period evaluated. It was also shown that the indirect impact of vaccination was more intense in reducing indicators of morbidity and mortality trends for individuals aged 60 years and over compared to those aged 18 to 59 years, and for the latter group, vaccination coverage was lower in the period evaluated, as COVID-19 vaccination for this group started in immunocompromised individuals and practically expanded in EW 20 to other population groups.

The interpretation of these results must take into account, at least, the limitation imposed by the use of administrative data, which may have underestimated the indicators analyzed, especially vaccine coverage, which depends on timely records of cases and vaccinated individuals in their respective information systems.

It must also be taken into account that the observed statistical association does not necessarily reflect a causal association between the increase in vaccination and the decrease in indicators of morbidity and mortality from COVID-19, as the reduction in cases and deaths that occurred during the vaccination period may have been an event that coincided with the end of an epidemic peak, such as that which occurred in 2020 when there were no COVID-19 vaccines yet. However, it is noteworthy that during vaccination in 2021, the reduction of cases and deaths from COVID-19 was more accelerated and intense than that which occurred in 2020, especially in the population aged 60 years and over, which was prioritized for vaccination and also achieved greater vaccine coverage compared to individuals aged 18 to 59 years. In addition, the reduction in hospitalizations in the older-age group had 54% of its occurrence explained solely by the increase in vaccination coverage (Table 3).

Another important consideration is the possible heterogeneity of vaccine coverage in subgroups within the population studied, which may have contributed to a reduction in morbidity and mortality, even with the apparent low vaccine coverage. For example, within the group of individuals aged 60 and over, there were individuals who were 80 years old or over, among others. According to P.C. Victoria et al (2021), four months after the start of COVID-19 vaccination, approximately 95% of Brazilians aged 80 years or older had already received at least the first dose of the vaccine.(16) It is important to remember that the risk of morbidity and mortality from COVID-19 is directly proportional to increasing age.(17) Therefore, by decreasing the number of susceptible individuals in the age group that also has the highest risk of morbidity and mortality from the disease, those authors observed a reduction in the percentage of deaths from this underlying cause in individuals aged 80 years or more, which went from 25% – 30% at the start of vaccination to 13% after four months of COVID-19 vaccination in Brazil.(16)

On the other hand, the severity trend in hospitalized cases was practically constant throughout the period evaluated, with a slight weekly reduction observed in the vaccination period, especially among individuals aged 60 years and over. Therefore, there was no statistically significant association between COVID-19 vaccination and the severity trend in both groups analyzed. The study population, consisting of patients hospitalized for COVID-19, may have influenced this result, as hospitalized individuals are more likely to progress to a severe clinical condition due to the disease.(18) In addition, there is a possible confounding factor that was not controlled in this study and may have influenced the result of this study; it is the presence of comorbidities, which in addition to increasing the risk for more severe clinical conditions of COVID-19, it was also adopted as an inclusion criterion for vaccination of priority groups, influencing vaccine coverage in different age groups, according to the National Plan of Vaccination.

However, despite the severity trend having been practically constant, the lethality trend in cases hospitalized for COVID-19 reduced considerably, during the period of vaccination, in both groups analyzed. It can be argued that, over time, with greater accumulated knowledge on the clinical management of cases, the reduction in lethality may have occurred due to an improvement in the quality of care, or even due to a reduction in the number of hospitalized patients, consequently alleviating the burden on health care services and workers, ensuring greater attention and intensive care to hospitalized patients, and therefore avoiding the worsening of cases and the consequent progression to death.(19) But as shown above, the proportion of severity in the cases was constant over time, therefore refuting these hypotheses and reinforcing the impact of vaccination in reducing mortality from COVID-19. Despite the increase in vaccination coverage, in both groups analyzed, did little to explain the decrease in lethality (6.3% for individuals aged 60 years and over, and 6.5% for individuals aged 18 to 59 years), each increase in vaccination coverage reduced by 0.7% and by 6.1%, respectively, the weekly lethality from COVID-19 in the two populations studied.

The increase in mortality associated with the increase in vaccination coverage for individuals aged 18 to 59 years, despite the statistically significant association, reflected much more the influence of outlier values that influenced the average and increased trend variability in the period analyzed, characterizing more a type I error, than a time association that weighs against vaccination. Furthermore, with the advance of vaccination in the elderly group and the reduction in morbidity and mortality from COVID-19 in this age group, the perception of risk has changed for younger individuals(20). With the easing of containment

measures, they also began to be more frequently exposed, resulting in a change in the morbidity and mortality profile of the disease, which began to affect this age group with greater intensity, as vaccine coverage among individuals aged 18 to 59 years was still incipient.

The COVID-19 vaccination trend showed a great difference between vaccination coverage for the first, second or single dose, in both groups evaluated. Initially, due to the worldwide unavailability of doses and the need to accelerate the national COVID-19 vaccination campaign, the application of the first dose to the largest possible number of individuals was prioritized for the most vulnerable groups, as the first dose was relatively effective, and the time until the application of the second dose could be long enough for the countries to receive more doses, and then complete the vaccine schedules with the second dose.

(21) However, the low vaccination coverage for the second dose in Brazil may also have occurred due to a false sense of security that was perceived by the population as a result of the decrease in morbidity and mortality that occurred during this period, therefore decreasing the adherence to vaccination to complete the vaccination schedule,(22) in addition to the possibility of underreporting of vaccine doses in the aforementioned information systems.

Vaccine hesitancy, which is the act of refusal or delay in vaccination, may lead to the accumulation of susceptible individuals, whether as unvaccinated individuals, incomplete vaccination schedules, or natural loss of acquired immunity, which allied to the maintenance of viral circulation, including VOCs of greater transmissibility, such as the Delta variant, may cause new epidemic waves that, with the increase in morbidity and mortality from COVID-19, could jeopardize the population's trust in vaccines and in vaccination as a whole.(23,24)

In the study conducted by Yi-Tui Chen (2021), the effect of COVID-19 vaccination was evaluated in eight countries that had reached, by May 2nd, 2021, at least 50% of their population vaccinated (Israel, United Arab Emirates, Chile, United Kingdom, United States of America [USA], Hungary, Qatar, and Serbia), in addition, he estimated the vaccination coverage needed to reach an inflexion point in the disease trend. In six of these countries (except the USA and the UK), a peak of cases was also observed after the start of vaccination and before obtaining mass immunity. When the reduction in disease cases began, vaccination coverage in these countries ranged from 1.46 to 50.91%, and the R² of the models ranged from 57.2% to 89.9%, i.e., the models also had a high explanatory power. For the USA and UK, Pearson coefficients were calculated, which showed a reduction in COVID-19 rates from the start of vaccination.(25)

However, in many of these countries, including Israel, the United Kingdom and the USA, there was an increase in COVID-19 cases even after reaching high vaccination coverage.(10,26,27) Several explanations have been put forward to explain this phenomenon, including the early relaxation of non-pharmacological measures (such as social distancing and the use of protective masks), the role of VOCs in greater transmissibility, the effectiveness of the vaccines used and the selection of priority groups for vaccination. (28)

Conclusions

COVID-19 vaccination in Brazil, in the first six months of the national campaign, had an impact on reducing morbidity and mortality from the disease in both adult and older-age age groups, even in the context of low vaccination coverage in a tropical country with a great diversity in terms of population, logistics, and recording information in the vaccination system.

In this regard, every effort must be made to increase vaccination coverage and establish a communication channel with the population, in a clear and direct way, to inform about the risks of not getting vaccinated or not completing the recommended vaccination schedule. Furthermore, it is important to design a strategy to mitigate vaccine hesitancy, including monitoring performance indicators, identifying partners who are working on this issue, and implementing strategies and activities based on successful experiences. The information systems must also be fed with reliable data that will reflect the vaccination scenario as close to reality as possible. Only with quality information will the impact of vaccination be ensured to accelerate, with greater security, the end of the public health emergency brought on by the COVID-19 outbreak.

Abbreviations

BIC3	Bayesian Information Traditional Criteria
COVID-19	Coronavirus 2019 disease
D1	First dose of COVID-19 vaccine
D2	Second dose of COVID-19 vaccine
E-SUS APS	Ministry of Health Health Information System for Primary Care (acronym in Portuguese)
IBGE	Brazilian Institute of Geography and Statistics (acronym in Portuguese)
95% CI	95% confidence interval
IRR	Incidence-rate ratios
USA	United States of America
WHO	World Health Organization
PMSV	Average weekly percentage of variation (acronym in Portuguese)
PSV	Weekly percentage of variation (acronym in Portuguese)
RNDS	National Health Data Network (acronym in Portuguese)
SAGE	Strategic Advisory Group of Experts on Immunization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
EW	Epidemiological week
SI-PNI	National Immunization Program Information System (acronym in Portuguese)
SIVEP-Gripe	Influenza Epidemiological Surveillance Information System (acronym in Portuguese)
SRAG	Severe Acute Respiratory Syndrome
ICU	Intensive care unit
VOCs	Variants of concern

Declarations

Ethical approval and consent to participate

Secondary publicly accessible data were used and therefore the need for ethical approval was waived.

Consent to publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. Furthermore, the original databases are publicly accessible and can be found in the links mentioned in the methods.

Conflict of interest

The authors declare that they have no conflicting interests.

Financing

No financing.

Authors' contributions

JP carried out the data collection, processing and analysis, bibliographical research, and drafting of the article. CMC, FF, LG contributed to the interpretation of the data. WNA contributed to the study conception and design. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Figures

Figure 1

Trends in the incidence of hospitalizations, severity, lethality and mortality from COVID-19 compared to vaccine coverage in individuals aged 60 years and over, Brazil, epidemiological week 8/2020-28/2021

Figure 2

Trends in the incidence of hospitalizations, severity, lethality and mortality from COVID-19 compared to vaccination coverage in individuals aged 18 to 59 years, Brazil, epidemiological week 8/2020-28/2021