The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study

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The Lancet Regional Health - Americas 2023;20: 100465

Published Online 13 March 2023
https://doi.org/10.1016/j.lana.2023.100465

Summary

Background Brazil started the COVID-19 mass vaccination in January 2021 with CoronaVac and ChAdOx1, followed by BNT162b2 and Ad26.COV2.S vaccines. By the end of 2021, more than 317 million vaccine doses were administered in the adult population. This study aimed at estimating the effectiveness of the primary series of COVID-19 vaccination and booster shots in protecting against severe cases and deaths in Brazil during the first year of vaccination.

Methods A cohort dataset of over 158 million vaccination and severe cases records linked from official national registries was analyzed via a mixed-effects Poisson model, adjusted for age, state of residence, time after immunization, and calendar time to estimate the absolute vaccine effectiveness of the primary series of vaccination and the relative effectiveness of the booster. The method permitted analysis of effectiveness against hospitalizations and deaths, including in the periods of variant dominance.

Findings Vaccine effectiveness against severe cases and deaths remained over 25% and 50%, respectively, after 19 weeks from primary vaccination of BNT162b2, ChAdOx1, or CoronaVac vaccines. The boosters conferred greater protection than the primary series of vaccination, with heterologous boosters providing marginally greater protection than homologous. The effectiveness against hospitalization during the Omicron dominance in the 60+ years old population started at 61.7% (95% CI, 26.1–86.2) for ChAdOx1, 95.6% (95% CI, 82.4–99.9) for CoronaVac, and 72.3% (95% CI, 51.4–87.4) for the BNT162b2 vaccine.

Interpretation This study provides real-world evidence of the effectiveness of COVID-19 vaccination in Brazil, including during the Omicron wave, demonstrating protection even after waning effectiveness. Comparisons of the effectiveness among different vaccines require caution due to potential bias effects related to age groups, periods in the pandemic, and eventual behavioural changes.

Funding Fundação Oswaldo Cruz (FIOCRUZ), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ), Pan American Health Organization (PAHO), Departamento de Ciência e Tecnologia da Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde do Ministério da Saúde do Brasil (DECIT/SCTIE/MS).

Keywords: COVID-19; COVID-19 vaccines; Effectiveness; Registry-based study; Brazil; Latin America; Pandemic

Abbreviations: VOC, Variant of Concern; VE, Vaccine Effectiveness; rVE, Relative Vaccine Effectiveness; MoH, Ministry of Health

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Research in context

Evidence before this study

We searched PubMed for research papers using the Medical Subject Headings term "COVID-19 vaccines", jointly with the search terms "protection" and "waning" not restricted by language. Results were complemented by a Google Scholar search using the same terms. We found that although knowledge of the duration of vaccine effectiveness is of key public health relevance, few studies have investigated the persistence of vaccine-dependent protection. No study was found addressing vaccine effectiveness in subgroups defined by age, vaccine brand, time since completion of the primary series and booster dose, region of residency, and the variant of concern.

Added value of this study

In this nationwide study with more than 150 million records, we observed that vaccination effectiveness varied as a function of age and vaccine. The vaccine protection progressively waned, with protection against severe disease remaining above 25% after 19 weeks and protection against death over 50% up to 20 weeks after completing the primary series of vaccination. The booster doses conferred greater protection than the primary series, with the heterologous booster providing marginally greater protection than the homologous booster. All primary series and booster vaccines conferred protection in the periods of dominance of the Omicron variant.

Implications of all the available evidence

Our findings suggest adequate levels of vaccine effectiveness for the primary series of all vaccines available in Brazil. Still, protection wanes progressively in all subgroups, with apparent influence by age and the vaccine. The booster doses continue to be an effective strategy for limiting the upsurge of severe cases and deaths, including in the VOC dominance scenarios.

Introduction

Since the start of the current severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) pandemic, more than 32 million confirmed cases and 670 thousand deaths due to coronavirus disease (COVID-19) had been reported in Brazil alone (as of July 01, 2022).[1] One key step to ending the pandemic is the deployment of vaccines with durable effectiveness. Brazil began vaccinating the population in mid-January 2021, prioritizing people at relatively high risk of severe disease (e.g., the elderly and people with chronic health conditions), vulnerable populations (e.g., homeless and indigenous people), health care workers, and further extending to the entire population by decreasing age. Vaccination started mostly with CoronaVac (Sinovac Biotech) and ChAdOx1 nCov-19 (AstraZeneca/Oxford University) vaccines. The BNT162b2 (Pfizer–BioNTech) and Ad26.Cov2.S (Johnson & Johnson–Janssen) vaccines were incorporated later in the campaign (May and June 2021, respectively).[2,3] However, the upsurge of Variants of Concern (VOCs) and an increase in reported breakthrough infections generated concerns about the vaccine's long-term protection.

Several observational studies have assessed the waning of the protective effect of COVID-19 vaccines over time.[4–11] However, these studies commonly estimated vaccine effectiveness (VE) for broadly defined periods or the analysis was restricted to specific vaccines and age groups/populations. Consequently, most of these studies were not adequately positioned to determine whether VE waning was due to declining protection from the primary series of vaccination or the emergence of a new VOC, or both.

Surveillance datasets in Brazil provide a substantial amount of data to assess VE in a real-world setting. Based on the surveillance data from COVID-19 severe cases and vaccination, with over 150 million records, we estimated the protection given by the four COVID-19 vaccines currently available and in use in Brazil against severe cases and deaths due to COVID-19 in the first year of mass vaccination.

Methods

Study design, population, and data source

This was a registry-based effectiveness study of a national health-record cohort with more than 158 million records, including over 2 million severe COVID-19 cases, where individual data were evaluated for tracking both the outcomes of interest (severe cases and deaths due to COVID-19) and their vaccination status over time. We used two datasets linked (please refer to Supplementary material 1 for details) by the Brazilian Ministry of Health (MoH): the National Immunization Program (NIP) records,[2] which comprise all individual-level data on vaccination, and the Severe Acute Respiratory Illness (SARI) dataset,[12,13] which contains all COVID-19 severe cases that lead to hospitalization and deaths. From the linked dataset, we extracted data on all individuals aged 20 years or older who had received at least one dose of CoronaVac, ChAdOx1 nCov-19, BNT162b2, or Ad26.COV2.S vaccines, or who had a severe COVID-19 illness. Along with the linked dataset, we used age-specific 2021 population estimates maintained by the MoH and the Brazilian Institute for Geography and Statistics (IBGE).[14]

The COVID-19 vaccination campaign started on January 17, 2021, which is the first epoch of the study. Vaccination events (primary series or booster doses) were observed from the start of the vaccination campaign until January 31, 2022 (Epidemiological week 05). Vaccination records indicate the date of the first, second, and booster doses and the vaccine received in each event.

Vaccination status definition

Individuals without any record of vaccination (first dose, second dose or booster) were considered unvaccinated. We considered as immunized those (i) with only the primary series of vaccination (i.e., two doses from the CoronaVac, ChAdOx1 nCov-19, and BNT162b2 vaccines or the single-dose Ad26.Cov2.S vaccine) and (ii) those with the primary series of vaccination plus a booster dose.

Outcomes of interest

The outcomes of interest were (i) COVID-19 severe cases, i.e., symptomatic COVID-19 cases leading to hospitalisation, regardless of death, and (ii) deaths due to COVID-19. The outcomes were registered in the dataset by the date of symptoms onset and the final case status (death, recovered or ignored). For each person in the cohort, an outcome of severe COVID-19 illness occurred whenever this person was notified as a severe COVID-19 case, using the date of symptoms onset as reference. Therefore, a record of severe COVID-19 illness after immunisation, either fully or booster-vaccinated, was classified as an immunised case. Individuals presenting the outcome prior to or without immunisation were classified as unvaccinated cases. The same classification applies to the death outcome, with individuals being classified depending on their vaccination status and symptoms onset. Records without a case registry in the national electronic record were assumed as not presenting the outcomes of interest.

Dominance of variant of concern (VOC) over time

Data on genomic samples were obtained from GISAID and filtered across Brazilian states.[15] We calculated the proportions of VOCs for each state and epidemiological week. A VOC with a frequency over 70% was considered the weekly dominating variant, allowing eventual transition periods without VOC dominance (i.e., epidemiological weeks without a VOC proportion over 70%) (Fig. S4 and Supplementary material 2).

Statistical modelling and analysis

Absolute vaccine effectiveness (VE) is the protection against the outcomes of interest of individuals vaccinated with the primary or booster-plus series, compared to the unvaccinated group. Relative vaccine effectiveness (rVE) is the protection against the outcomes of interest of booster-plus vaccinated compared to the risk in individuals with only the primary series of vaccination. For both VE and rVE analysis, we excluded records (1) missing essential covariates such as age and state of residence, (2) of individuals younger than 20 years old, (3) with incomplete primary vaccination registries or with atypical pair of doses for the two-dose regimen, such as heterologous primary series, and (4) with date of vaccination and/or outcome out of the study period (Jan 17 2021 to Jan 31 2022). The number of records excluded are detailed in the STROBE flow diagram in Fig. S1 at Supplementary material 1.

The analysis of the absolute VE (i.e., using the group of unvaccinated individuals as a point of comparison) was stratified by vaccine when the two doses were homologous (CoronaVac, ChAdOx1 nCov-19, BNT162b2 or Ad26.Cov2.S). In the rVE (i.e., using the primary series of vaccination as a comparator), we analyzed only the ChAdOx1 nCov-19 and BNT162b2 vaccines, given that both comprised almost 93% of the boosters administered. Other vaccines used as boosters were excluded (for details on the exclusions, please refer to Fig. S1 at Supplementary material 1). The VE and rVE were assessed in 4-week intervals and stratified by age into two age groups: 20–59 years and ≥60 years.

In the primary analysis, we compared (i) those who completed the primary series of vaccination to the unvaccinated (i.e., VE), (ii) those who had received a booster shot with those individuals who had received only the primary series of vaccination (i.e., rVE), and (iii) VE and rVE during the dominance of the Omicron variant. In a secondary analysis, we also compared individuals boosted to those unvaccinated and the VE and rVE for the periods of Delta and Gamma VOC dominance.

Cases of severe COVID-19 were aggregated into two age groups (20–59 and 60+ years old), vaccination status (unvaccinated and other combinations of vaccination schemes), and state of residency. Time was divided into calendar-time windows t of size n weeks. Individuals in a state of residency l and age group a, if vaccinated, were classified within these windows as immunized with a number s immunization weeks. For instance, for $n = 4$ weeks, $s = 1$ for people with 0–3 weeks after immunization, $s = 2$ for 4–7 weeks, and so forth. For unvaccinated individuals, parameter s do not vary. A number of $X_{t,s,a,l,v}$ people in window t with immunization schedule in s-interval is stratified by age group a, state l, and vaccine status v (primary scheme with each vaccine or primary scheme with vaccine plus booster). The methodology considers the total person-time $T_{t,s,a,l,v}$ at which people could be infected and develop the outcomes of interest by $T_{t,s,a,l,v} = n\ X_{t,s,a,l,v}$. For a combination i, composed of age group $a(i)$, state $I(i)$, and vaccination status v_i ($v_i = 1$ for vaccinated, $v_i = 0$ for unvaccinated),

calendar window t, and immunization status s, a total Y_i developing of one of the outcomes is modeled as

$$Y_i \sim Poisson(\lambda_i)$$

where $\log(\lambda_i) = \log(D_i) + \gamma_{h(i)} + \beta_{a(i),s(i)}\, v_i$, $\gamma_{h(i)}$ and $\beta_{a(i),s(i)}$ are random effects, in particular $\beta_{a(i),s(i)}$ is an age-varying effect dependent on the immunization interval, and $h(i)$ is an index unique for a combination of immunization time, age group, and state. The term D_i is the person time component obtained from the database. The random effects $\gamma_{h(i)}$ evaluates the outcome rate for unvaccinated in a given age group, state, and immunization status. The random effect $\beta_{a(i),s(i)}$ indicates how much this outcome rate changes due to the immunization.

Since groups are potentially stratified by specific primary series or a combination of the primary scheme plus booster dose, the vaccinated status indicates this subgroup. The analysis requires a minimum m of vaccinated persons by calendar window and immunization period such that $X_{t,s,a,l,v} \geq m$ to avoid small subsamples. In this work, $m = 20$. For the unvaccinated group, the person-time component requires an assessment of the total time that unvaccinated people are at risk of severe cases within the time window, this estimate is obtained indirectly via vaccination coverage. The proportion c_t of people with at least one dose divided by the population estimate per age group and state, yields the age- and state-specific coverage of vaccination at time t. For a window with bounds b_1 and b_2, the person-time component is $nP_a(1-(c_{b1}+ c_{b2})/2)$, where P_a is the population estimate in the age group a. Whenever the final vaccine coverage for a state/age group exceeded 95%, the corresponding population for the whole study period was resized to maintain coverage c_i bounded at 95%. This resizing avoids small number effects possibly incurred due to uncertainties in the population estimates, following the estimates of vaccination coverage adopted by the Center for Disease Control and Prevention.[16]

A Bayesian analysis allows the estimation of all coefficients, including $\beta_{a(i),s(i)}$, the parameters $\gamma_{h(i)}$, and other transformed quantities. The prior distribution for parameters $\gamma_{h(i)}$ and $\beta_{a(i),s(i)}$ were normal distributions with a mean equal to 0 and a precision of 0.01. Estimation of parameters is obtained with MCMC simulation with 3 chains, 6000 iterations, and a 4000 burn-in period. This estimation permits obtaining the rate ratio between the rate R_v of severe COVID-19 events for a vaccinated group and the rate R_u for an unvaccinated group, given by $R_v/R_u = \exp(\beta_{a(i),s(i)})$. Vaccine effectiveness (VE) is given by $1 - R_v/R_u$. The Bayesian analysis allows a direct computation of uncertainty intervals.

Protection of Booster doses - rVE

The analysis is similar to the one for VE. However, the comparison is between groups indicated by variable w_i, defining combinations of booster doses and the primary series as a comparison group, such that $w_i = 1$ for vaccinated people with booster dose b and primary series p, and $w_i = 0$ for vaccinated people with only primary series p. Hence, in this analysis, a similar mixed-effects Poisson model describes the outcomes, replacing the variable v with the variable w.

A Bayesian analysis again permits estimation of $\beta_{a(i),s(i)}$, thus obtaining the rate ratio, defined as the ratio between the rate R_b of severe COVID-19 event for a group vaccinated with booster doses and the rate R_v for a group vaccinated with only the primary series, given by $R_b/R_v = exp(\beta_{a(i),s(i)})$. The rVE is given by $1 - R_{vb}/R_{uv}$.

Analysis over periods of variant dominance

Calendar windows and immunisation periods are further classified by variants of dominance in their initial weeks. The statistical analysis follows the same reasoning by restricting the intervals to the VOC to be analyzed and extending the random effects to also be adjusted by VOC, such that $\beta_{a(i),s(i),u(i)}$ depends on age group $a(i)$, immunization period $s(i)$, and the variant of concern $u(i)$.

Analysis for death outcomes

Without loss of generality, this same framework is used to analyze death as an outcome of interest.

The R language (version 4.1.0) was used for data manipulation and exploratory data analysis and JAGS was used to perform MCMC simulation[17,18] to estimate model parameters. We followed the STROBE reporting guidelines (Fig. S1 and Table S1 in Supplementary material 1).[19]

Ethics statement

The study was conducted in accordance with fundamental ethical principles of the Declaration of Helsinki and the Brazilian National Health Council on research involving human beings. The Research Ethics Committee approved the study protocol of the Evandro Chagas National Institute of Infectious Diseases- Fiocruz (CAAE: 51567721.9.0000.5262).

Role of the funding source

The funders had no role in the study design, data analysis, data interpretation, or writing of the report. All the authors had final responsibility for the decision to submit for publication.

Results

Descriptive statistics and characteristics of vaccination

Brazil has had four COVID-19 epidemic waves up to February 2022. The first occurred between May and October 2020, before the immunisation campaign; the second during February and April 2021, in the periods of dominance of the Gamma variant; the third occurred

between June and August 2021, during the Delta dominance; and the last at the end of 2021, during the upsurge of the Omicron variant (Fig. 1).

During the first year of the COVID-19 vaccination program, more than 377 million doses were administered. Most first doses (58.8 million) and second doses

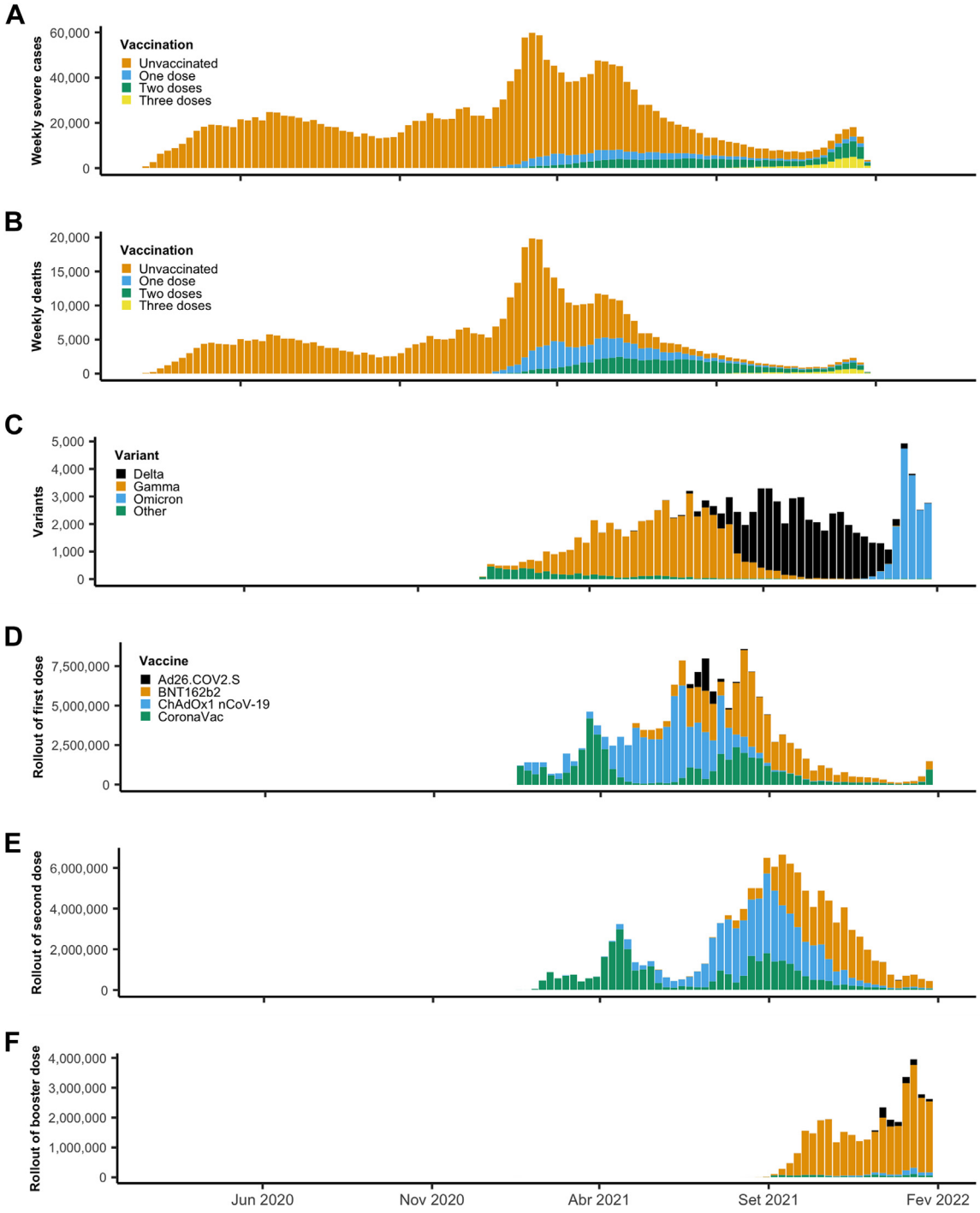

Fig. 1: **Weekly severe cases, deaths, variants and vaccine uptake from national datasets in Brazil.** (A) weekly number of COVID-19 severe cases; (B) weekly number of deaths due to COVID-19; (C) weekly number of variants among sequenced SARS-CoV-2 samples; (D) vaccine uptake of the first dose; (E) vaccine uptake of the second dose; (F) vaccine uptake of the booster dose.

(48.1 million) were ChAdOx1 nCoV-19 vaccines. In contrast, most booster vaccines administered were BNT162b2 (33.1 million), accounting for almost 90% of booster vaccines administered (Fig. 1 and Table 1). Most individuals with ChAdOx1 nCoV-19 primary series were 50–59 years old (27.5%) and 40–49 years old (22.9%). The primary series with the BNT162b2 vaccine were more frequent in the groups of 20–29 (33.0%) and 30–39 years old (28.0%). Conversely, most primary series of CoronaVac vaccine were in 20–29 (21.9%) and 70–79 (19.8%) years old individuals. Lastly, the single-dose Ad26.COV2.S vaccine was administered more frequently in the 40–49 years old group (45.5%) but corresponded to only 4% of the vaccines administered in Brazil. As expected, the Southeast region concentrated most of the doses administered in Brazil due to its population size, representing 42% of the country's population. The distribution of the first, second and booster doses of the vaccines by age group and vaccine over time is presented in the supplementary material (Fig. S2).

Most severe cases of COVID-19 among the individuals who completed the primary series with the ChAdOx1 nCoV-19 vaccine were in the 80+ years (31.5%) and 60–69 years (27.4%) groups, while the severe cases in the ChAdOx1 nCoV-19 booster recipients occurred more frequently in the 80+ (42.3%) and 70–79 years old (22.4%) groups. Most severe cases among the recipients of the BNT162b2 occurred in the 50-59- and 40-49-years old groups (28.9% and 23.0%, respectively), while cases in booster recipients were concentrated in the 80+ (41.5%) and 70–79 years (36.0%) old groups. Severe cases among the CoronaVac recipients occurred in the older groups (i.e., 70–79 and 80+ years old). Deaths among the recipients of the ChAdOx1 nCoV-19 vaccine were more concentrated in the 80+ years old group (31.4%, 40.0% and 34.2%, respectively). Conversely, deaths in those with the BNT162b2 primary series concentrated in the 50–59 and 80+ years old groups (30.4% and 40.0%) (Table 2). The weekly incidence of severe cases and deaths are presented in Fig. S3.

As described in the Introduction, the rollout of the first dose of a COVID-19 vaccine started in January 2020. Roll out of the second dose started in July 2021, which is also when the Gamma VOC dominance started to decline (Fig. 1). Roll out of booster doses, the majority of which were BNT162b2 vaccines, started after September 2021, reaching more than 2 million doses weekly in October 2021 and becoming more significant after January 2022.

Absolute and relative vaccine effectiveness for severe cases

The absolute effectiveness compared the groups of vaccinated and unvaccinated individuals, whereas the relative effectiveness compared vaccinated with a primary scheme plus booster and people with only the primary scheme. Variations in the primary scheme might induce different baseline risks. In individuals aged 20–59 years with ChAdOx1 nCoV-19 as the primary series of vaccination, absolute effectiveness against severe cases was 81.1% (95% Credible Interval–CI, 80.3–81.9) in the first four weeks after vaccination (Fig. 2 and Supplementary material 3). The rVE in the initial weeks was 43.7% (95% CI, 18.8–63.8) for the homologous booster (i.e., ChAdOx1 nCoV-19) and 66.5% (95% CI, 62.8–70.0) for the heterologous booster with the BNT162b2 vaccine (Fig. 2A). In individuals with CoronaVac as the primary vaccine series, the effectiveness was 84.7% (95% CI, 83.7–85.5) in the first four weeks. The rVE was 73.0% (95% CI, 67.8–77.6) for the BNT162b2 booster and 93.8% (95% CI, 76.1–99.7) for the ChAdOx1 nCoV-19 (Fig. 2B) in the first four weeks. In the recipients of the BNT162b2 as a primary series, the VE was 90.3% (95% CI, 89.5–91.0) in the first four-week interval. The rVE of the homologous booster was 36.6% (95% CI, 21.6–50.4), and the ChAdOx1 nCoV-19 booster conferred a 39.9% (95% CI, −15.3-77.2) protection (Fig. 2C). The VE of the Ad26.COV2.S peaked at 70.7% (95% CI, 66.9–74.2) after 20 weeks, with rVE of 82.4% (95% CI, 63.2–93.7) for the BNT162b2 booster (Fig. 2D) in the initial weeks. The same analysis in the population aged 60 years or older led to similar results, with higher protection among the older population, except for the primary series of the CoronaVac and its ChAdOx1 nCoV-19 booster. The absolute effectiveness of the booster doses is shown in Fig. S5.

Vaccine effectiveness against death

The effectiveness of COVID-19 vaccines when assuming death as the outcome showed similar patterns (Fig. 3 and Supplementary material 4). As expected, the protection against deaths was superior to those observed against severe cases, irrespective of the vaccine dose and age group. The primary series of vaccination provided high levels of protection, with effectiveness above 50% for the timeframe up to 19 weeks for most vaccines, except for CoronaVac among the elderly. The ChAdOx1 nCoV-19 and BNT162b2 booster vaccines conferred higher protection relative to the primary series.

Vaccine effectiveness in the periods of dominance of the Omicron variant

The vaccine effectiveness against severe cases in persons who received a primary series of the ChAdOx1 nCoV-19, CoronaVac, Ad26.COV2.S or BNT162b2 and after a booster dose with either ChAdOx1 nCoV-19 or BNT162b2, during the dominance of the Omicron variant, are shown in Fig. 4 and Supplementary material 7. The primary series of vaccination in the younger group ranged from 83.7% (95% CI, 74.3–90.8) for CoronaVac to 96.2% (95% CI, 58.8–100.0) for the Ad26.COV2.S vaccine, and from 61.7% (95% CI,

	ChAdOx1 nCoV-19			BNT162b2			CoronaVac			Ad26.COV2.S	
	1st dose (%)	2nd dose (%)	Booster (%)	1st dose (%)	2nd dose (%)	Booster (%)	1st dose (%)	2nd dose (%)	Booster (%)	1st dose (%)	Booster (%)
Sex											
Female	30,830,381 (52.7)	25,659,514 (53.3)	615,332 (54.5)	26,616,219 (51.0)	20,321,759 (52.3)	18,981,352 (57.3)	23,090,206 (53.7)	19,247,380 (54.5)	665,146 (57.0)	2,114,175 (45.8)	708,272 (48.45)
Male	27,600,227 (47.3)	22,499,055 (46.7)	513,807 (45.5)	25,530,100 (49.0)	18,552,186 (47.7)	14,122,825 (42.7)	19,911,494 (43.3)	16,062,593 (45.5)	500,320 (43.0)	2,504,900 (54.2)	753,534 (51.55)
Age group											
20–29 years	6,048,079 (10.5)	4,381,186 (9.2)	110,915 (9.9)	12,773,101 (37.4)	9,412,804 (33.0)	2,388,519 (7.2)	9,366,210 (23.7)	7,398,433 (21.9)	61,811 (5.3)	481,977 (10.5)	132,505 (9.1)
30–39 years	10,824,049 (18.8)	8,440,699 (17.7)	174,707 (15.6)	9,592,566 (28.1)	7,975,906 (28.0)	4,054,154 (12.3)	7,659,218 (19.4)	6,478,403 (19.2)	96,357 (8.3)	1,459,651 (32.0)	423,332 (29.3)
40–49 years	13,369,051 (23.2)	10,922,112 (22.9)	253,371 (22.7)	7,077,063 (20.7)	6,573,000 (23.1)	5,027,590 (15.3)	4,161,076 (10.5)	3,548,816 (10.5)	119,595 (10.3)	2,072,114 (45.5)	676,264 (46.7)
50–59 years	15,014,931 (26.1)	13,100,899 (27.5)	295,712 (26.5)	4,075,323 (11.9)	4,053,906 (14.2)	6,337,143 (19.3)	2,400,848 (6.0)	2,087,599 (5.1)	155,759 (13.4)	482,381 (10.6)	182,232 (12.6)
60–69 years	9,596,846 (16.6)	8,437,141 (17.7)	192,365 (17.2)	451,352 (1.2)	354,692 (1.2)	7,631,714 (23.2)	5,866,500 (14.8)	5,314,526 (15.7)	240,369 (20.7)	41,108 (0.9)	21,780 (1.5)
70–79 years	1,036,430 (1.8)	896,164 (1.9)	55,611 (5.0)	76,192 (0.2)	58,870 (0.2)	5,216,913 (15.9)	7,496,631 (19.0)	6,709,033 (19.8)	255,449 (22.0)	9603 (0.2)	5962 (0.4)
≥80 years	1,675,190 (2.9)	1,419,620 (2.9)	31,287 (2.8)	29,445 (0.1)	37,474 (0.1)	2,161,194 (6.5)	2,522,239 (6.3)	2,211,167 (6.5)	228,909 (19.8)	3378 (0.1)	3170 (0.2)
Region											
North	4,872,851 (8.4)	4,028,094 (8.4)	140,734 (12.5)	4,439,811 (8.5)	2,893,479 (7.5)	1,770,922 (5.3)	2,646,159 (6.2)	2,110,163 (6.0)	11,805 (1.0)	287,298 (.0.3)	55,786 (3.8)
Northeast	12,773,952 (22.0)	10,818,075 (22.5)	123,674 (11.0)	12,763,436 (24.6)	8,760,300 (22.6)	6,563,017 (19.9)	9,255,961 (21.65)	7,687,622 (21.9)	14,127 (1.2)	822,317 (17.9)	228,963 (15.7)
Southeast	26,658,066 (45.8)	20,528,116 (42.8)	685,164 (60.9)	21,563,899 (41.6)	17,135,635 (44.3)	15,646,672 (47.4)	21,771,455 (50.9)	17,355,368 (49.4)	1,068,122 (92.0)	2,085,602 (45.4)	601,684 (41.3)
South	9,368,212 (16.1)	8,584,766 (17.9)	75,959 (6.7)	8,462,171 (16.3)	6,522,700 (16.86)	6,351,667 (19.2)	5,978,449 (13.9)	5,327,704 (15.1)	57,222 (4.9)	868,986 (18.9)	380,219 (26.1)
Center-West	4,444,304 (7.6)	3,959,082 (8.26)	98,844 (8.7)	4,607,848 (8.8)	3,356,887 (8.6)	2,623,927 (7.8)	3,094,237 (7.2)	2,631,376 (7.4)	8965 (0.8)	529,395 (11.5)	188,923 (13.0)
Total	58,430,725	48,158,645	1,129,141	52,146,446	38,873,993	33,104,252	43,001,824	35,310,037	1,165,468	4,619,083	1,461,808

Table 1: **Baseline characteristics of the vaccinated individuals by vaccine type and dose in Brazil from January 17, 2021 to January 31, 2022.**

Characteristic	Unvaccinated		ChAdOx1 nCoV-19						BNT162b2						CoronaVac						Ad26.COV2.S			
			≥1st dose (%)		2nd dose (%)		Booster (%)		≥1st dose (%)		2nd dose (%)		Booster (%)		≥1st dose (%)		2nd dose (%)		Booster (%)		1st dose (%)		Booster	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Sex																								
Female	779,908 (44.7)	164,340 (43.3)	73,005 (48.8)	24,054 (45.8)	29,210 (50.8)	7349 (46.3)	234 (53.0)	59 (40.3)	10,280 (52.3)	1817 (42.4)	4235 (55.6)	651 (42.4)	12,720 (54.6)	3060 (48.6)	114,282 (51.0)	41,552 (47.4)	83,366 (51.0)	26,694 (47.0)	2056 (54.0)	498 (52.8)	1130 (36.2)	223 (34.4)	34 (45.3)	29 (41.4)
Male	963,025 (55.3)	215,088 (56.7)	76,582 (51.2)	28,421 (54.2)	28,241 (49.2)	8534 (53.7)	208 (47.0)	87 (59.7)	9359 (47.7)	2469 (57.6)	3387 (44.4)	885 (57.6)	10,556 (45.4)	3230 (51.4)	110,076 (49.0)	46,169 (52.6)	79,724 (49.0)	30,115 (53.0)	1751 (46.0)	445 (47.2)	1994 (63.8)	426 (65.6)	41 (54.7)	41 (58.6)
Age group																								
20–29 years	84,216 (4.8)	6156 (1.6)	2957 (2.0)	346 (0.7)	1234 (2.2)	103 (0.6)	3 (0.7)	0	3189 (18.2)	224 (5.4)	1378 (19.8)	77 (5.1)	166 (0.7)	17 (0.3)	3628 (1.6)	241 (0.3)	2397 (1.5)	126 (0.2)	9 (0.2)	3 (0.3)	177 (5.7)	18 (2.8)	5 (6.7)	1 (1.4)
30–39 years	201,171 (11.6)	20,172 (5.3)	7087 (4.7)	1342 (2.6)	2242 (3.8)	322 (2.0)	6 (1.4)	2 (1.4)	3330 (19.0)	467 (11.2)	1325 (19.0)	152 (10.1)	343 (1.5)	80 (1.3)	5106 (2.3)	566 (0.6)	3238 (2.0)	253 (0.4)	11 (0.3)	3 (0.3)	716 (23.0)	98 (15.1)	11 (14.7)	6 (8.6)
40–49 years	297,234 (17.1)	40,785 (10.8)	14,965 (10.0)	3823 (19.1)	4498 (7.9)	880 (5.5)	24 (5.4)	10 (6.8)	4257 (24.2)	1010 (24.1)	1603 (23.0)	326 (21.7)	388 (1.7)	229 (3.6)	5790 (2.6)	1032 (1.2)	3766 (2.3)	571 (1.0)	23 (0.6)	7 (0.7)	1410 (45.3)	239 (36.9)	24 (32.0)	20 (28.6)
50–59 years	362,953 (20.8)	68,826 (18.1)	31,862 (21.4)	10,033 (19.1)	10,354 (18.1)	2302 (14.5)	34 (7.7)	22 (15.1)	5113 (29.1)	1531 (36.6)	2016 (28.9)	457 (30.4)	707 (3.0)	455 (7.2)	6409 (2.9)	1587 (1.8)	4198 (2.6)	940 (1.7)	53 (1.4)	15 (1.6)	561 (18.0)	141 (21.8)	9 (12.0)	11 (15.7)
60–69 years	339,719 (19.5)	87,697 (23.1)	43,685 (29.3)	14,987 (28.6)	15,704 (27.4)	3858 (24.3)	89 (20.1)	28 (19.2)	1100 (6.3)	503 (12.0)	398 (5.7)	219 (14.6)	3631 (15.6)	1095 (17.4)	40,282 (18.0)	14,183 (16.2)	27,275 (16.8)	8283 (14.6)	278 (7.3)	65 (6.9)	135 (4.3)	65 (10.0)	5 (6.7)	8 (11.4)
70–79 years	260,162 (14.9)	81,416 (21.5)	11,761 (7.9)	5457 (10.4)	5216 (9.1)	2061 (13.0)	99 (22.4)	34 (23.3)	320 (1.8)	250 (6.0)	116 (1.7)	139 (9.3)	8384 (36.0)	1897 (30.2)	91,799 (41.0)	36,910 (42.1)	67,953 (41.7)	23,029 (40.5)	834 (21.9)	167 (17.7)	79 (2.5)	44 (6.8)	15 (20.0)	16 (22.9)
≥80 years	197,578 (11.3)	74,381 (19.6)	36,913 (24.7)	16,452 (31.4)	18,038 (31.5)	6342 (40.0)	187 (42.3)	50 (34.2)	260 (1.5)	198 (4.7)	133 (1.9)	131 (8.7)	9645 (41.5)	2512 (40.0)	70,876 (31.7)	33,179 (37.8)	53,989 (33.2)	23,593 (41.5)	2599 (68.3)	683 (72.4)	35 (1.1)	43 (6.6)	6 (8.0)	8 (11.4)
Region																								
North	115,440 (6.6)	32,733 (8.6)	8024 (5.4)	3061 (5.8)	3577 (6.2)	1086 (6.8)	49 (11.1)	22 (15.1)	944 (4.8)	203 (4.7)	330 (4.3)	83 (5.4)	733 (3.1)	272 (4.3)	7353 (3.3)	3382 (3.9)	5178 (3.2)	1919 (3.4)	5 (0.1)	0	107 (3.4)	32 (4.9)	4 (5.3)	8 (11.4)
Northeast	234,297 (13.4)	53,300 (14.0)	19,599 (13.1)	8192 (15.6)	7429 (12.9)	3072 (19.3)	39 (8.8)	28 (19.2)	2525 (12.9)	770 (18.0)	939 (12.3)	406 (26.4)	3204 (13.8)	1565 (24.9)	26,912 (12.0)	11,395 (13.0)	19,084 (11.7)	7461 (13.1)	1 (0.0)	1 (0.1)	299 (9.6)	115 (17.7)	5 (6.7)	13 (18.6)
Southeast	883,939 (50.7)	181,848 (48.0)	80,538 (53.8)	28,117 (53.6)	29,565 (51.5)	7871 (49.6)	305 (69.0)	87 (59.6)	9840 (50.1)	2000 (46.7)	4151 (54.5)	717 (46.7)	12,365 (53.1)	2948 (46.9)	125,040 (55.7)	48,040 (54.8)	87,335 (53.5)	29,926 (52.7)	3776 (99.2)	939 (99.6)	1528 (48.9)	276 (42.5)	32 (42.7)	29 (41.4)
South	336,562 (19.3)	73,598 (19.4)	28,105 (18.8)	8555 (16.3)	11,851 (20.6)	2417 (15.2)	15 (3.4)	3 (2.1)	4280 (21.8)	783 (18.3)	1492 (19.6)	195 (12.7)	4868 (20.9)	988 (15.7)	44,807 (20.0)	16,598 (18.9)	35,552 (21.8)	11,679 (20.6)	19 (0.5)	3 (0.3)	813 (26.0)	131 (20.2)	16 (21.3)	10 (14.3)
Center-West	172,794 (10.0)	37,954 (10.0)	13,323 (8.9)	4552 (8.7)	5029 (8.8)	1438 (9.1)	34 (7.7)	6 (4.1)	2051 (10.4)	530 (12.4)	710 (9.3)	135 (8.8)	2107 (9.1)	517 (8.2)	20,258 (9.0)	8309 (9.5)	15,950 (9.8)	5826 (10.3)	6 (0.2)	0	377 (12.1)	95 (14.6)	18 (24.0)	10 (14.3)
Total	1,743,033	379,433	149,589	52,477	57,451	15,884	442	146	19,640	4286	7622	1536	23,277	6290	224,371	87,725	163,100	56,812	3807	943	3124	649	75	70

Table 2: **Characteristics of the population with outcome registries according to vaccination in Brazil from January 17, 2021 to January 31, 2022.**

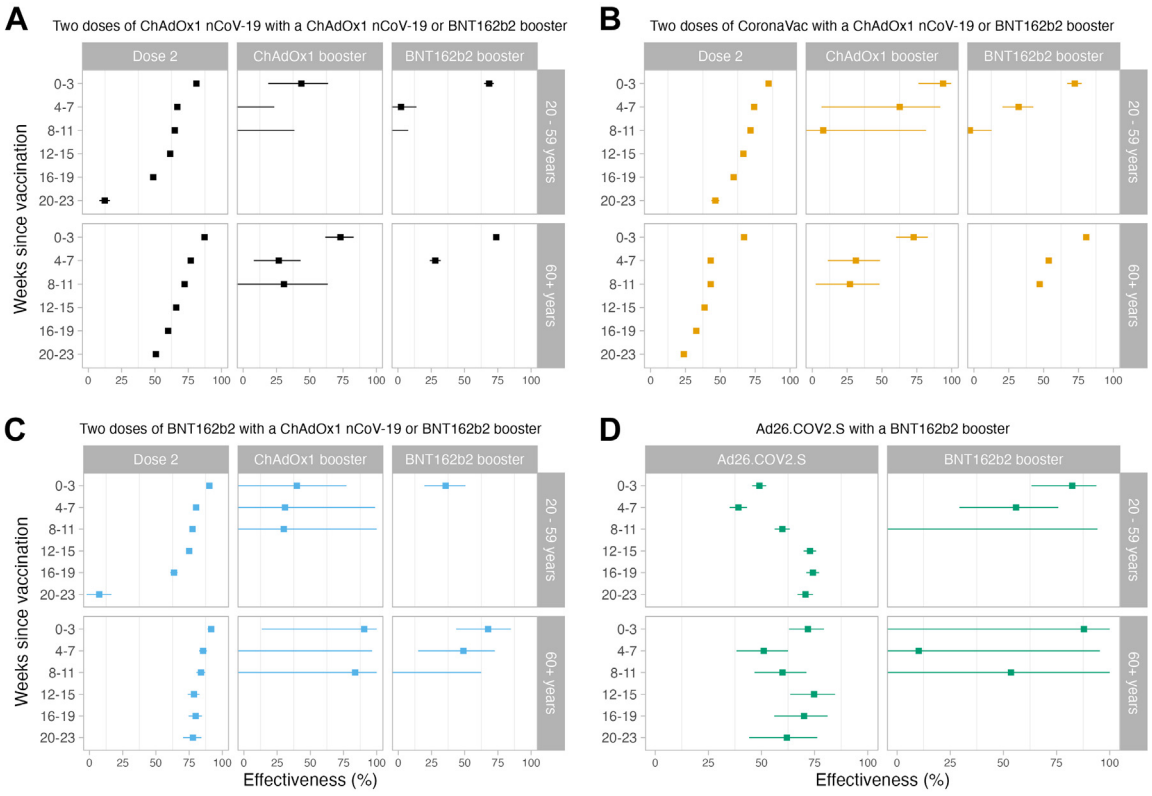

Fig. 2: **Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against severe cases after completing the vaccine primary series and booster according to the primary series for age groups by length of the time since vaccination**. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19 (ChAdOx1 as booster was not significant). Panel rows correspond to age groups and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0–100%).

26.1–86.2) to 95.6% (95% CI, 82.4–99.9), for ChAdOx1 nCoV-19 and CoronaVac, in the older group, respectively. Regardless of age and vaccine, the protection of the primary series of vaccination remained above 50% for more than 15 weeks. All booster shots were more effective than the primary series, with the relative protection lasting at least 11 weeks. The vaccine's protection in the periods of dominance of the other VOCs is presented in Supplementary material 1 (Figs. S6 and S7) and Supplementary materials 5 and 6. Data in Supplementary Material 8 contains the sizes of person-time components given the vaccines and age groups.

Discussion

The current study, based on registry data with over 158 million records compiled by the Brazilian MoH, indicates that the current vaccines were highly effective against severe cases and deaths during the first year of the vaccination campaign and in the periods of dominance of specific VOC. Our results provide evidence that the VE does not completely disappear, and 20 weeks after the primary series of vaccination the protection still reached 25% irrespective of received vaccine or age group. The booster doses significantly increased the protection offered by the primary series, with rVE remaining for at least 11 weeks after boosting. Results also show that a heterologous booster dose provided good protection against severe cases and deaths. These findings suggest that booster doses, which were mostly BNT162b2, were critical in the first months of 2022 when the entrance of the Omicron variant occurred, with high effectiveness for all adults and irrespective of primary series. During the dominance of the Omicron variant, the VE waned to about 50% after 19 weeks, except for the ChAdOx1 nCoV-19 recipients in the older group. These results are consistent with VE estimations in Brazil, the US, the UK, Italy and Sweden that reported a waning of the VE over shorter follow-up periods (between 3 and 9 months).[5–10,20–23] Our

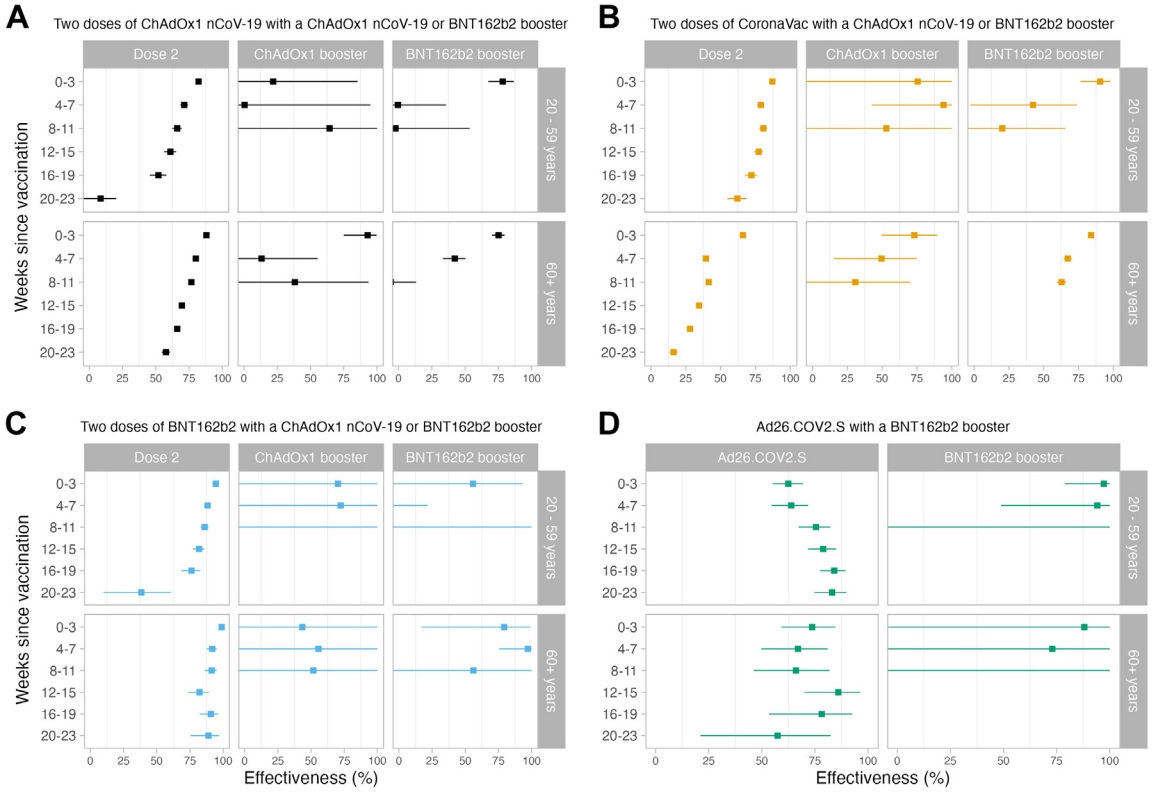

Fig. 3: **Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against death after completing the vaccine primary series and booster according to the primary series for age groups by length of the time since vaccination**. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19 (ChAdOx1 as booster was not significant). Panel rows correspond to age groups and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0–100%).

results expand such evidence with an additional vaccine (i.e., CoronaVac), considering the VOCs, using a longer follow-up and following a larger population.

The uncertainty in estimating VE for the single-dose Ad26.COV2.S was higher than any other COVID-19 vaccine used in Brazil. This result is a function of the specific rollout of Ad26.COV2.S vaccine that occurred from June to August 2021 and reached mainly adults aged 30–39 and 40–49 years, corresponding to only 4% of the vaccines administered in Brazil. The same reasoning applies to the ChAdOx1 nCoV-19 booster, which represented only a small fraction of the booster doses administered in Brazil (approx. 3%), resulting in larger intervals for the rVE estimates. Consequently, due to the fewer observations, we could not estimate the rVE of the ChAdOx1 nCov-19 booster in recipients of the Ad26.Cov2.S. The VE of Ad26.Cov2.S exhibited a different pattern of increasing effectiveness over the evaluated time frames that could be explained by its different recommendations of a single dose in the primary series. Hence, individuals' immune response after the booster dose were similar to that of naive immunized in the initial weeks after the primary series with Ad26.Cov2.S. Unexpected findings, such as some of the rVE estimates, may occur in observational studies and should not be immediately considered evidence of a harmful effect of vaccination, such as vaccine-associated enhanced disease (sometimes called VAED). Given that the absolute VE estimates were higher, irrespective of the vaccine, the lower values of rVE certainly are not VAED-related. The most reasonable explanations are differences in the comparison groups, especially differential behavioural changes (e.g., booster recipients lifting mask use), unmeasured confounding and the natural waning protection.[24–26]

To the best of our knowledge, this is the first study to use data over 12 months to assess the VE of the COVID-19 vaccination for all vaccines used in Brazil. The methodology has advantages over the screening method described in the guidelines of the World Health Organization (WHO) due to the use of rate ratios and stratification by age groups and states, a sound approach

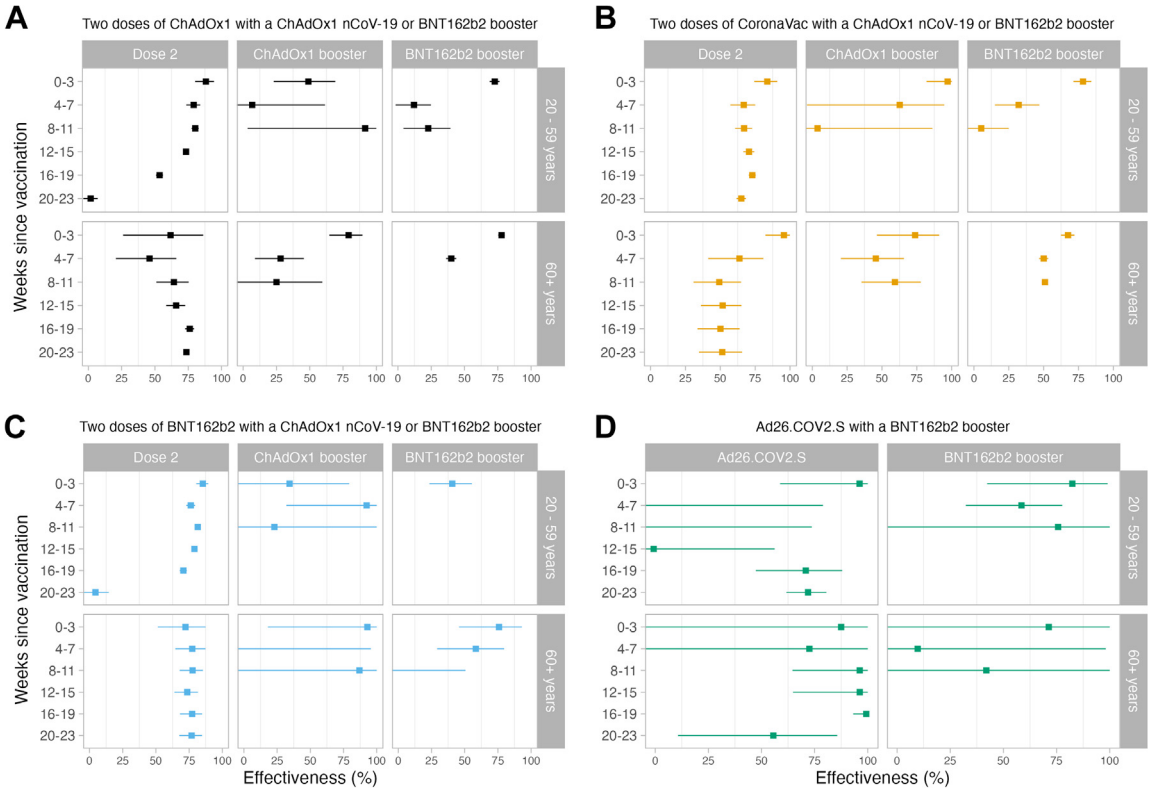

Fig. 4: **Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against severe cases after completing the vaccine primary series and booster according to the primary series for age groups by the length of the time since vaccination in periods of dominance of the Omicron variant**. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19. Panel rows correspond to age groups, and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0–100%).

given the variability of incidences across a large country such as Brazil. Of note is that this methodology is similar to the methods employed to measure the effectiveness of other vaccination programs such as Influenza.[26,27] In addition, the large dataset provided the most extensive and robust evidence of the durability of VE in Brazil. Nevertheless, our study has some limitations. First, like all observational studies, our results might be affected by confounding beyond those already accounted for with adjustments by age, time, and location. However, we do not have information on other key factors that may affect the risk of infection, such as sociodemographic, behavioural, and clinical factors that may differ between comparison groups.

Due to the lack of randomisation of individuals in real-world settings, observational studies are more subject to bias, which leads to systematic deviations of the estimated VE from the true VE. When compared to other observational study designs, such as the test-negative case control, our study has some limitations, including the impossibility of dealing with differences in health-seeking behaviour due to lack of behavioural information and collider bias, although such bias might also occur in test-negative studies.[26,28] However, our choice to use only severe cases instead of all symptomatic cases minimises these bias effects.[26] Furthermore, the estimates depend on the quality of surveillance registries and on the projections of the resident population by IBGE, which are based on the most recent census data of 2010. However, the databases we used correspond to the best available evidence on both COVID-19 vaccination and outcomes and were largely used in many studies in Brazil.[8,9,29–36] Still, the methodology can be adapted to changing epidemiological scenarios, and its use in permanent monitoring of the effectiveness should be pursued to investigate potential confounders.

Testing protocols varied during the current pandemic, so different collection methods and tests were used throughout the country. Thus, the sensitivity and specificity of tests also varied, potentially causing misclassification. Beyond this, there were differences in factors such as the timing of introduction, dose interval and eligibility for all vaccines. Consequently, this should

prompt some caution when comparing estimated protection levels among different vaccines, as the calendar period and interval between doses differ for each vaccine and, consequently, the baseline risk. For instance, a significant number of elderly people had CoronaVac as primary scheme early in the vaccination process. By contrast, younger people had either ChAdOx1 nCov-19 or BNT162b2 in their primary scheme a few months after vaccination started. This effect might impact the estimates of both absolute and relative effectiveness due to different risks in the baselines.

The distribution of vaccines also varied over time in the country. In October 2021, the MoH recommended shortening the interval for the primary series of the ChAdOx1 nCoV-19 vaccine (from 12 to 8 weeks), and in November, the interval between the primary series and the booster dose was also shortened (from 24 to 20 weeks) and an additional dose of Ad26.COV2.S was recommended 60 days after the first dose.

Furthermore, the states could (and did) adjust their vaccination protocols along with the MoH recommendations, making it hard to account for such differences in the vaccination protocols employed by each state. Decentralization of actions is one of the pillars of the Brazilian Health System (*Sistema Único de Saúde*, SUS). Consequently, the states and municipalities may change their protocols, such as those regarding testing requirements and immunisation schedules.[37] For example, the states of Pará and Mato Grosso do Sul introduced booster vaccines prior to the MoH recommendation. Moreover, vaccine shortages also affected rollout differentially throughout the country: in states such as Rio de Janeiro and São Paulo, a two-weeks shortage of ChAdOx1 nCoV-19 caused the replacement of the second dose to the BNT162b2.

Our findings indicate that the primary series of vaccination of the ChAdOx1 nCoV-19, CoronaVac, BNT162b2 or Ad26.COV2.S confer adequate levels of protection against severe cases and deaths, although waning of immunity does occur over time. Boosting with ChAdOx1 nCoV-19 or BNT162b2 significantly increased protection levels against severe cases and death. These findings reiterate the booster dose's public health value for minimising the risk of both severe cases and death and, thus, support advocating for maximising coverage of booster doses. Future work should further analyse the protection of the current booster vaccines for longer periods of follow-up and assess the protection given by the booster vaccines other than the ChAdOx1 nCoV-19 and BNT162b2, as well as that provided by the additional booster doses and disentangle the vaccines' direct and indirect effects.

Contributors

DAMV and TGN conceived the idea for the study. TGN coordinated the project and secured funding. All authors contributed to the study design. DAMV, CVBdS and TGN had access to the raw data. DAMV and CVBdS conducted the analysis. DAMV, CVBdS and CJS drafted the manuscript. The authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. All authors contributed to the interpretation of the study results, critically revised the draft and approved the final version of the manuscript.

Data sharing statement

Data supporting the manuscript were from datasets maintained by the Brazilian Ministry of Health that linked the vaccination and surveillance data. The dataset resulting from the linkage was only accessible due to specific project with Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde (Brazilian Ministry of Health). Requests for these data should be made directly to the Brazilian Ministry of Health. Unlinked, anonymized, individual-level data are freely available at https://opendatasus.saude.gov.br.

Declaration of interests

DAMV, PML, MFCG, LSB, OGC, AGP, NCMV, LPF and TGN are affiliated with Fundação Oswaldo Cruz, which manufactures the ChAdOx nCoV-19 vaccine in Brazil through a full technology transfer agreement with AstraZeneca. VBGP is a Brazilian Ministry of Health employee at the National Immunization Program (NIP), being responsible for the pharmacovigilance of the vaccines used by the NIP. DAMV, TGN and MFCG are invited, unpaid members of the Technical Advisory Board for COVID-19 immunization in the Brazilian Ministry of Health. MFCG received travel and lunch expenses for a meeting promoted by the Butantan Institute, the manufacturer of CoronaVac in Brazil. All other authors declare no competing interests.

Acknowledgements

CJS, GLW and CVBdS acknowledge support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ) (GLW grant number E-26/210.180/2020). LPF received funds from the Brazilian Ministry of Health (Project VPEIC-001-FIO-20). DAMV is grateful for support from CNPq/Brazil (Ref. 441057/2020-9, 309569/2019-2). We also thank the Coordenação Geral do Programa Nacional de Imunizações, part of the Brazilian Ministry of Health, for providing the anonymized dataset used in the study. Authors would like to thank GISAID for the access to the dataset of lineages of SARS-CoV-2 virus in Brazil. The authors had support from INOVA Fiocruz, CNPq, CAPES (Finance Code 001), and Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde (Brazilian Ministry of Health), and the Pan American Health Organization (PAHO).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100465.

References

1 Ministério da Saúde. Painel Coronavírus. https://covid.saude.gov.br/; 2020. Accessed August 23, 2022.
2 Ministério da Saúde. Dados da campanha Nacional de Vacinação contra Covid-19. https://opendatasus.saude.gov.br/dataset/covid-19-vacinacao; 2022. Accessed September 4, 2022.
3 Ministério da Saúde. Vacinômetro COVID-19. https://infoms.saude.gov.br/extensions/DEMAS_C19_Vacina_v2/DEMAS_C19_Vacina_v2.html; 2022. Accessed September 4, 2022.
4 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385:585–594. https://doi.org/10.1056/nejmoa2108891.
5 Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. *N Engl J Med*. 2022;386:340–350. https://doi.org/10.1056/nejmoa2115481.
6 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. *N Engl J Med*. 2022;386:1532–1546. https://doi.org/10.1056/nejmoa2119451.
7 Lin D-Y, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. *N Engl J Med*. 2022;386:933–941. https://doi.org/10.1056/nejmoa2117128.

8 Katikireddi SV, Cerqueira-Silva T, Vasileiou E, et al. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. *Lancet*. 2022;399:25–35. https://doi.org/10.1016/S0140-6736(21)02754-9.

9 Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. *Nat Med*. 2022;28:838–843. https://doi.org/10.1038/s41591-022-01701-w.

10 Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet*. 2021;398:1407–1416. https://doi.org/10.1016/S0140-6736(21)02183-8.

11 Bernal JL, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ*. 2021;373:n1088. https://doi.org/10.1136/bmj.n1088.

12 Ministério da Saúde. SRAG 2021 - Banco de Dados de Síndrome Respiratória Aguda Grave - incluindo dados da COVID-19. https://opendatasus.saude.gov.br/dataset/srag-2021-e-2022; 2021. Accessed August 14, 2022.

13 Ministério da Saúde. SRAG 2020 - Banco de Dados de Síndrome Respiratória Aguda Grave - incluindo dados da COVID-19. https://opendatasus.saude.gov.br/dataset/srag-2020; 2020. Accessed August 14, 2022.

14 Instituto Brasileiro de Geografia e Estatística. Projeção da população brasileira. https://www.ibge.gov.br/apps/populacao/projecao/index.html; 2022. Accessed March 1, 2022.

15 Shu Y, McCauley J. GISAID: global initiative on sharing all influenza data – from vision to reality. *Euro Surveill*. 2017;22:2–4. https://doi.org/10.2807/1560-7917.ES.2017.22.13.30494.

16 Center For Disease Control and Prevention. *How CDC estimates vaccination coverage*; 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-vaccinations.html. Accessed November 21, 2021.

17 Plummer M. JAGS: a program for analysis of Bayesian graphical models using Gibbs sampling. In: *Proceedings of the 3rd international workshop on distributed statistical computing*; 2003. Vienna. http://www.r-project.org/conferences/DSC-2003/

18 R Core Team. *R: A Language and Environment for Statistical Computing* 2022. Vienna, Austria.

19 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbrouckef JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ*. 2007;85:867–872. https://doi.org/10.2471/BLT.07.045120.

20 Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. *Science*. 2022;375:331–336. https://doi.org/10.1126/science.abm0620.

21 Nordström P, Ballin M, Nordström A. Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden. *Lancet*. 2022;399:814–823. https://doi.org/10.1016/S0140-6736(22)00089-7.

22 Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 booster vaccines against COVID-19-related symptoms, hospitalization and death in England. *Nat Med*. 2022;28:831–837. https://doi.org/10.1038/s41591-022-01699-1.

23 Corrao G, Franchi M, Cereda D, et al. Persistence of protection against SARS-CoV-2 clinical outcomes up to 9 months since vaccine completion: a retrospective observational analysis in Lombardy, Italy. *Lancet Infect Dis*. 2022;22:649–656. https://doi.org/10.1016/S1473-3099(21)00813-6.

24 Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. *Bull World Health Organ*. 1985;63:1055–1068.

25 Munoz FM, Cramer JP, Dekker CL, et al. Vaccine-associated enhanced disease: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2021;39:3053–3066. https://doi.org/10.1016/j.vaccine.2021.01.055.

26 World Health Organization. *Evaluation of COVID-19 vaccine effectiveness: interim guidance 17, March 2021*. WHO; 2021. reference number: WHO/2019-nCoV/vaccine_effectiveness/measurement/2021.1. https://apps.who.int/iris/rest/bitstreams/1337417/retrieve. Accessed April 5, 2021.

27 Baum U, Auranen K, Kulathinal S, Syrjänen R, Nohynek H, Jokinen J. Cohort study design for estimating the effectiveness of seasonal influenza vaccines in real time based on register data: the Finnish example. *Scand J Public Health*. 2020;48:316–322. https://doi.org/10.1177/1403494818808635.

28 Westreich D, Hudgens MG. Invited commentary: beware the test-negative design. *Am J Epidemiol*. 2016;184:354–356. https://doi.org/10.1093/aje/kww063.

29 Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. *BMJ*. 2021;374:n2015. https://doi.org/10.1136/bmj.n2015.

30 Castro MC, Gurzenda S, Macário EM, França GVA. Characteristics, outcomes and risk factors for mortality of 522 167 patients hospitalised with COVID-19 in Brazil: a retrospective cohort study. *BMJ Open*. 2021;11:1–9. https://doi.org/10.1136/bmjopen-2021-049089.

31 de Souza ML, Ichihara MYT, Sena SOL. *Sistemas de informação para a COVID-19. Construção de conhecimento no curso da pandemia da COVID-19: aspectos biomédicos, clínico-assistenciais, epidemiológicos e sociais*. vol. 44. Salvador: Edufba; 2020. https://doi.org/10.9771/9786556300757.003.

32 Santos CVB, Cavalcante JR, Pungartnik PC, Guimarães RM. Transição da idade de casos, internações e óbitos em internações por Covid-19 no município do Rio de Janeiro. *Rev Bras Estud Popul*. 2022;39:1–10. https://doi.org/10.20947/s0102-3098a0195.

33 Santos CVB, Cavalcante JR, Pungartnik PC, Guimarães RM. Space-time analysis of the first year of covid-19 pandemic in the city of rio de janeiro, Brazil. *Rev Bras Epidemiol*. 2021;24:e210046. https://doi.org/10.1590/1980-549720210046.

34 Cavalcante JR, Xavier DR, dos Santos CVB, Pungartnik PC, Guimarães RM. Spatial analysis of the origin-destination flow of admissions for severe acute respiratory syndrome caused by COVID-19 in the Metropolitan Region of Rio de Janeiro. *Rev Bras Epidemiol*. 2021;24:1–6. https://doi.org/10.1590/1980-549720210054.

35 Santos CVB, de Noronha TG, Werneck G, Villela DAM. Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: a retrospective observational study. *Lancet Reg Health Am*. 2023;17:100418. https://doi.org/10.1016/j.lana.2022.100418.

36 Azevedo e Silva G, Jardim BC, Santos CVB. Excesso de mortalidade no Brasil em tempos de COVID-19. *Cien Saude Colet*. 2020;25:3345–3354. https://doi.org/10.1590/1413-81232020259.23642020.

37 *Brasil. Lei No 8080. Câmara Dos Deputados 1990*; 1990:1–19. http://www.planalto.gov.br/ccivil_03/leis/l8080.htm. Accessed July 5, 2022.