Effectiveness of the fourth dose of COVID-19 vaccines against severe COVID-19 among adults 40 years or older in Brazil: a population-based cohort study

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Summary

Background The emergence of COVID-19 variants with immune scape and the waning of primary vaccine schemes effectiveness have prompted many countries to indicate first and second booster COVID-19 vaccine doses to prevent severe COVID-19. However, current available evidence on second booster dose effectiveness are mostly limited to high-income countries, older adults, and mRNA-based vaccination schemes scenarios. We aimed to investigate the relative vaccine effectiveness (rVE) of the fourth dose compared to three doses for severe COVID-19 outcomes in Brazil; and compare the rVE of a fourth dose with an mRNA vaccine compared to adenovirus-based product in the same settings.

Methods We performed a target emulated trial using a population-based cohort of individuals aged 40 years or older who have received a homologous primary scheme of CoronaVac, ChAdOx1, or BNT162b2, and any third dose product and were eligible for the fourth dose in Brazil. The primary outcome was COVID-19 associated hospitalization or death. We built Cohort A matching individuals vaccinated with a fourth dose to individuals who received three doses to estimate the rVE of the fourth dose. We built Cohort B, a subset of Cohort A, matching mRNA-based (mRNA) to adenovirus-based fourth dose vaccinated individuals to compare their relative hazards for severe COVID-19.

Findings 46,693,484 individuals were included in Cohort A and 6,763,016 in Cohort B. 45% of them were aged between 40 and 60 years old, and 48% between 60 and 79 years old. In Cohort A, the most common previous series was a ChAdOx1 two-dose followed by BNT162b2 (44%), and a CoronaVac two-dose followed by a BNT162b2 (36%). Among those fourth dose vaccinated, 36.9% received ChAdOx1, 32.7% Ad26.COV2.S, 25.8% BNT162b2, and 4.7% CoronaVac. In Cohort B, among those who received an adenovirus fourth dose, 53.7% received ChAdOx1 and 46.3% received Ad26.COV2.S. The estimated rVE for the primary outcome of four doses compared to three doses was 44.1% (95% CI 42.3–46.0), with some waning during follow-up (rVE 7–60 days 46.8% [95% CI 44.4–49.1], rVE after 120 days 33.8% [95% CI 18.0–46.6]). Among fourth dose vaccinated individuals, mRNA-based vaccinated individuals had lower hazards for hospitalization or death compared to adenovirus-vaccinated individuals

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(HR 0.81, 95% CI 0.75–0.87). After 120 days, no difference in hazards between groups was observed (HR 1.35, 95% CI 0.93–1.97). Similar findings were observed for hospitalization and death separately, except no evidence for differences between fourth dose brands for death in Cohort B.

Interpretation In a heterogeneous scenario of primary and first booster vaccination combinations, a fourth dose provided meaningful and durable protection against severe COVID-19 outcomes. Compared to adenovirus-based booster, a fourth dose wild-type mRNA vaccine was associated with immediate lower hazards of hospitalization or death unsustained after 120 days.

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Keywords: COVID; Vaccine; Booster; Fourth; Effectiveness

Research in context

Evidence before this study

We searched the PubMed database for previous evidence on the second booster (fourth dose) COVID-19 vaccine effectiveness on severe outcomes using the search terms "COVID-19", "coronavirus", "vacc*", "effect", "fourth OR booster" between inception until October 1st, 2023. We found observational studies showing a protective relative vaccine effectiveness (rVE) against severe COVID-19 of four doses compared to only three doses for both monovalent and bivalent mRNA vaccine products, particularly for older adults aged 60 years or older, and nursing-home residents. This protective effect was higher at the immediate post-vaccination period and had some waning over-time. Most studies included older adults, vaccinated and boosted with mRNA-based regimens, from high-income countries (HIC) such as the United States, Sweden, South Korea, Israel, Italy among others. Only a few studies included younger adults, adenovirus-based boosters, and heterogenous primary vaccination schemes in their analysis. Therefore, current available evidence is still insufficient to provide reliable guidance on vaccine effectiveness for a large number of vaccinated individuals, particularly those living in low and upper-middle income countries (LMIC), vaccinated with inactivated or adenovirus primary regimens and younger than 60 years old.

Added value of this study

This is one of the first studies to investigate the rVE of a fourth dose in a heterogenous and diverse scenario of previous vaccinations regimens and younger adults (aged 40 years and older), and the first to directly compare the effectiveness of a fourth dose mRNA-based vaccine compared to adenovirus-based vaccine boosters. We have shown that, in a predominantly two-dose primarily vaccinated population with ChAdOx1 and CoronaVac, a fourth dose of COVID-19 vaccine provided meaningful and sustained (≥120 days) protection against hospitalization and/or death when compared to only three doses vaccinated individuals. This finding was consistent among most represented subgroups of primary vaccine regimens and, importantly, among individuals from the general population aged 40–59 years, reassuring the role of booster vaccination in the general population with heterogeneous primary vaccination context. Additionally, we have shown that a fourth dose mRNA-based booster provided lower hazards of hospitalization or death compared to adenovirus-based booster in the immediate period after vaccination, but not after 120 days, suggesting that an adenovirus-based booster might be a reasonable choice for booster, particularly where a mRNA is not available.

Implications of all the available evidence

The emergence of new COVID-19 strains with immune scape and the relative waning of vaccine protection over-time has led the World Health Organization (WHO) to indicate booster doses to restore protection and prevent hospitalizations and deaths. Our results provide evidence to support the decision to second booster adults aged 40 years and older in a low-and-middle income country with different previous vaccine combinations. Available evidence reinforces the protective role against severe COVID-19 of the fourth dose for middle and older-aged adults, including wild-type strain vaccine products and adenovirus-based ones. Overall, vaccine effectiveness seems to be consistent across different primary scheme regimens. The relative waning of vaccine protection over-time indicates the need for additional boosters taking into account endemic periods of increased infection and groups at increased risk of poor outcomes.

Introduction

The development of effective vaccines against severe COVID-19 disease has prevented millions of deaths worldwide.[1] In 2021, the emergence of the Omicron variant of concern (VOC), with increased immune escape and decreased vaccine effectiveness,[2–5] prompted

many countries to indicate a first booster dose to restore protection, particularly against severe disease. In 2022, the World Health Organization (WHO) recommended a second booster dose for adults 60 years and older and those at increased risk, but it's adoption was highly heterogeneous among countries,[6] partially explained by the lack of comprehensive literature up to that date.

Population-based studies have shown that a second booster dose increases protection against severe COVID-19[7–21] for both monovalent[9,11,13,18] and bivalent[8,10,14,15,19] vaccine types, although some waning of protection was observed during follow-up.[11,12,18,19] The studies mostly included older adults[11–13,16,18,19,21] and long-term care facilities residents[7,12,14] living in high-income countries (HIC)[8,9,11–15,18,19,21] who received a mRNA vaccine booster after a mRNA primary scheme.[7–10,12–16,18,19,21] Few studies have been performed in low and middle-income countries (LMIC),[17,20] investigated a broad set of boosters,[17] heterogeneous primary schemes[11,17,20] or effectiveness in middle-aged adults.[15,17,20] Therefore, current available evidence is insufficient to guide vaccination policies in under-represented contexts.

Brazil had high vaccination rates and administered adenovirus-based, inactivated, and mRNA vaccine types as primary vaccinations schemes and first boosters. In Brazil, a fourth dose with either an adenovirus or mRNA-based product was recommended to all adults aged 40 years or older in addition to those at increased risk, providing a diverse scenario compared to the current literature. We aimed to: (i) investigate the relative vaccine effectiveness (rVE) of the fourth dose compared to three doses for the prevention of severe COVID-19 outcomes in Brazil; and (ii) compare the relative vaccine effectiveness of a fourth dose with an mRNA vaccine compared to adenovirus-based product in the same settings.

Methods

Study design, settings, and data source

We conducted a target trial emulation using a population-based cohort study between February 2022, and September 2022, in Brazil. The national COVID-19 vaccination campaign for the primary vaccination scheme started on January 17, 2021, the administration of the first booster (*third dose*) dose began for the general population on September 6, 2021, and second booster dose (*fourth dose*) early February 2022 for one state (Mato Grosso do Sul), following by early March 2022 for another state (Pará), then the national campaign in middle March 2022. The primary series used in Brazil were homologous schemes of Sinovac CoronaVac (two doses), Oxford-AstraZeneca ChAdOx1 (two doses), Pfizer BNT162b2 (two doses), Janssen Ad26.COV2.S (single dose), and heterologous combinations of the above products in periods of vaccine shortage. All four vaccine products were approved for use as a third or fourth dose; however, the vast majority of doses for the third dose was BNT162b2[22] and the fourth doses concentrated in ChAdOx1, Ad26.COV2.S and BNT162b2. The fourth dose campaign was initially indicated for health professionals and risk groups and was further expanded to all adults aged 40 years during the study period. The minimum required interval between third and fourth doses was four months.

We have previously evaluated the effectiveness of the primary series of Sinovac CoronaVac and Oxford-AstraZeneca ChAdOx1, and the additional protection of a third dose in Brazil.[22–24] Following the structure already in place, we constructed an individual-level national cohort of vaccinated individuals and their COVID-related health outcomes in Brazil by deterministic linkage of three different databases: (i) eSUS, which collects information of any individual suspected to have mild COVID-19, including any notification independently of test results; (ii) SIVEP-Gripe which collects information on any severe acute respiratory infection, including all notified COVID-19 hospitalizations and deaths; and (iii) the national vaccination database (SI-PNI), where COVID-19 vaccinations were registered. The source list of the cohort was the SI-PNI. Notification to these three systems is compulsory in Brazil. We additionally linked the built cohort to the mortality registry system (SIM) to determine deaths by other causes. We extracted eSUS, SIVEP-Gripe, SI-PNI, and SIM on September 12, 2022, and used data until September 05, 2022. The data management and pseudo-anonymization was conducted in a secure environment at the Ministry of Health. This study was approved by the ethical committee for research of Federal University of Mato Grosso do Sul (CAAE: 43289221.5.0000.0021).

Study population, exposure definitions, and outcomes

We included all adults (i) aged 40 years or more, (ii) previously vaccinated with a two-dose homologous primary vaccination scheme of the most common combinations: CoronaVac (Cov), ChAdOx1 (Az) or BNT162b2 (Pf), (iii) who received the first booster dose with any vaccine, and (iv) were alive and eligible to the second booster. Patients with demographic data inconsistencies were excluded (Fig. 1).

The exposure of interest for the first aim of this study was any fourth dose COVID-19 vaccination. The exposure of interest for the second aim of this study was whether the fourth dose was a mRNA-based vaccine (mRNA) or an adenovirus-based vaccine. We built two matched cohorts: 1) Cohort A included all adults eligible for the fourth dose vaccination, and 2) Cohort B, a subset of Cohort A, included only patients who received the fourth dose of a mRNA or adenovirus product, excluding those individuals who received CoronaVac as fourth dose (Fig. 1), because of the limited number of individuals in this group.

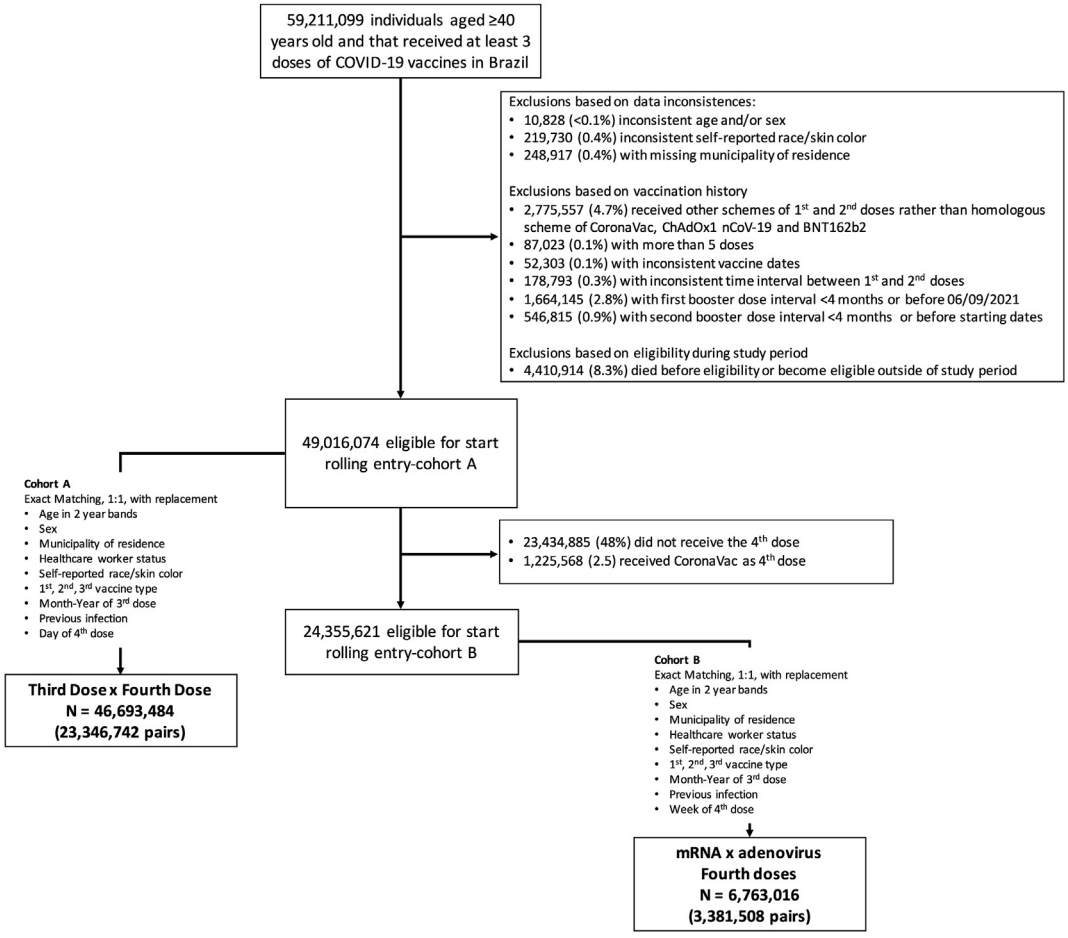

Fig. 1: **Study flowchart**.

Our primary outcome was a composite outcome of COVID-19 hospitalization or death. We defined it by a COVID-19-associated hospitalization that occurred within 21 days of symptom onset from individuals with a positive RT-qPCR or rapid antigen test for SARS-CoV-2, or a COVID-19 death that occurred within 28 days of symptoms onset from individuals with a positive RT-qPCR or rapid antigen test for SARS-CoV-2, consistent with prior research groups.[24–27] We also considered in the primary outcome hospitalizations and deaths without laboratory testing available that were finally classified as COVID-19 in SIVEP-Gripe based on clinical-epidemiological criteria as defined by the Ministry of Health and previously validated.[28,29] We used this approach to avoid any potential differential misclassification and because we expect very few events without laboratory confirmation. Areas with less access to healthcare and vaccination are more likely to have clinically defined COVID-19 instead of lab-confirmed COVID-19, which results in differential outcome misclassification by geography.[28,30]

For secondary outcomes, we evaluated hospitalization and death separately, and COVID-19 hospitalization with severe acute respiratory failure. We defined COVID-19 hospitalization with acute respiratory failure for patients receiving either non-invasive or invasive respiratory support during their stay, aiming to increase the specificity for hospitalizations due to COVID-19. However, we expect limited impact on vaccine effectiveness because SIVEP-Gripe is a dedicated database for severe acute respiratory infections and not an administrative database for all-cause hospitalizations.

Matching and follow-up

We emulated a pragmatic target trial of COVID-19 vaccination using rolling entry matching (REM).[31] We conducted exact matching on age (bins of two years), sex, self-declared race/skin color, healthcare worker status, any previous confirmed infection before the fourth dose campaign start, prior vaccine scheme (first, second and third doses), month and year of the third dose, and the municipality of residence. We selected

matching variables based on data availability and following a Direct Acyclic Graph (DAG) framework for proper confounding adjustment (Figure S1). For Cohort A, we matched fourth dose recipients on the date of vaccination (time zero) with eligible but as yet unvaccinated individuals (i.e., individuals with three doses eligible to the fourth) in a 1:1 ratio. We used a dynamic matching scheme, updating on a daily basis to add individuals who become eligible for the fourth dose and removing individuals after death or documented infection. For Cohort B we emulated a head-to-head trial,[32] when fourth dose mRNA vaccinated individuals were matched with fourth dose adenovirus vaccinated counterparts at the date of vaccination (time zero), and dynamic matching was updated on a weekly basis to maximize the pool of potential pairs for matching. After matching, pairs were followed until the first occurrence of an event of interest (e.g., COVID-19 hospitalization and/or death). Patients were right-censored if: (i) had COVID-19 infection but did not have an event of interest after a window of susceptibility from the date of symptoms (21 days for hospitalization analyses and 28 days later for death analyses); (ii) died of any-cause (for COVID-19 hospitalization outcome); (iii) died of non COVID-19 causes (for COVID-19 death, and combined COVID-19 death and COVID-19 hospitalization outcomes); (iv) the paired-control with three doses and eligible for the fourth dose received a fourth dose (for cohort A, both censored at the time of control vaccination). Other pairs were administratively censored at the end of the study period (September 05, 2022).

Statistical analysis

The analysis was pre-specified, and the sample size was pragmatic. We calculated and plotted the cumulative incidence between groups with the Kaplan-Meyer estimator and performed the log-rank test to compare time-to-event outcomes between groups. We analyzed Cohort A and Cohort B with Cox proportional hazard models to derive hazard ratios (HR) and their 95% confidence intervals (CI). rVE was estimated as 100× (1 minus the HR). The Cox models were stratified on matched-pairs to guarantee precise and unbiased standard variance,[33,34] and to deal with built-in selection bias (i.e., both individuals of each pair must be at risk for each time period analysed[32]). In addition, Cox proportional hazards assumption was investigated by visual inspection of Schoenfield residuals. The origin and start times were the same and defined by date of matching. We estimated rVE for the period 7+ days after the fourth dose and report time-period estimates of rVE (report time intervals 7–60, 61–120, >120 days) to assess potential waning.[32–34] We explored rVE in subgroups based on previous knowledge of effect modifiers in this population: age (<60, 60–79, ≥80 years old), health care worker status, previous vaccination schemes (product type of primary scheme, product type of booster), and time from third dose. Subgroup analyses were evaluated with an interaction term between the vaccine and the sub-group of interest and evaluated with a likelihood-ratio test.

We conducted one sensitivity analysis to evaluate potential healthcare access bias.[32,35,36] We run the main analysis on the matched pairs who were both tested by COVID-19 RT-qPCR or rapid antigen tests at least once, independent of test result, since 2020 (i.e., the cohort of tested individuals).

We investigated potential bias via several methods. First, we visually inspected the cumulative incidence and estimated rVE and HR during the immediate post-vaccination period (0–6 days), when no biological protection of the booster dose is expected, and daily estimates in the first 10 days after matching.[32,37] We ran three additional post-hoc analyses focused on the 0–6 day period: (i) using symptom onset date instead of date of event; (ii) excluding those matched pairs when either individual have had any entry in the surveillance systems in the previous 21 days from matching; and (iii) using any symptomatic COVID-19 case as an endpoint. We aimed to better control for those individuals which were potentially already infected before matching with approaches i and ii, while with approach iii we explored whether the potential bias magnitude would be different between any symptomatic COVID-19 and severe events, since the expected rVE is higher for severe compared to mild COVID-19.

The present study followed STROBE guidelines in reporting observational studies. Statistical significance alpha was set to 5%. We performed all analyses in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Role of funding source

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

Results

Of 49,016,074 individuals vaccinated with three doses eligible to match for Cohort A, 23,346,742 pairs (N = 46,693,484) were included, and of 24,355,621 individuals eligible to match for Cohort B, 3,381,508 pairs were included (N = 6,763,016) (Fig. 1). The distribution of fourth doses during the study period is shown in Figure S2. A limiting factor for finding matching pairs in Cohort B was several periods when mRNA predominated over adenovirus vaccines and vice-versa (Figure S3). Covariates were well balanced between matched-pairs in both cohorts (Table 1). For Cohort A, 45% (20,901,566/46,693,484) of patients were between 40 and 60 years old, and 7.2% (3,337,074/46,693,484) were 80 or more years old. The two most common previous vaccination

schemes were a ChAdOx1 two-dose primary vaccination followed by a BNT162b2 booster dose (44.9%, 20,984,586/46,693,484), and a CoronaVac two-dose primary vaccination followed by a BNT162b2 booster dose (35.9%, 16,740,020/46,693,484). Homologous three-doses schemes were uncommon (13.5%, 6,323,730/46,693,484) with a homologous BNT162b2 scheme being more frequent (7.3%, 3,424,550/46,693,484). Among those that received a fourth dose in cohort A, 36.9% (8,608,742/23,343,742) received ChAdOx1, 32.7% (7,631,204/23,343,742) Ad26.COV2.S, 25.8% (6,011,800/23,343,742) BNT162b2, and 4.7% (1,094,996/23,343,742) CoronaVac. Cohort B had baseline characteristics similar to those observed for Cohort A. In cohort B, among those who received an adenovirus fourth dose, 53.7% (1,814,665/3,381,508) received ChAdOx1 and 46.3% (1,566,843/3,381,508) received Ad26.COV2.S.

In Cohort A, the median follow-up time was 48 [IQR 19–76] days and there were 15,691 COVID-19 hospitalizations or deaths, with 15,176 hospitalizations and 3973 deaths. There were 11,194 hospitalizations with at least one sign/symptom of respiratory distress (dyspnoea, hypoxaemia, respiratory discomfort) and 9068 hospitalizations with need of respiratory support. Among the

	Cohort-A (Third vs Fourth dose)		Cohort-B (Comparison of fourth dose types)	
	Third dose	Fourth dose	mRNA	Adenovirus
n	23,346,742	23,346,742	3,381,508	3,381,508
Age, mean (SD), years	61.3 (12)	61.3 (12)	61.1 (12)	61.1 (11.2)
Age groups, n (%)				
40–59	10,450,783 (44.8)	10,450,783 (44.8)	1,501,337 (44.4)	1,501,337 (44.4)
60–79	11,227,422 (48.1)	11,227,422 (48.1)	1,672,219 (49.5)	1,672,219 (49.5)
80+	1,668,537 (7.1)	1,668,537 (7.1)	207,952 (6.1)	207,952 (6.1)
Male, n (%)	9,940,591 (42.6)	9,940,591 (42.6)	1,377,126 (40.7)	1,377,126 (40.7)
Self-reported race/skin colour, n (%)				
White	9,071,933 (38.9)	9,071,933 (38.9)	1,086,540 (32.1)	1,086,540 (32.1)
Non-white	8,002,721 (34.3)	8,002,721 (34.3)	1,202,948 (35.6)	1,202,948 (35.6)
Missing	6,272,088 (26.9)	6,272,088 (26.9)	1,092,020 (32.3)	1,092,020 (32.3)
Healthcare worker, n (%)	2,687,839 (11.5)	2,687,839 (11.5)	354,346 (10.5)	354,346 (10.5)
Region, n (%)				
North	785,972 (3.4)	785,972 (3.4)	173,184 (5.1)	173,184 (5.1)
Northeast	5,007,844 (21.4)	5,007,844 (21.4)	689,981 (20.4)	689,981 (20.4)
Central-West	1,458,314 (6.2)	1,458,314 (6.2)	341,021 (10.1)	341,021 (10.1)
Southeast	12,592,442 (53.9)	12,592,442 (53.9)	1,829,517 (54.1)	1,829,517 (54.1)
South	3,502,170 (15.0)	3,502,170 (15.0)	347,805 (10.3)	347,805 (10.3)
Previous documented infection, n (%)				
None	22,393,718 (95.9)	22,393,718 (95.9)	3,304,048 (97.7)	3,304,048 (97.7)
No-Omicron	477,050 (2.0)	477,050 (2.0)	36,243 (1.1)	36,243 (1.1)
Omicron	475,974 (2.0)	475,974 (2.0)	41,217 (1.2)	41,217 (1.2)
Previous vaccine scheme (1st-2nd-3rd vaccine products), n (%)				
Az-Az-Pf	10,492,293 (44.9)	10,492,293 (44.9)	1,585,354 (46.9)	1,585,354 (46.9)
CoV-CoV-Pf	8,370,010 (35.9)	8,370,010 (35.9)	1,230,726 (36.4)	1,230,726 (36.4)
Pf-Pf-Pf	1,712,275 (7.3)	1,712,275 (7.3)	281,221 (8.3)	281,221 (8.3)
Az-Az-Az	916,023 (3.9)	916,023 (3.9)	97,894 (2.9)	97,894 (2.9)
CoV-CoV-CoV	533,567 (2.3)	533,567 (2.3)	57,098 (1.7)	57,098 (1.7)
Az-Az-CoV	362,850 (1.6)	362,850 (1.6)	31,312 (0.9)	31,312 (0.9)
Pf-Pf-Az	338,223 (1.4)	338,223 (1.4)	44,995 (1.3)	44,995 (1.3)
Az-Az-JJ	315,948 (1.4)	315,948 (1.4)	28,064 (0.8)	28,064 (0.8)
CoV-CoV-Az	124,894 (0.5)	124,894 (0.5)	9712 (0.3)	9712 (0.3)
Pf-Pf-JJ	122,122 (0.5)	122,122 (0.5)	11,947 (0.4)	11,947 (0.4)
CoV-CoV-JJ	31,181 (0.1)	31,181 (0.1)	1721 (0.1)	1721 (0.1)
Pf-Pf-CoV	27,356 (0.1)	27,356 (0.1)	1464 (<0.1)	1464 (<0.1)
Interval between third dose and enrolment, median [IQR], (days)	173 [151, 198]	174 [152, 198]	175 [153, 198]	175 [153, 198]

Az, Oxford-AstraZeneca ChAdOx1; CoV, CoronaVac; JJ, Janssen (Ad26.COV2.S), IQR, interquartile-range; Pf, Pfizer (BNT162b2); SD, standard deviation.

Table 1: **General characteristics of the matched population.**

15,691 hospitalizations or deaths, 15,551 (99.1%) were associated with laboratory-confirmed COVID-19. In Cohort B, the median follow-up time was median 82 [IQR 63–123] days and there were 3031 COVID-19 hospitalizations and/or deaths, with 2979 hospitalizations and 548 deaths. There were 1975 hospitalizations with at least one sign/symptom of respiratory distress (dyspnoea, hypoxaemia, respiratory discomfort) and 1664 hospitalizations with need of respiratory support. Among the 3031 hospitalizations and/or deaths, 2991 (98.7%) were laboratory-confirmed COVID-19.

The estimated rVE of the fourth dose compared to three doses (Cohort A) for the prevention of COVID-19 hospitalization or death was 44.1% (95% CI 42.3–46.0%) (Fig. 2A). In a time-stratified analysis, decreasing effectiveness over time since vaccination was observed (rVE 7–60 days 46.8 [95% CI 44.4–49.1], rVE after 120 days 33.8% [95% CI 18.0–46.6], Fig. 3), Secondary outcomes of hospitalization and death separately provided similar results, with slightly increased protection for death (rVE 7–60 days 60.8% [95% CI 56.9–64.4], rVE after 120 days 47.6% [95% CI 27.4–62.2], Fig. 3 and Figure S4). Subgroup analysis showed higher rVE for patients aged between 60 and 79 years old compared to other age groups, and those with 180 days or more between third and fourth dose compared to a shorter interval (Figure S5). We did not find statistically significant interaction by healthcare worker status, previous infection or previous mRNA receipt.

Among people who received a fourth dose (Cohort B), the estimated HR of hospitalization or death was 0.81 (95% CI 0.75–0.87) times lower among people who received a mRNA dose compared to people who received an adenovirus dose (Fig. 2B). Expanded time-periods showed decreased on the difference between mRNA-based and adenovirus-based booster (7–60 days 0.78 95% CI 0.69–0.87, 61–120 days 0.78 95% CI 0.71–0.86, 341 after 120 days 1.35 95% CI 0.93–1.97, Fig. 4). Secondary outcomes analysis showed similar results, except not statistically difference for death across any time-period (Fig. 4 and Figure S6). Subgroup analysis showed greater benefit from a mRNA booster compared to adenovirus for young patients and patients who received previous homologous vaccination series of ChAdOx1 and CoronaVac and a third dose of BNT162b2. No differences were found for health-care worker status, previous infection or third to fourth-dose interval (Figure S7).

Sensitivity analysis analyzing only the tested-population yielded comparable estimates to the main analysis for the primary and secondary outcomes in Cohort A (Figure S8). In contrast, estimates in the tested-population moved towards the null for the primary and secondary outcomes in Cohort B (Figure S9).

When evaluating the bias-indicator period (Figures S10–S12), we observed higher protection for earlier days after the fourth dose compared to later days, likely achieving a plateau in Cohort A. There is a reduction in the potential bias when evaluating the tested-population and excluding those notified 21 days before the enrollment (Figure S13). There is no evidence for difference in risk of severe COVID-19 during the first 6 days when comparing mRNA and AND-based fourth doses in Cohort B (Figure S14). For both cohorts, the bias-indicator estimates were smaller than the main analysis when the outcome was symptomatic disease.

Discussion

In a large population cohort of individuals at least 40 years of age with heterogeneous COVID-19 primary and boosting vaccination schemes, we have shown that a fourth dose provided clinically meaningful protection for severe COVID-19 outcomes compared to three doses. The protection from a fourth dose was sustained after 120 days, albeit with apparent waning over time. In addition, among those who received a fourth dose, the hazard of severe COVID-19 events was lower for those that received a mRNA-based fourth dose compared to adenovirus-based fourth dose. This difference was greater in the initial 120 days and mainly driven by hospitalization.

Previous population-based studies in Israel,[13] Canada,[9,21] United-States,[14] Denmark,[8] Sweden,[8] Italy,[19] South Korea,[11] Singapore,[15] Chile[20] and Hungary[17] have shown additional protection against severe events (hospitalization or death) after a fourth dose. Estimated rVE after monovalent BNT162b2 ranged from 16% (95% CI 9–22%) in Singapore to 64% (CI 57–75%) in Israel. Direct comparison between monovalent and bivalent (BA.4–5 and/or BA.1) mRNA-boosters yielded conflicting results: bivalent boosters provided additional protection when compared to monovalent doses in Singapore[15] (rVE bivalent 88% vs monovalent 16%) and Italy[19] (rVE BA.4–5 50.6%, BA.1 49.3% and monovalent 26.9%), but no difference was observed in a combined analysis of data from Denmark, Finland, Norway, and Sweden (rVE BA.4–5 vs monovalent [33.8% 95% CI –2.7% to 70.3%] and BA.1 vs monovalent [0.8% 95% CI –49.0% to 50.7%]).[8]

We found a rVE of 44% against severe COVID-19 for the fourth dose compared to three doses. A study in South Korea where approximately 72% of the population had ChAdOx1 in the primary scheme reported a rVE of 70.6% (95% CI 55.4–80.6) one month after the fourth dose and 62.1% (95% CI 45.5–73.7%) three months after the fourth dose[11] which were higher than our estimates. This might be partially explained by the exclusive use of only mRNA-based fourth doses in South Korea, compared to the 25% of mRNA fourth doses in Brazil. Studies with more similar population settings (younger adults, mix-primary vaccinations schemes including inactivated vaccines) in Chile[20] and Hungary[17] have reported high fourth dose vaccine effectiveness; however, comparisons to our results are limited because of the referential group. Both studies compared fourth-

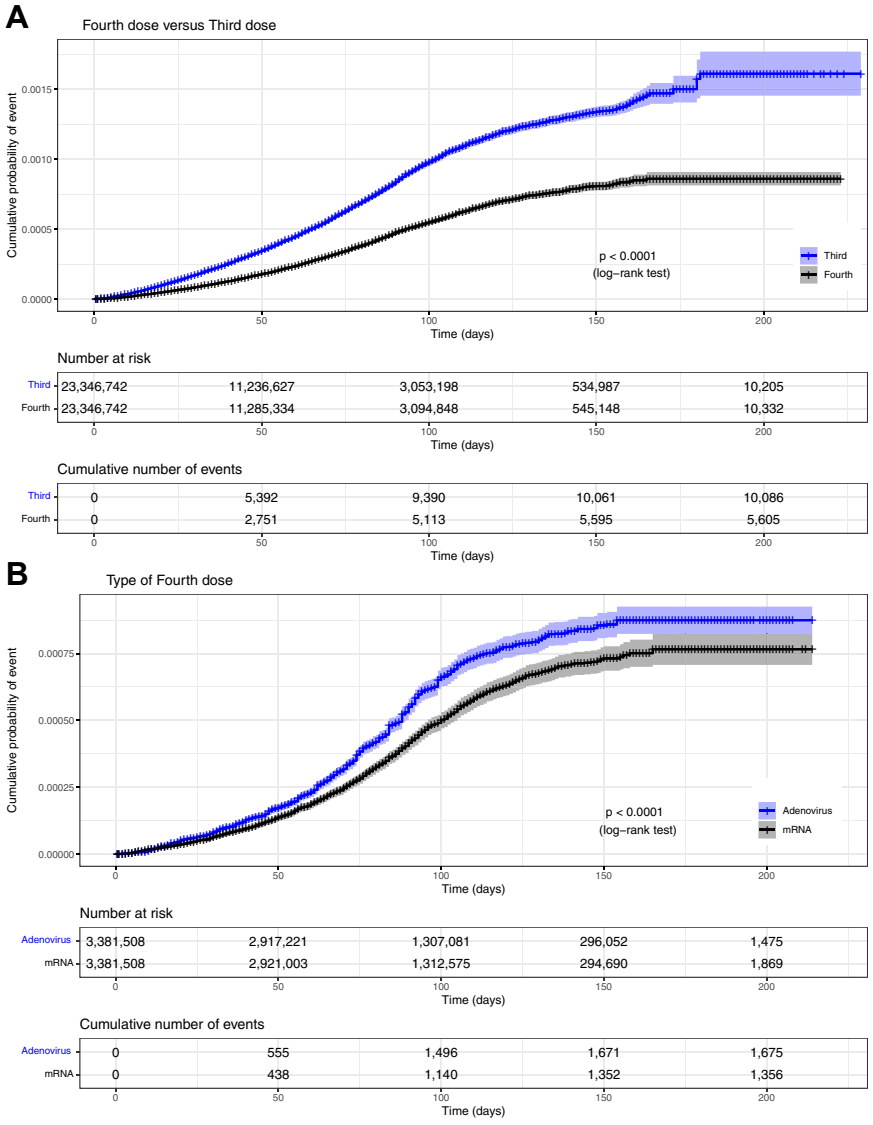

Fig. 2: **Cumulative probability of event hazard for hospitalization or death comparing (A) fourth dose against fourth dose eligible (third dose) and (B) type of fourth dose.**

dose recipients to unvaccinated individuals while we compared to three doses boosted patients. Our results are in the range of rVE reported by other HIC income countries; however such comparisons are limited due to differences regarding the age of population included, types of primary and booster vaccination products administered (most mRNA vaccines used in HIC) and heterogeneity of the proportion of patients with previous COVID-19. We found higher rVE for adults aged in-between 60 and 80 years old and those with increased time between third and fourth dose. These findings can be explained by the higher relative baseline risk of serious events for these groups: older adults have less sustained protection during follow-up compared to younger adults,[16,38] and all patients will have decreased antibody production 6-months after vaccination.

Fourth dose rVE had some waning after 120 days in our cohort, but maintained clinically meaningful protection after 120 days. Previous findings from South Korea,[11] Italy,[18,19] Sweden,[12] have shown decreased effectiveness over time but shorter follow-up when compared to our study. Serological studies among health-care workers in Israel have shown that 120 days after a mRNA second booster dose, IgG levels return to pre-booster dose levels.[39] In addition, previous studies reported meaningful waning after two and three doses of mRNA predominant vaccine types[2] but to a lesser extent after adenovirus-based vaccines.[5] This might

Hospitalization or Death	n / PY	rVE (95% CI)	P–value
7–60 days	3069 / 2154662	46.8% (44.4–49.1)	<0.0001
61–120 days	2078 / 779758	39.6% (36.2–42.9)	<0.0001
120+ days	150 / 107152	33.8% (18.0–46.6)	0.0002
Hospitalization			
7–60 days	3152 / 2156092	47.2% (44.9–49.5)	<0.0001
61–120 days	2156 / 780937	39.5% (36.2–42.7)	<0.0001
120+ days	156 / 107300	33.8% (18.3–46.3)	0.0001
Hospitalization with Respiratory Support			
7–60 days	1757 / 2154716	49.3% (46.3–52.2)	<0.0001
61–120 days	1278 / 779810	38.6% (34.1–42.8)	<0.0001
120+ days	91 / 107159	31.1% (9.1–47.9)	0.0085
Death			
7–60 days	585 / 2156226	60.8% (56.9–64.4)	<0.0001
61–120 days	582 / 781085	48.2% (42.7–53.2)	<0.0001
120+ days	57 / 107320	47.6% (27.4–62.2)	0.0001

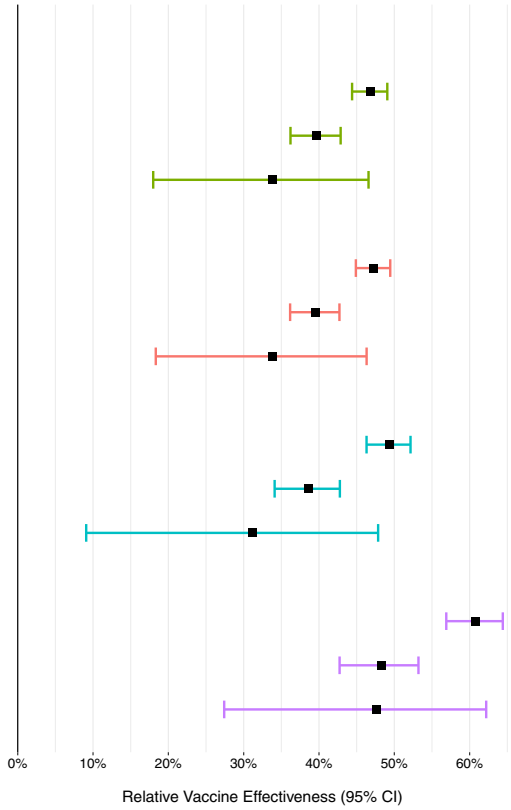

Fig. 3: **Relative vaccine effectiveness of the fourth dose compared to fourth dose eligible (third dose) in Cohort A, evaluating potential waning through expanded time-periods for the primary and secondary outcomes**. The black dot represents the point estimate of rVE and the coloured stickers represent the 95% CI. CI denotes confidence interval, PY person-years, and rVE relative vaccine effectiveness.

explain the durable protection we found (75% of fourth doses were adenovirus-based product types) and also the lack of differences between mRNA and adenovirus vaccine after 120 days. This finding provides reassurance about the durable benefit of adenovirus boosters, although a higher short-term protection was observed for mRNA-based boosters. Further studies are needed to evaluate the effectiveness of vaccine type when programmes want to protect during a season (e.g., winter), when the product with less waning during the first 3–4 months would perform better.

The main strength of the current study is the large population included, which encompasses middle and older-aged individuals, and the variety of COVID-19 products used for both initial and booster doses. This variety reflects what occurred in most LMICs during the pandemic, but is scarcely represented in the current literature. Additionally, we provided a direct comparison of adenovirus and mRNA-based fourth dose which has not been previously examined in these settings. Other strengths include longer period estimates of effectiveness, including the period of four months after boosting, and the target-emulated trial with several sensitivity and exploratory analyses, showing consistent results.

This study also has some limitations. First, because of the observational nature of the study, residual bias can not be discarded, as shown by the inspection of the immediate period after vaccination (bias-indicator period), particularly on Cohort A. We tried to minimize confounding by setting a target-emulated trial and by adjusting for all observed variables with likely association with the exposure and outcome and we conducted sensitivity analyses aiming to tackle some of the potential bias and the results were comparable. However, the lack of granular individual data, particularly the presence of comorbidities or immune-suppression, which are known risk factors for severe COVID-19, limited confounders adjustments (unmeasured confounders). We also acknowledge a residual bias by self-reported colour/race, because we used a missing indicator category, thus representing a category that mixes groups. The decision to use a missing indicator was pragmatic, because we planned to use this variable in the exact matching, the size of the database and the lack of other variables to properly model an imputation model. This also precluded us from evaluating a potential effect modification by this variable. Additionally, the bias-indicator pattern observed during the early days

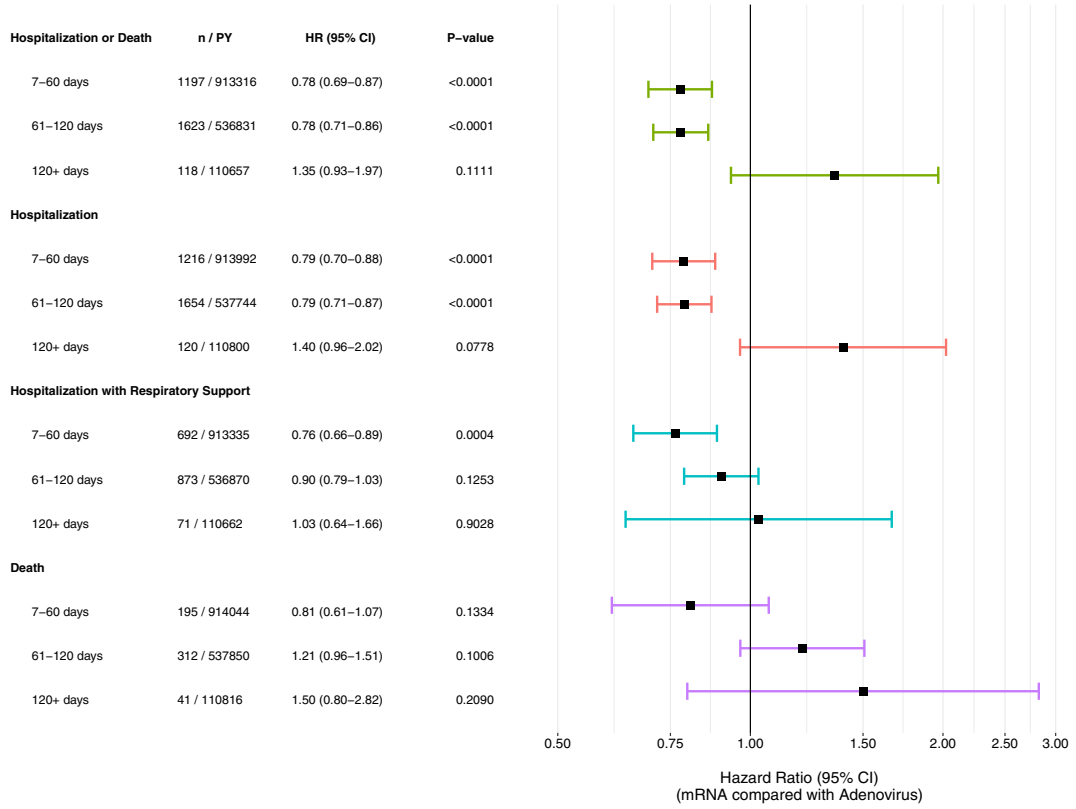

Fig. 4: **Hazard ratio for the comparison between a fourth dose with mRNA compared with adenovirus adenovirus vaccine evaluating potential waning through expanded time-periods for the primary and secondary outcomes in Cohort B**. The black dot represents the point estimate of HR and the coloured stickers represent the 95% CI. CI denotes confidence interval, HR hazard ratio, and PY person-years.

has been observed in previous studies and was a transient phenomenon, resembling the "healthy vaccine bias".[16,32] Second, estimation of hazard-ratios may vary over-time and produce built-in selection bias during follow-up, previously described in vaccine studies and other epidemiological cohorts To better address this limitation, we calculated time-specific hazard-ratios to allow for varying hazards ratios over time, which are indeed expected in vaccination studies due to waning, and we calculate the HR within the stratum of matched pairs, guaranteeing both vaccinated and matched control are in the risk set in each period. However, residual built-in selection bias is still expected due to the intrinsic nature of HRs; thus the reported HRs are a weighted average of the period-specific HRs.[40] Third, we used national surveillance databases which are subject to incomplete information and under-notification. However, because we evaluated only severe COVID-19 outcomes, we expect dismissible underreporting. Fourth, the administration of vaccines has shifted the profile of hospitalized patients and some patients might have died mainly because of underlying chronic diseases and frailty rather than directly due to COVID-19. To address this issue, we investigated the need for respiratory support during hospitalization, a potential proxy for hospitalized patients with acute respiratory failure directly attributed to COVID-19. In addition, although the cut-off used for the temporal association of COVID-19 symptoms and serious outcomes is consistent with previous research,[24–27] particularly during primary vaccination, they may still not capture all potential associated cases, specially after triplet vaccination when patients may have less severe outcomes, but still die of complications of the infection after months. Lastly, we have examined only wild-type mRNA boosters as per the national Brazilian vaccination campaign and not bivalent BA1/2 and BA4/5 vaccine boosters, limiting any comparative effectiveness analysis between them.

In conclusion, we have found that a fourth booster dose provided sustained protection against COVID-19-related hospitalizations or death for adults aged 40 years and older. In addition, although decreased hazards favoring mRNA-based fourth dose compared to adenovirus-based booster was observed in the initial follow-up, after 120 days there were no significant differences. These findings provide reassuring evidence of the benefit of the fourth dose, particularly for countries where a mix of inactivated, adenovirus

and mRNA-based vaccines were administered in primary vaccination schemes. We also showed meaningful protection for younger adults which were not included in WHO guidelines,[6] informing the debate on which ages should be contemplated in future policies and studies.

Contributors

All authors conceived the study. DATC, NED, JRA, AIK, JC, and OTR contributed equally as senior authors. FLN and OTR led the statistical analyses. MSST, DHT and OTR curated and validated the data. FLN wrote the first draft of the manuscript. MDTH, ABA, GVAF, MLL, MSST and RDO provided supervision. All authors contributed to, and approved, the final manuscript. OTR and JC had verified the data. JC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

Any information for assessing the databases must be addressed to the Brazilian Ministry of Health at https://datasus.saude.gov.br/, and requests can be addressed to datasus@saude.gov.br. Our agreement with the Ministry of Health for accessing the databases patently denies authorization of access to the full datasets by a third party because of privacy and ethical/legal issues.

Declaration of interests

MDTH reports a contract from Merck and Dohme (to the University of Florida) for research unrelated to this manuscript. DATC reports a contract from Pfizer Inc. Paid to the University of Florida for research unrelated to this manuscript. ML received grants from the NIAID for COVID-19 prevention with correctional facilities. AIK received funding from Beatrice Kleinberg Neuwirth Family Fund, Sendas Family Fund, Regeneron, Merck, Reckitt Global Hygiene Institute, Paul Hastings LLD, National Academy of Sciences Engineering and Medicine, and is on the Board of Directors (unpaid) of the American Society of Tropical Medicine and Hygiene. JC received funding from Sanofi, MSD, Bill and Melinda Gates Foundation, Valneva/Butantan and payment/honoraria from Foro Latinoamericano para Asesores Médicos en Vacunas 2023 (Pfizer), Pfizer Emerging Markets Advance Speaker Training 2024 (Pfizer). Also, JC is on the Brazil advisory board for mRNA-1273 vaccine (Modern/Zodiac), RSV maternal vaccine (Pfizer) and Qdenga vaccine (Takeda). NED received funding from the NIH/NIAID R01-AI139761, Emergent Biosolutions, and Bavarian Nordic. OTR acknowledges funding from the END-VOC Project (Horizon 2021–2024), funded by the European Union under grant agreement no. 101046314. OTR acknowledges support from the Spanish Ministry of Science and Innovation through the Centro de Excelencia Severo Ochoa 2019–2023 programme (CEX2018-000806-S) and from the Generalitat de Catalunya through the Centres de Recerca de Catalunya (CERCA) programme. The remaining authors declare they have no competing interests.

These institutions had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100755.

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