Effectiveness of the CoronaVac vaccine in the elderly population during a P.1 variant-associated epidemic of COVID-19 in Brazil: A test-negative case-control study

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Keywords
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Abstract

Background Mass vaccination is being used in response to coronavirus disease (COVID-19) epidemics, including those driven by emerging variants of concern. We evaluated the effectiveness of the inactivated whole-virus vaccine, CoronaVac, against symptomatic COVID-19 in the elderly population of São Paulo State, Brazil during widespread circulation of the P.1 variant.

Methods We conducted a test-negative, case-control study of adults ≥70 years of age from São Paulo State from January 17 to April 29, 2021, during which vaccination with a two-dose regimen of CoronaVac was implemented. We identified RT-PCR-confirmed COVID-19 cases and controls who had a symptomatic illness with a negative RT-PCR test from national surveillance and state vaccination databases. Controls were pair-matched to cases by age category, sex, race, municipality, prior COVID-19 status, and date of RT-PCR testing. We estimated vaccine effectiveness, adjusted for age and comorbidities, using conditional logistic regression.

Findings We selected 7,950 matched pairs with a mean age of 76 years from 26,433 COVID-19 cases and 17,622 test-negative controls. Adjusted vaccine effectiveness was 18.2% (95% CI, 0.0 to 33.2) and 41.6% (95% CI, 26.9 to 53.3) in the period 0-13 and ≥14 days, respectively, after the 2nd dose. Administration of a single vaccine dose was not associated with reduced odds of COVID-19. Vaccine effectiveness ≥14 days after the 2nd dose declined with increasing age and was 61.8% (95% CI 34.8 to 77.7), 48.9% (95% CI 23.3 to 66.0) and 28.0% (95% CI 0.6 to 47.9) among individuals 70-74, 75-79 and ≥80 years of age, respectively ($p_{interaction}$ = 0.05).

Interpretation CoronaVac was 42% effective in the real-world setting of extensive P.1 transmission, but significant protection was not observed until completion of the two-dose regimen. These findings underscore the need to maintain non-pharmaceutical interventions when mass vaccination with CoronaVac is used as part of an epidemic response.

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Research in context

Evidence before this study

We searched Pubmed for articles published from inception of the pandemic until May 10, 2021, with no language restrictions, using the search terms “vaccine”, “COVID-19”, “SARS-CoV-2”, “elderly”, “age”, “older”. There are no studies reporting the real-world effectiveness of COVID-19 vaccines against P.1, and few studies reporting real-world effectiveness of COVID-19 vaccines among elderly individuals.

Added value of this study

In a population based matched test-negative case-control study conducted in a setting with widespread P.1 variant transmission, we observed that two-doses of CoronaVac was effective in preventing symptomatic COVID-19 among those aged 70 years or older, a population remarkably underrepresented in phase 3 clinical trials. There was no evidence for protection after the first dose. We observed a significant decline in effectiveness at older ages.

Implications of all the available evidence

Our results showed that the inactivated COVID-19 vaccine CoronaVac likely needs the complete two-dose schedule for protection against symptomatic disease among the elderly. Additionally, effectiveness of the two-dose schedule decreased with age. These results have direct implications for national vaccination programs using CoronaVac, highlighting that non-pharmaceutical interventions should be in place throughout vaccination campaigns. Further research is needed on how to optimize the vaccination of the very elderly (≥80 years), considering different vaccine types or dosing schedules by age.

Introduction

The SARS-CoV-2 pandemic has caused 3.3 million deaths worldwide as of early May 2021,[1] and elderly individuals have suffered disproportionate morbidity and mortality.[2] Since the beginning of the pandemic the development of an effective vaccine against SARS-CoV-2 was a priority, and several vaccines have been tested and licensed for use. A key public health question is whether the licensed vaccines are effective in the elderly, who may have impaired immune responses,[3] and who were underrepresented in the clinical trials.[4,5]

Brazil is one of the countries most affected by the COVID-19 pandemic, totaling more than 15 million cases and 421,000 deaths as of early May 2021.[1,6] Variants of Concern (VOC) have likely played a role in the recent surges across Brazil.[7] The P.1 VOC,[8] which was first detected in Manaus and has accrued mutations associated with decreased neutralization,[9,10] now consists of the majority of new infections in Brazil.[7,11]

Several vaccines against COVID-19 have been proven efficacious in Phase III trials and are being used in mass vaccination campaigns across the globe, including Sinovac's CoronaVac vaccine.[4,12] Evidence for the effectiveness of vaccination in real-world setting has come primarily from countries with rapid roll-out of the vaccine, such as Israel[13] and the United Kingdom.[14] However, evidence of effectiveness in groups that were not well represented in clinical trials, such as the elderly, and against VOCs, remains limited.

We aimed to evaluate the real-world effectiveness of CoronaVac in the general population ≥70 years in São Paulo State, the most populous state in Brazil (~46 million inhabitants), where P.1 is the predominant circulating variant.

Methods

Study setting

The State of São Paulo (23°3'S, 46°4'W) has 645 municipalities and 46 million inhabitants and its capital, São Paulo city, has 12 million inhabitants.[15] Its population ≥70 years is projected as 3.23 million by 2020.[15] São Paulo State reported 2,997,282 COVID-19 cases (cumulative incidence rate: 6,475 per 100,000 population) and 100,649 deaths (cumulative mortality: 217 per 100,000 population) by 9 May 2021.[16] The State Secretary of Health of Sao Paulo (SES-SP) initiated its COVID-19 vaccination campaign on 17 January 2021 and is administering two vaccines during the study period, CoronaVac and ChAdOx1. As of 29 April 2021, 10.7 million doses (7.1 million first doses and 3.5 million second doses) have been administered in the State. We analysed only CoronaVac because of the low coverage of ChAdOx1 during the study period. The suggested interval for CoronaVac in Brazil during the study period was 21 or 28 days.

Study design

We conducted a retrospective, test-negative,[17,18] matched case-control study to estimate the effectiveness of CoronaVac in reducing the odds of the primary outcome of symptomatic RT-PCR-confirmed SARS-CoV-2 infections. The study population was individuals aged ≥70 years who had a residential address in São Paulo State and with complete information, which was consistent between data sources, on age, sex, and residence, and vaccination status and dates. For this study, we selected cases and matched controls who had a positive and negative SARS-CoV-2 RT-PCR test result, respectively, during the study period of January 17 to April 29, 2021.

The study design and statistical analysis plan were specified in advance of extracting information from data sources and are described in a publicly available protocol

(https://github.com/juliocroda/VebraCOVID-19) and the Supplement. The study was approved by the Ethical Committee for Research of Federal University of Mato Grosso do Sul (CAAE: 43289221.5.0000.0021).

Data Sources

We identified eligible cases and controls, their demographic characteristics, and chronic comorbidities by linking the state laboratory testing registry of the public health laboratory network (GAL) and national healthcare and surveillance databases (e-SUS and SIVEP-Gripe). We determined the vaccination status by linking these databases with the state vaccination registries (Vacina Já). The record linkage was done by the São Paulo State Government – PRODESP – using CPF numbers (Brazilian citizens' unique identifier code) and sent to the researchers anonymized. Notification to these systems is compulsory in Brazil. We retrieved VOC information from the GISAID database.[11]

Selection of cases and matched controls

Cases were selected from the study population who had symptomatic COVID-19, defined as a symptomatic individual with a positive SARS-CoV-2 RT-PCR test result from a respiratory sample that was collected during the study period and the absence of a positive RT-PCR test in the preceding 90-day period; and who did not receive a dose of ChAdOx1 vaccine before sample collection. Controls were selected from the study population who did not have a SARS-CoV-2 infection, defined as a symptomatic individual with a negative SARS-CoV-2 test result from a respiratory sample that was collected during the study period and the absence of a positive RT-PCR test in the subsequent 14-day period, the preceding 90-day period, or previously in the study period; and did not receive a dose of ChAdOx1 vaccine before sample collection. Symptomatic illness was defined as the presence of one or more

reported COVID-19 related symptoms[19] with an onset within 0-10 days before the date of sample collection.

We matched one test-negative control to each case according to a time window of ±3 days between the case sample collection date; age category defined in 5-year age bands (70-74, 75-79, etc.); municipality of residence; race (defined as brown, black, yellow, white, or indigenous); and prior COVID-19-like illness (defined as having had at least one episode of symptomatic respiratory illness in surveillance databases from the beginning of the pandemic to the start of the study, regardless of viral test confirmation). Matching factors were chosen from variables that were associated with vaccination coverage or timing, and with SARS-CoV-2 infection risk or healthcare access (see protocol). Upon identification of each case, a single control was chosen from the set of all eligible matching controls, and each control was matched to at most one case.

Statistical analysis

We analyzed the effectiveness of the full two-dose schedule of CoronaVac against symptomatic SARS-CoV-2 infection, in the period of time starting 14 days after administration of the second dose. To understand the timing of vaccine effectiveness, we evaluated the association between vaccination with two doses in the period 0-13 days after administration of the second dose, and vaccination with a single dose in the period starting 14 days after administration of the first dose. Finally, we evaluated the exposure of receiving the first vaccine dose from 0 to 13 days before the sample collection date. An association during this period, where the vaccine likely has no or limited effectiveness,[4,20,21] may serve as an indicator of unmeasured confounding in the effectiveness estimate. The reference group for vaccination status was individuals who had not received a first vaccine dose before the date of sample collection.

We used conditional logistic regression to estimate the odds ratio (OR) of vaccination among cases and controls. 1-OR provided an estimate of vaccine effectiveness under the assumptions of a test-negative design.[22] We included as covariates in the adjusted model: age as a continuous variable, and COVID-19-associated comorbidities (cardiovascular, renal, neurological, haematological, or hepatic comorbidities, diabetes, chronic respiratory disorder, obesity, or immunosuppression). We conducted one pre-specified subgroup analysis by age groups, and five additional *post hoc* subgroup analyses, by sex, number of chronic comorbidities (none vs. at least one), the two most frequent chronic comorbidities (cardiovascular disease and diabetes), and region of residence ("Grande São Paulo" health region vs. others). We did not evaluate the pre-specified subgroup analysis by previous infection because of small numbers of previously infected individuals among case-control pairs. For these analyses, we assessed the difference in vaccine effectiveness 14 days after the second dose with an interaction term with each subgroup of interest. Finally, in an exploratory analysis, we evaluated vaccine effectiveness in weekly time windows following vaccination (0-6, 7-13, 14-20, 21-27, and ≥28 days following first and second dose).

Power calculation

After generating matched case-control pairs and before performing the analyses, we simulated the power of the data set to identify a vaccine efficacy of 40% comparing those with two doses ≥14 days after the second dose to those who had not received a vaccine (see the protocol for details). After extracting the surveillance databases on 6 May 2021, we determined that the power of the study was 99.9%.

All analyses were done in R, version 4.0.2.

Role of the funding source

All funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Health Secretary of State of São Paulo and PRODESP reviewed the data from the study, but the academic authors retained editorial control. OTR, MDTH, MSST, and JC had full access to de-identified data in the study and OTR and MDTH verified the data, and all authors approved the final version of the manuscript for publication.

Results

COVID-19 epidemic and vaccination campaign in São Paulo State

COVID-19 incidence in São Paulo state increased from November 2020 to January 2021, declining slightly thereafter but with a large peak in infections occurring in March 2021 (Figure 1A and Figure S1). The vaccination campaign started on January 17, 2021 and vaccinated 4.50 million (2.57 million first doses and 1.92 million second doses) with CoronaVac among the population ≥70 years by April 29, 2021, resulting in a coverage of about 80% and 60% for the first dose and second dose (Figure 1B-D). Incidence in the population continued to rise after initiation of the vaccination campaign and peaked in late March. The prevalence of the P.1 VOC increased sharply from December 2020 onwards, making up 83% (1,815/2,190) of genotyped isolates between March to April 2021 (Figure 1E).

Study population

Among 92,130 individuals eligible for inclusion in the study population (Figure 2), 44,055 RT-PCR tests were performed during the study period in individuals displaying COVID-19 symptoms. 15,900 RT-PCR tests conducted among 15,852 individuals were selected into matched pairs (see Table S1 for description of discordant pairs, and Figure S2 for timing of discordant pairs).

Table 1 shows the distribution of characteristics between individuals with positive and negative RT-PCR tests in the study population and among matched cases and controls. Individuals receiving positive RT-PCR tests in the study population had more documented comorbidities, while the proportion of individuals with previous COVID-19-like illness was very low. Among those who received at least one dose of vaccine before their RT-PCR sample collection date, the average time from first dose to sample collection date was 23 days among cases and 24 days among controls (see Figure S3 for full distribution of timing of RT-PCR sample collection relative to vaccination).

Vaccine effectiveness

Adjusted effectiveness of the two-dose schedule was 41.6% (95% CI 26.9 to 53.3) in the period ≥14 days after administration of the second dose (Table 2). In the period 0-13 days after administration of the second dose, adjusted vaccine effectiveness was low (18.2%, 95% CI 0.0 to 33.2). There was no association between vaccination with a single dose and symptomatic SARS-CoV-2 infection.

Vaccine effectiveness increased with increasing time after vaccination, plateauing at 49.4% (95% CI 26.9 to 65.0) at 21 days following the second dose. A single dose was 38.0% effective (95% CI 14.1 to 55.3) at preventing symptomatic COVID-19 in the period starting 28 days after the first dose (supplementary Figure 4).

Adjusted vaccine effectiveness in the period ≥14 days after the 2nd dose declined with increasing age and was 61.8% (95% CI 34.8 to 77.7), 48.9% (95% CI 23.3 to 66.0) and 28.0% (95% CI 0.6 to 47.9) among individuals 70-74, 75-79 and ≥80 years of age, respectively ($p_{interaction}$ = 0.05)(Figure 3). Vaccine effectiveness was lower among individuals with reported diabetes but not significantly different from

those without reported diabetes (VE 26.9% vs. 45.6% , $p_{interaction}$ = 0.12). Vaccine effectiveness did not differ among sub-groups with difffering sex, numbers of comorbidities, reported cardiovascular disease, or regions of residence (Table S2).

Discussion

This test-negative case-control study estimated effectiveness of 41.6% (95% CI 26.9 to 53.3) against symptomatic COVID-19 of a two-dose schedule of CoronaVac in an elderly population during a period of widespread P.1 transmission. This estimate is consistent with the results from a randomized controlled trial conducted among healthcare workers in Brazil, which estimated efficacy of 50.7% (95% CI 35.6 to 62.2) against symptomatic COVID-19 and 83.7% (95% CI 58.0 to 93.7) against symptomatic COVID-19 requiring medical assistance.[4] However, we have addressed several key evidence gaps in the understanding of the effectiveness of CoronaVac: 1) the vaccine did not appear to have any effectiveness until 14 days after the second dose in this population; 2) the vaccine was effective in a region and during a time period in which the P.1 variant of concern was 83% prevalent; 3) the vaccine was effective in this population aged 70 years and above, although effectiveness declined with age; and 4) vaccine effectiveness appeared to be maintained among individuals with comorbidities associated with severe COVID-19 outcomes.

Our results provide evidence that the effectiveness of CoronaVac takes weeks to develop and requires a full schedule to achieve maximum effectiveness. This finding has direct implications for public health decisions in countries using CoronaVac and possibly other inactivated vaccines, such as the majority of low-income and middle-income countries. For example, in Brazil, of the 9,972,111 who were vaccinated with CoronaVac, 1,298,194 (13%) have not received the second dose. Because of the need for the completed schedule, it is imperative to keep non-pharmaceutical interventions (NPIs) in place and

advise vaccinated individuals of their reduced protection until a minimum of 14 days after the second dose. Additionally, protection against symptomatic COVID-19 from mass vaccination at the population level will take a prolonged period (Figure 1) compared to other vaccines that showed greater effectiveness after the first dose.[13,23] These findings should be emphasized within the framework of clear communication during the pandemic by public health authorities, strengthening the population confidence in the vaccines.

This study was conducted in a setting with estimated 83% prevalence of the P.1 VOC, suggesting that the effectiveness of CoronaVac is maintained even when transmission of P.1 is widespread. Further studies are required to determine whether effectiveness is different against P.1, but this study provides encouraging evidence that mass vaccination with CoronaVac can be a powerful intervention in other countries experiencing P.1-associated COVID-19 epidemics, such as Chile.

Within this elderly population, we observed a strong decrease in vaccine effectiveness with increasing age, with estimated effectiveness ranging from 61.8% (95% CI 34.8 to 77.7) among 70-74 year olds to 28.0% (95% CI 0.6 to 47.9) among ≥80 year olds. The RCT of CoronaVac in Brazil reported no difference in efficacy among elderly individuals or among individuals with underlying diseases. However, only 5.1% of the trial population was aged over 60. Our result is consistent with real-world studies of other vaccines, which have estimated low vaccine effectiveness in residents of long-term care facilities in Denmark,[24] skilled nursing facilities in the USA,[25] and in individuals ≥80 years in Israel.[26] Our finding of potentially lower effectiveness of this vaccine among elderly individuals with diabetes needs to be further validated. If confirmed, vaccination programs could consider different vaccines or additional doses for some age and risk groups.

This study has limitations that should be acknowledged. We evaluated CoronaVac effectiveness against symptomatic disease, but a detailed evaluation of effectiveness with regards to severity, hospitalization and deaths is needed to inform public health planning. A preliminary aggregated analysis using weekly times series of COVID-19 deaths in Brazil showed a relative decrease among those ≥80 years compared with all ages after the vaccination with CoronaVac and ChAdOx1 in the country,[27] suggesting a discernible impact of vaccination on the most severe outcomes. We could not evaluate the vaccine effectiveness in those with or without previous infection because of the limited number of previously positive individuals by RT-PCR and rapid antigen tests. Previous COVID-19-like illness was less common in those with positive RT-PCR before matching, showing likely some degree of protection of previous infection. The estimated seroprevalence of COVID-19 in the São Paulo State capital (~12million) in those ≥60 years was 19.9% (95% CI, 14.9-29.9) in January 2021 before vaccination.[28] Finally, as this is an observational study, there is likely unmeasured confounding. The "bias-indicator" association between recent vaccination with a single dose 0-13 days before sample collection was close to null, suggesting that vaccinated and unvaccinated individuals did not differ greatly in their underlying risk of testing positive for SARS-CoV-2, independently of vaccination.[12,14] However, this does not preclude time-varying changes in behavior or testing practices following vaccination introducing bias to our effectiveness estimate.

We found that a two-dose schedule of CoronaVac was effective in preventing symptomatic COVID-19 even among elderly individuals and in a setting with extensive P.1 variant transmission. However, the development of protection starting only 14 days after completion of the full schedule, and the declining effectiveness among older age groups, underscores the need to maintain NPIs during mass vaccination with CoronaVac, and to consider prioritizing other vaccines among ≥80 year olds until more data can be gathered on effectiveness against severe outcomes.

Author contributions

All authors conceived the study. OTR and MDTH completed analyses with guidance from JRA, DATC, AIK, and JC. MSST, OTR and MDTH curated and validated the data. OTR and MDTH wrote the first draft of the manuscript. WNA, MA, RS, AMS, BCA, SHHF, CFC provided supervision. All authors contributed to, and approved, the final manuscript. JC is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

Deidentified databases as well as the R codes will be deposited in the repository https://github.com/juliocroda/VebraCOVID-19

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Figure 1. Incidence of reported COVID-19, vaccination coverage, and prevalence of variants of concern from Oct 1, 2020 to April 29, 2021 in São Paulo State, Brazil.

Panel A shows the 14-day rolling average of daily age group-specific incidence of reported COVID-19 (cases per 100,000 population). Panels B, C and D show daily cumulative vaccination coverage amongst the age groups ≥90, 80-89 and 70-79 years, respectively. Population estimates for age groups were obtained from national projections for 2020.[15] Panel E shows the monthly prevalence of P.1, P.2 and B.1.1.7 variants among genotyped SARS-CoV-2 isolates in the GISAID database (extraction on May 12th 2021).[11] Vertical bars, from left to right in each panel, show the dates that adults ≥90, 80-89 and 70-79 years of age in the general population became eligible for vaccination

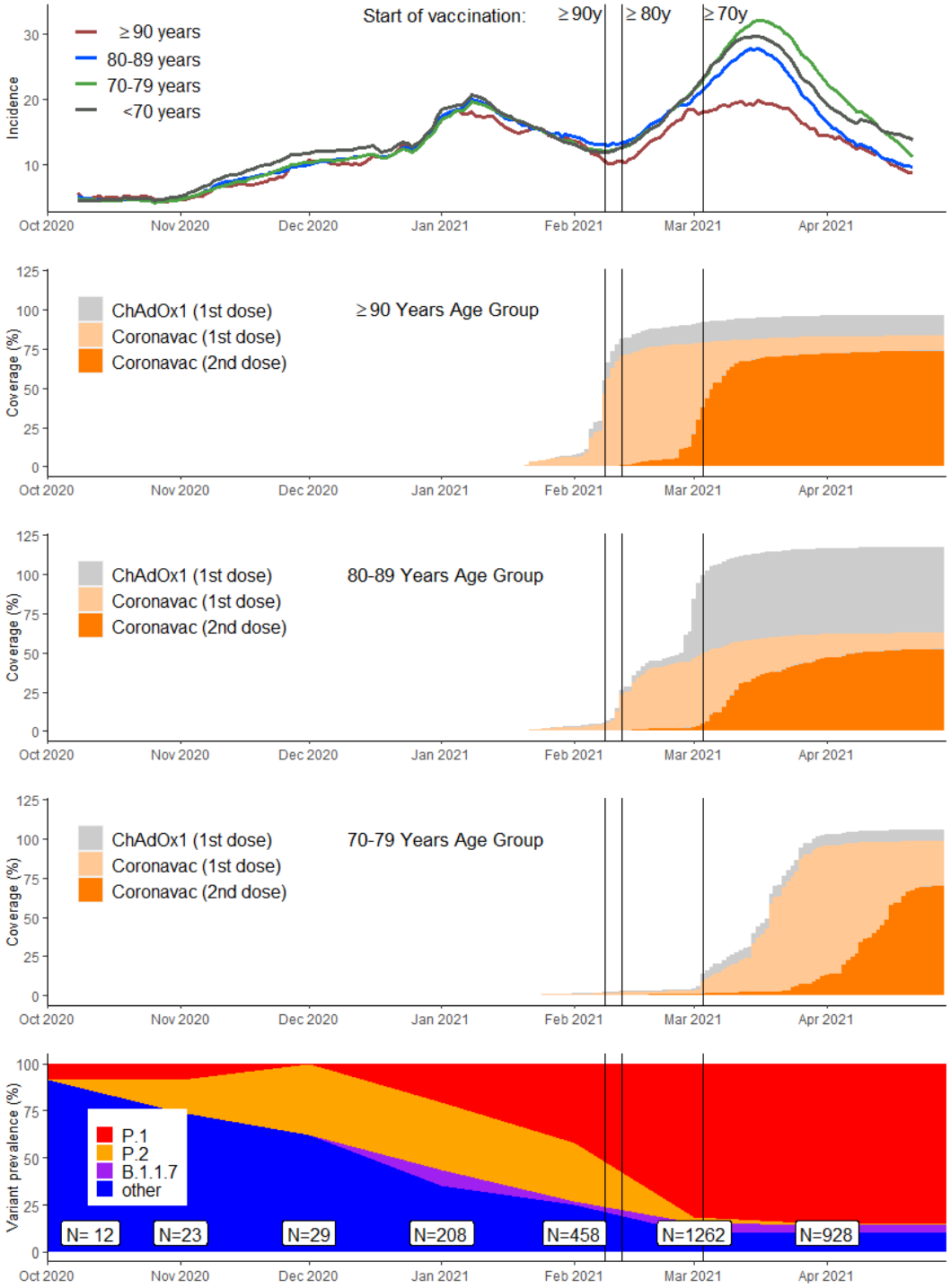


Figure 2. Flowchart for study population identification from surveillance databases, and selection of matched cases and controls.

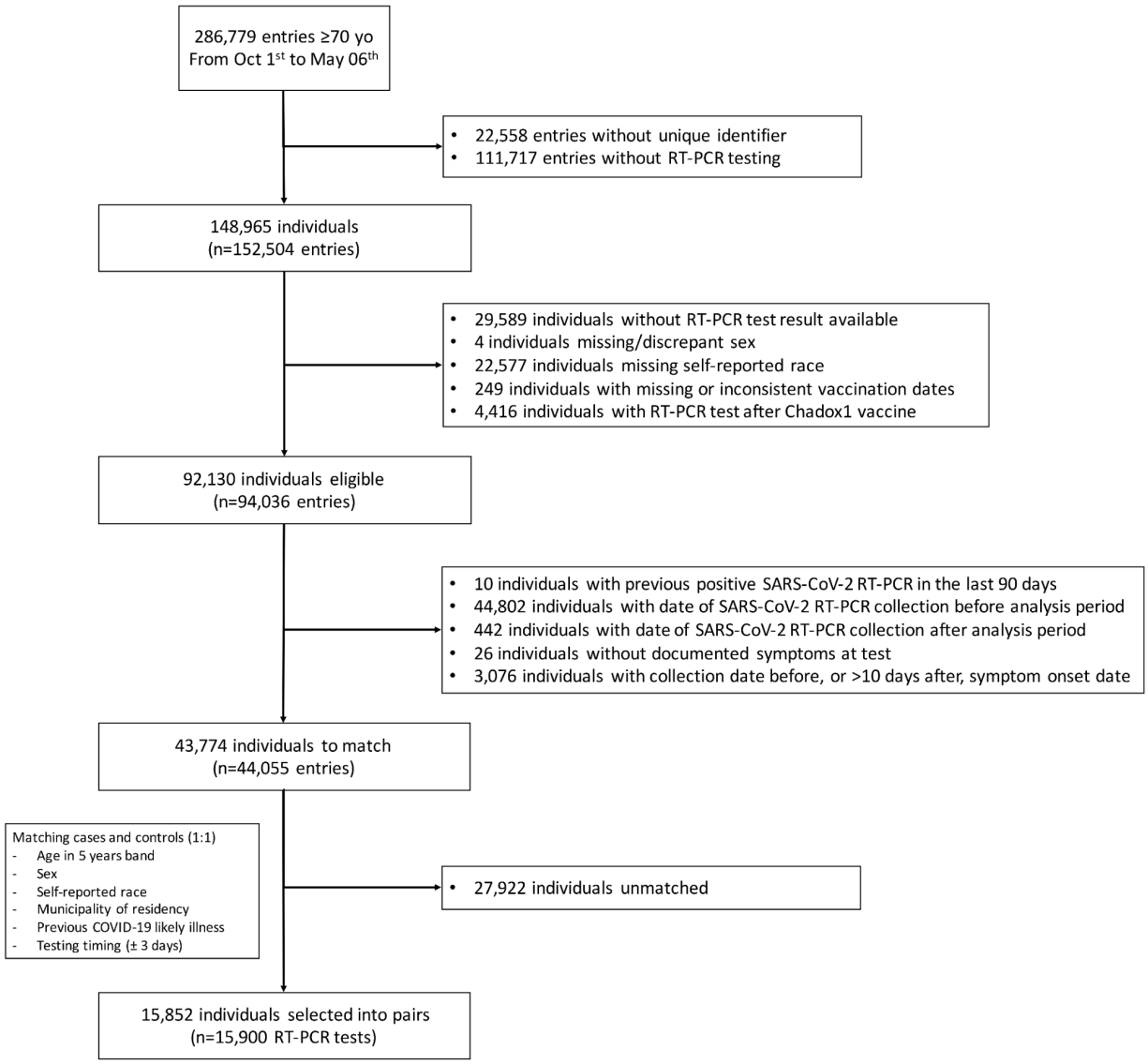


Figure 3. Adjusted vaccine effectiveness during the period ≥14 days after the 2nd CoronaVac dose for subgroups of adults ≥70 years of age.

These estimates are adjusted vaccine effectiveness for the period ≥14 days after the second CoronaVac dose in a conditional logistic regression model adjusted by age (continuous) and number of comorbidities and with an interaction term between the category of interest and the term for period ≥14 days after the second CoronaVac dose.

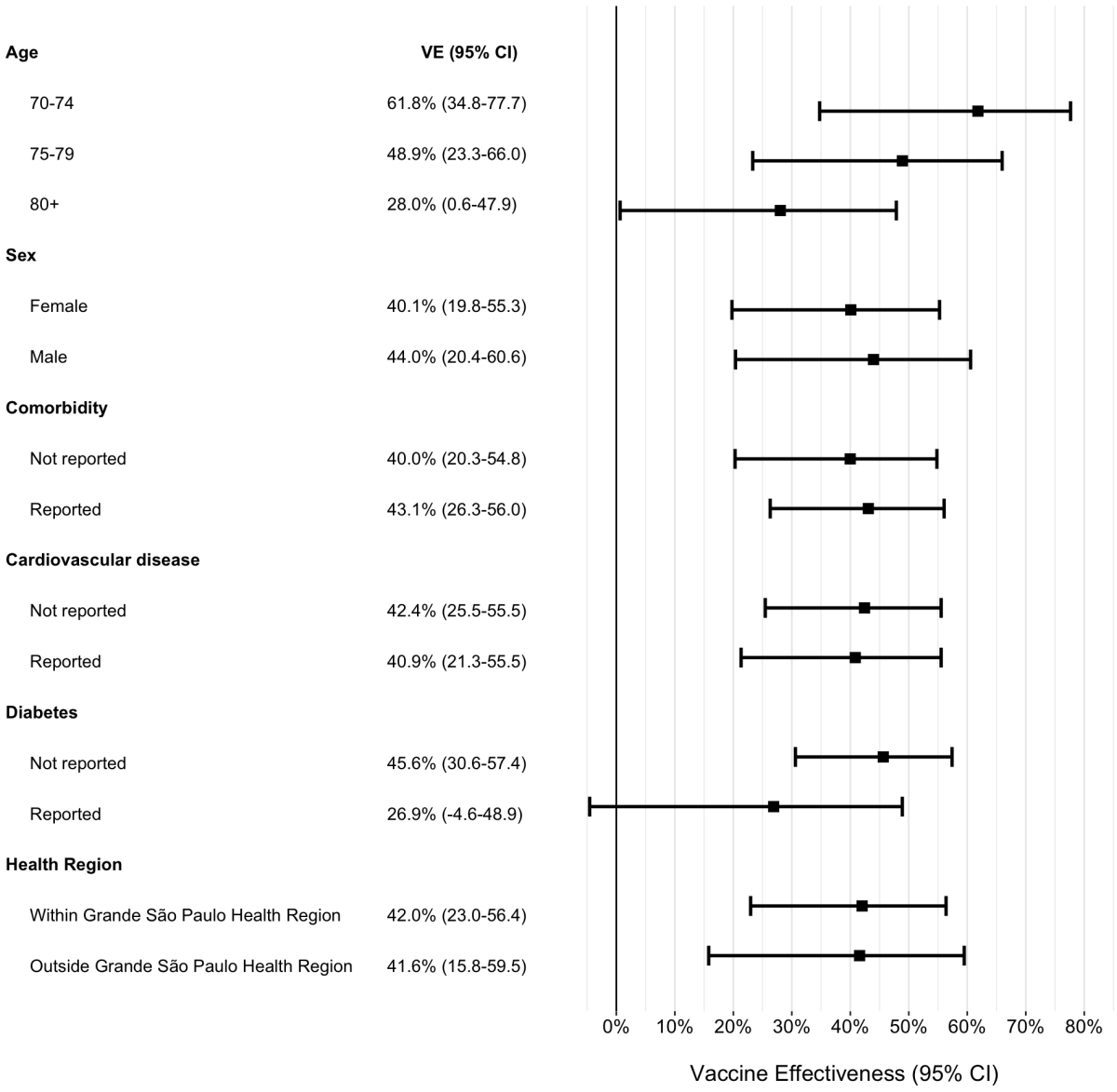


Table 1. Characteristics of adults ≥70 years of age who were eligible for matching and selected into case-test negative pairs.

	Eligible cases and controls		Matched pairs	
Characteristics*	**Test-negative (n=17,622)**	**Test-positive (n=26,433)**	**Controls (n=7,950)**	**Cases (n=7,950)**
Demographics				
Age, mean (SD), years	77.53 (6.78)	76.71 (6.19)	76.15 (5.84)	76.15 (5.82)
Age categories, n (%)				
70-79 years	12,123 (68.8)	19,673 (74.4)	6,150 (77.4)	6,150 (77.4)
80-89 years	4,301 (24.4)	5,437 (20.6)	1,510 (19.0)	1,510 (19.0)
≥90 years	1,198 (6.8)	1,323 (5.0)	290 (3.6)	290 (3.6)
Male sex, n (%)	7,689 (43.6)	12,431 (47.0)	3,276 (41.2)	3,276 (41.2)
Self-reported race[†], n (%)				
White/Branca	13,415 (76.1)	19,796 (74.9)	6,420 (80.8)	6,420 (80.8)
Brown/Pardo	3,192 (18.1)	4,983 (18.9)	1,301 (16.4)	1,301 (16.4)
Black/Preta	785 (4.5)	1,258 (4.8)	191 (2.4)	191 (2.4)
Yellow/ Amarela	226 (1.3)	390 (1.5)	38 (0.5)	38 (0.5)
Indigenous/Indigena	4 (0.0)	6 (0.0)	-	-
Residence in “Grande São Paulo” Health Region, n (%)	12,381 (70.3)	16,538 (62.6)	4,259 (53.6)	4,259 (53.6)
Comorbidities				

Reported number‡, n (%)				
None	10,027 (56.9)	12,668 (47.9)	4,510 (56.7)	3,564 (44.8)
One or two	6,984 (39.6)	12,548 (47.5)	3,151 (39.6)	3,994 (50.2)
Three or more	611 (3.5)	1,217 (4.6)	289 (3.6)	392 (4.9)
Cardiovascular disease , n (%)	5,293 (30.0)	10,079 (38.1)	2,375 (29.9)	3,252 (40.9)
Diabetes, n (%)	3,233 (18.3)	6,533 (24.7)	1,314 (19.0)	2,092 (26.3)
Prior SARS-CoV-2 exposure				
Reported COVID-19-like illness**, n (%)	685 (3.9)	354 (1.3)	35 (0.4)	35 (0.4)
SARS-CoV-2 viral test result** ††, n (%)	66 (0.4)	13 (0.0)	1 (0.0)	4 (0.1)
Vaccination status				
Not vaccinated, n (%)	11,986 (68.0)	17,233 (65.2)	5,485 (69.0)	5,561 (69.9)
Single dose, within 0-13 days, n (%)	1,446 (8.2)	2,976 (11.3)	747 (9.4)	762 (9.6)
Single dose, ≥14 days, n (%)	1,797 (10.2)	3,312 (12.5)	843 (10.6)	851 (10.7)
2nd dose, within 0-13 days, n (%)	1,041 (5.9)	1,533 (5.8)	437 (5.5)	421 (5.3)
2nd dose, ≥14 day, n (%)	1,352 (7.7)	1,379 (5.2)	438 (5.5)	355 (4.5)
Interval between 1st and 2nd dose, mean (SD), days	25 (6)	30 (12)	25 (6)	29 (11)
Interval between 1st dose and RT-PCR testing, mean (SD), days	28 (19)	23 (16)	24 (17)	23 (16)
Interval between 2nd dose and RT-PCR testing, mean (SD), days	20 (15)	17 (14)	18 (15)	17 (14)

*Continuous variables displayed as mean (SD), categorical variables displayed as n (%)

[†]Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e Estatísticas) https://biblioteca.ibge.gov.br/visualizacao/livros/liv63405.pdf

[‡]Comorbidities included: cardiovascular, renal, neurological, haematological, or hepatic comorbidities, diabetes, chronic respiratory disorder, obesity, or immunosuppression

[**]Prior to the start of the study on 17 January, 2021.

** Reported illness with COVID-19 associated symptoms in the eSUS and SIVEP-Gripe databases between 1 February, 2020 and 16 January, 2021.

[††] Defined as SARS-CoV-2 RT-PCR or antigen detection.

Table 2: Effectiveness of CoronaVac against symptomatic COVID-19 in adults ≥70 years of age.

	OR (95% CI)	VE (95% CI)	p-value
Unadjusted Analysis			
Single dose, within 0-13 days vs. unvaccinated*	0.97 (0.85-1.12)	2.7% (-11.7-15.3)	0.70
Single dose, ≥14 days vs. unvaccinated*	0.91 (0.78-1.05)	9.5% (-5.3-22.3)	0.20
2nd dose, within 0-13 days vs. unvaccinated*	0.81 (0.66-0.98)	19.5% (1.9-34)	0.03
2nd dose, ≥14 days vs. unvaccinated*	0.60 (0.48-0.74)	40.5% (25.8-52.3)	<0.001
Adjusted analysis			
Single dose, within 0-13 days vs. unvaccinated*	0.98 (0.85-1.12)	2.5% (-12.2-15.3)	0.72
Single dose, ≥14 days vs. unvaccinated*	0.90 (0.77-1.04)	10.5% (-4.4-23.3)	0.16
2nd dose, within 0-13 days vs. unvaccinated*	0.82 (0.67-1.00)	18.2% (0.0-33.2)	0.05
2nd dose, ≥14 days vs. unvaccinated*	0.58 (0.47-0.73)	41.6% (26.9-53.3)	<0.001
Age, years	1.00 (0.98-1.02)	-	0.90
Number of comorbidities†			
One-Two vs. None	1.65 (1.54-1.76)	-	<0.001

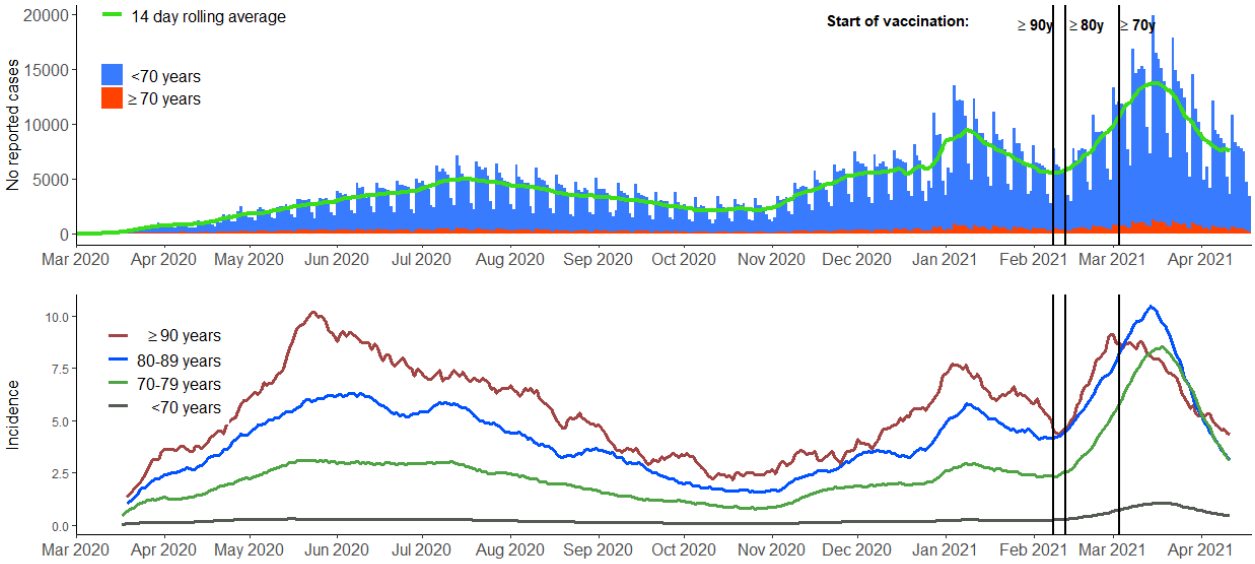
Three or more vs. None	1.74 (1.48-2.05)	-	<0.001

*At date of index sample collection for cases and controls

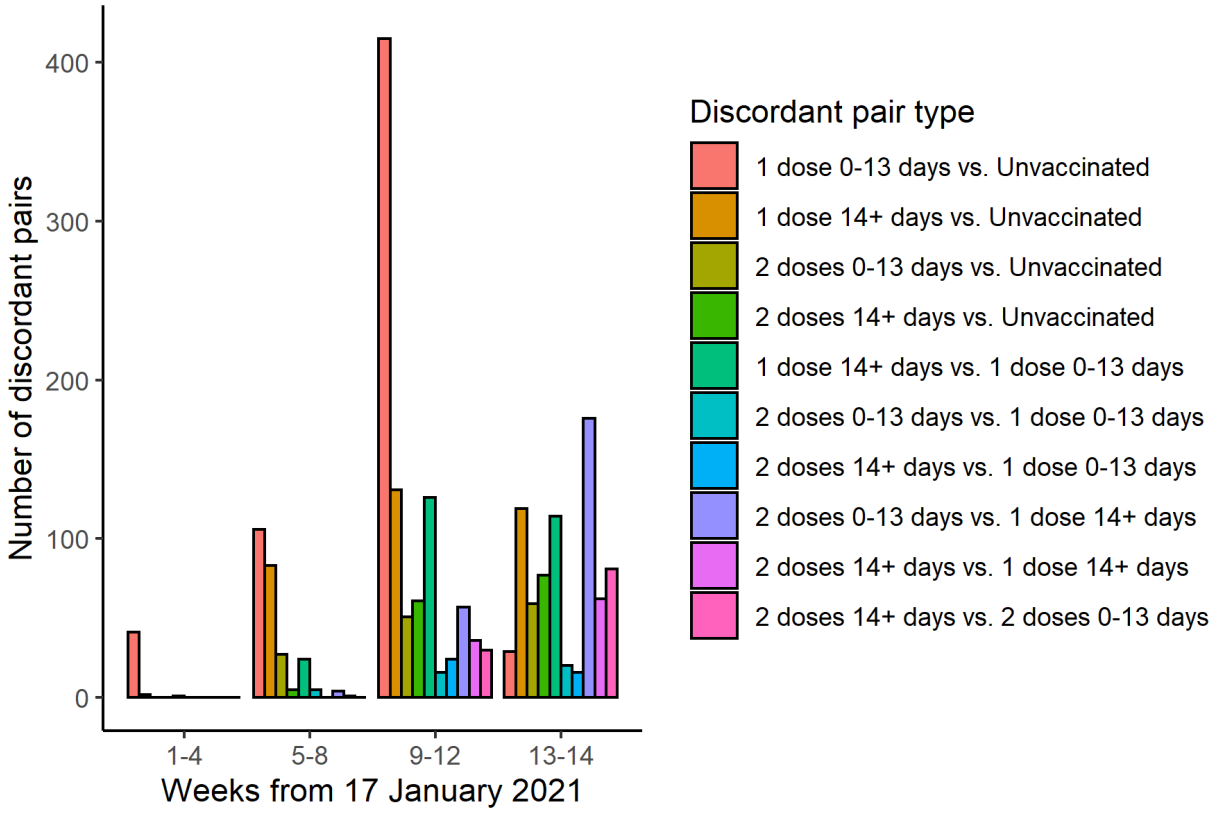
† Comorbidities included: cardiovascular, renal, neurological, haematological, or hepatic comorbidities, diabetes, chronic respiratory disorder, obesity, or immunosuppression

Supplementary appendix

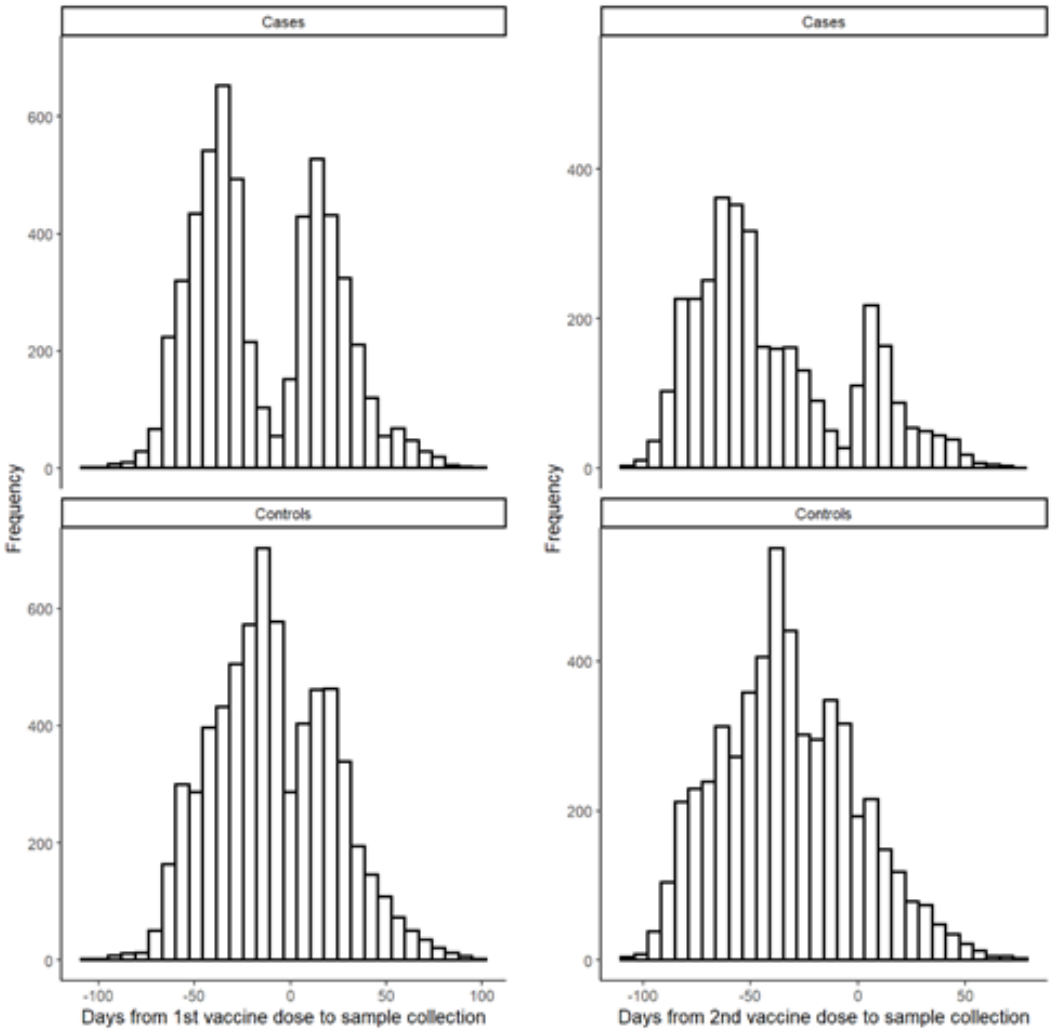
Supplementary Figure 1. Daily cases (Panel A) and incidence (Panel B, per 100,000 population) of reported COVID-19 from Mar 15, 2020 to Apr 29, 2021 in São Paulo State, Brazil. Green lines in Panel A and lines in Panel B show the 14-day rolling average of daily counts and incidences, respectively. Population estimates for age groups were obtained from national projections for 2020.[15] Vertical bars, from left to right in each panel, show the dates that adults ≥90, 80-89 and 70-79 years of age in the general population became eligible for vaccination.



Supplementary Figure 2. Timing of enrolment of discordant case-control pairs by vaccination category



Supplementary Figure 3. Timing of RT-PCR sample collection date relative to 1st (left column) and 2nd (right column) vaccine dose date, among cases (top row) and controls (bottom row) who were vaccinated during the study period.



Supplementary Table 1. Distribution of concordant and discordant matched case-control pairs.

	Cases				
Controls	Unvaccinated	Single dose, dose 1 within 0-13 days	Single dose, dose 1 ≥14 days	Two doses, dose 2 within 0-13 days	Two doses, dose 2 ≥14 days
Unvaccinated	4,920	290	168	55	52
Single dose, dose 1 within 0-13 days	301	286	131	15	14
Single dose, dose 1 ≥14 days	167	134	379	119	44
Two doses dose 2 within 0-13 days	82	26	118	166	45
Two doses, dose 2 ≥14 days	91	26	55	66	200

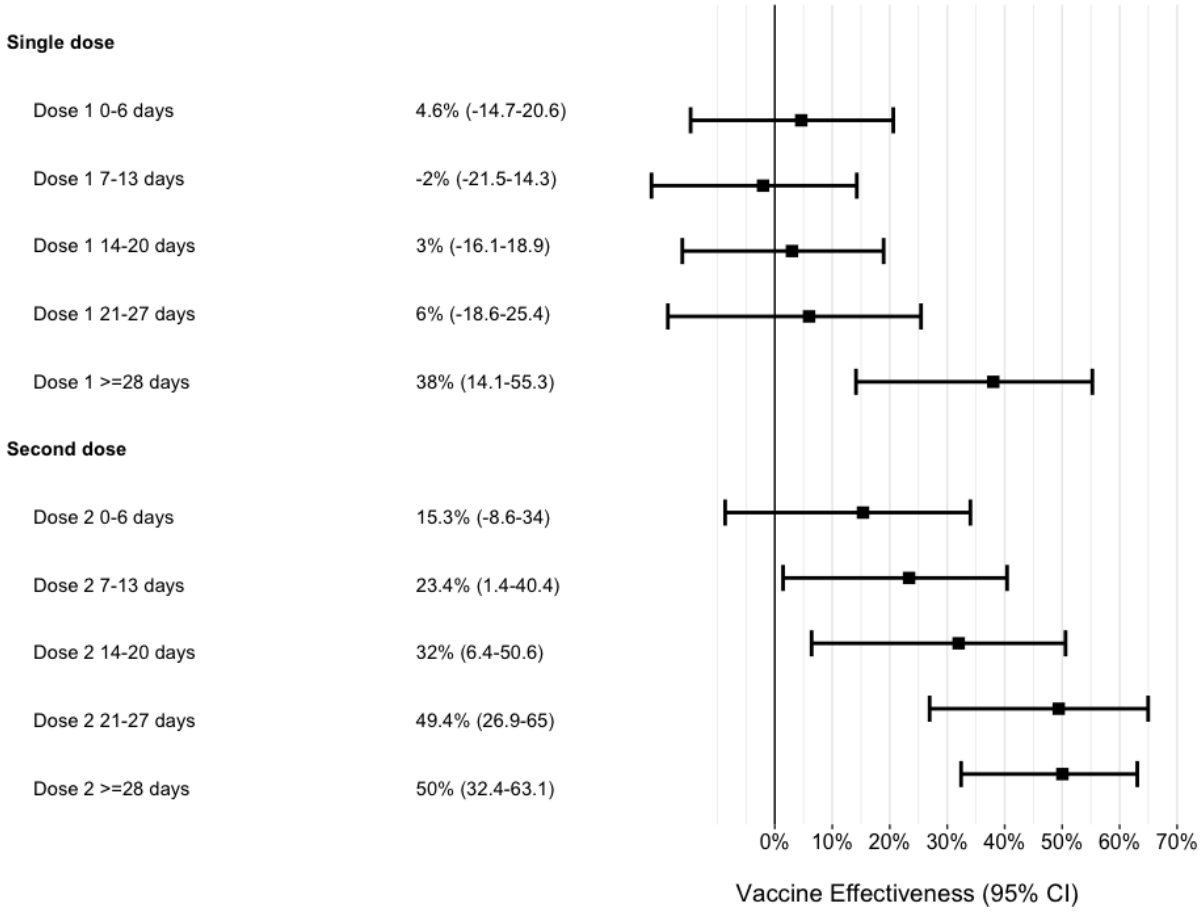
Supplementary Table 2. Estimated effectiveness of CoronaVac, according to time intervals after administration of single dose and 2nd dose, in subgroups of adults ≥70 years of age. All models are adjusted by age (continuous) and number of comorbidities, and include an interaction term between the subgroup of interest and vaccinations with 2 doses, ≥14 days after 2nd vaccine dose.

Variable	Adjusted OR (95% CI)	Adjusted VE (95% CI)	p-value for interaction
Age			
70-74 (n=8,178)			
≥14 days after 2nd vaccine dose	0.38 (0.22-0.65)	61.8% (34.8-77.7)	
75-79 (n=4,122)			
≥14 days after 2nd vaccine dose	0.51 (0.34-0.77)	48.9% (23.3-66.0)	0.05
80+ (n=3,600)			
≥14 days after 2nd vaccine dose	0.72 (0.52-0.99)	28.0% (0.60-47.9)	
Sex			
Females (n=9,348)			
≥14 days after 2nd vaccine dose	0.60 (0.45-0.80)	40.1% (19.8-55.3)	
Males (n=6,552)			0.85
≥14 days after 2nd vaccine dose	0.56 (0.39-0.80)	44.0% (20.4-60.6)	
Comorbidities			
No reported (n=8,074)			
≥14 days after 2nd vaccine dose	0.60 (0.45-0.80)	40.0% (20.3-54.8)	
Reported (n=7,826)			0.81
≥14 days after 2nd vaccine dose	0.57 (0.44-0.74)	43.1% (26.3-56.0)	
Cardiovascular disease			
No reported (n=10,273)			0.86

≥14 days after 2nd vaccine dose	0.58 (0.45-0.75)	42.4% (25.5-55.5)	
Reported (n=5,627)			
≥14 days after 2nd vaccine dose	0.59 (0.45-0.79)	40.9% (21.3-55.5)	
Diabetes			
No reported (n=12,294)			
≥14 days after 2nd vaccine dose	0.54 (0.43-0.69)	45.6% (30.6-57.4)	0.12
Reported (n=5,627)			
≥14 days after 2nd vaccine dose	0.73 (0.51-1.05)	26.9% (-4.6-48.9)	
Health regional area			
“Grande São Paulo” (n=7,382)			
≥14 days after 2nd vaccine dose	0.58 (0.44-0.77)	42% (23.0-56.4)	
Not “Grande São Paulo” (n=8,518)			0.66
≥14 days after 2nd vaccine dose	0.58 (0.41-0.84)	41.6% (15.8-59.5)	

Supplementary Figure 4. Adjusted vaccine effectiveness of CoronaVac for adults ≥70 years of age according to the extended time period after the first and second doses.

Adjusted by age (continuous term) and number of comorbidities on a conditional logistic regression model.



PROTOCOL

Evaluation of Vaccine Effectiveness in Brazil against COVID-19 (VEBRA-COVID) Sub-Study: A Test-Negative Case-Control Study on the Effectiveness of COVID-19 Vaccines amongst the General Population of São Paulo State in Brazil

Version: 01.3 / April 30th 2021

Table 1. Protocol Revisions

Changes in Version 1.3	Justification
Addition of ChAdOx1 exposure times	We added the time windows following the first and second doses of ChAdOx1 to be 0-13 days, 14-27 days and ≥28 days
Revised expected vaccine effectiveness	In the VEBRA-COVID analysis of the elderly (≥70 years of age) in São Paulo, we aimed to answer the research question of whether vaccines had a real-world effectiveness of public health value rather than whether they had a real-world effectiveness that was consistent with efficacy estimates from RCTs. Thus, we powered the study for a real world effectiveness above a lower threshold of 40%, below which the value of the vaccination would require reconsideration.
Change of matching criteria from CEP (5 digits) to Municipality and self-reported race	We based this decision on three main reasons: 1 – A great proportion of municipalities in São Paulo State has a unique CEP (zipcode), so everyone in that municipality has the same CEP. For these municipalities, we would lose within municipality socioeconomic information 2 – We observed a larger proportion of invalid CEPs mainly in the e-SUS database compared with the SIVEP-Gripe database, which may introduce potential bias since SIVEP-Gripe has a higher proportion of severe COVID-19 cases 3 – A significant number of unique CEPs were inconsistently placed in more than one municipality.
Addition of outcomes for the cohort analysis of test-positive cases	We added ICU admission and respiratory support, occurring within 21 days of initial SARS-CoV-2 test positivity. We also changed hospitalization from occurring within 14 days to within 21 days of initial SARS-CoV-2 test positivity.

I. Background

Since the emergence of severe acute respiratory virus coronavirus 2 (SARS-CoV-2), Brazil has experienced one of the world's highest incidence and mortality rates in the world, with over 13 million reported infections as of the middle of April 2021.[1–3] São Paulo, the most populous state in Brazil (~ 46 million inhabitants), is the state with highest number of cases and deaths: 2,827,833 cases and 92,548 deaths as by April 24th 2021.[4] Variants of Concern (VOC) also had a key role on the recent several surges in Brazil and São Paulo State. The P.1 VOC, which was first detected in Manaus on Jan 12, 2021, [5–7] and now consists the majority of new infections, being dominant in several states in Brazil. P1. has accrued mutations associated with decreased neutralization,[8,9] and has since spread throughout Brazil, synchronizing the epidemic in country in a scenario of relaxed non-pharmacological interventions.

The rapid development of novel vaccines against COVID-19 allowed countries to start vaccine distribution programs within a year of the identification of the novel virus. Among the first vaccines to be developed was Sinovac's CoronaVac vaccine.[10–12] Phase III trials were conducted in Turkey, Chile, Singapore and Brazil. The Brazilian trial was conducted among a study population of healthcare professionals, and reported that the effectiveness of CoronaVac after 14 days following completion of a two dose schedule was 50.7% (95% CI 36.0-62.0) for all symptomatic cases of COVID-19, 83.7% (95% CI 58.0-93.7) for cases requiring medical attention, and 100% (95% CI 56.4-100) for hospitalized, severe, and fatal cases.[12] CoronaVac was approved for emergency use on 17 January in Brazil, and used to vaccinate healthcare workers and the general population. AstraZeneca-Oxford's ChAdOx1 vaccine[13,14] was approved on the same day and was administered beginning on 23 January 2021. In Brazil, ChAdOx1 schedule is for 12 weeks between first and second dose.

As vaccine programs continue, there has been much interest in estimation of vaccine effectiveness through observational studies, and specifically in settings where VOC are circulating. Such studies have advantages over clinical trials, including increased size and follow-up time, and reduced cost. However, as vaccinated and unvaccinated individuals are likely different in their SARS-CoV-2 risk and healthcare access, these studies must address bias through design and analysis. Several studies have demonstrated the effectiveness of COVID-19 vaccines against infection caused by the B.1.1.7 variant.[15] However, large-scale real-world investigations on vaccine effectiveness have not been conducted in regions where the P.1 variant is prevalent.

We propose a test-negative case-control study[16,17] of the general population from the São Paulo State to evaluate the effectiveness of COVID-19 vaccines in preventing symptomatic disease in a setting of widespread P.1 VOC transmission.[6] The study will initially evaluate the effectiveness of COVID-19 vaccines, CoronaVac and ChAdOx1 amongst the population with age ≥70 years, since the vaccination campaign prioritized this age group in its first months. We will expand the study population as additional age groups become eligible for vaccination. Furthermore, we expect that additional vaccines will be approved and will evaluate their effectiveness. We will therefore continue to amend the protocol and its objectives accordingly to address these new questions.

II. Objectives

To estimate the effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection amongst the general population from the São Paulo State. Our initial analyses will focus on estimating vaccine effectiveness in the age group of ≥70 years.

III. Methods

1. Study Design: We will conduct a retrospective matched case-control study, enrolling cases who test positive for SARS-CoV-2 and controls who test negative for SARS-CoV-2 amongst the general population (Section 3) as of the day that the COVID-19 vaccination campaign was initiated at the study sites. The study will evaluate vaccine effectiveness on the primary outcome of symptomatic SARS-CoV-2 infection. We will identify cases and matched controls by extracting information from health surveillance records and ascertain the type and data of vaccination by reviewing the state COVID-19 vaccination registry. In this design, one minus the odds ratio (1-OR) of vaccination comparing cases and controls estimates the direct effect of vaccination on the disease outcome. In a separate

analysis, we will assess the association between vaccination and hospitalization and/or death among individuals who have tested positive for SARS-CoV-2.

2. IRB and Ethics Statement: The protocol has been submitted to the Ethical Committee for Research of Federal University of Mato Grosso do Sul (CAAE: 43289221.5.0000.0021). The work of investigators at the University of Florida, Yale University, Stanford University, and Barcelona Institute for Global Health was conducted to inform the public health response and was therefore covered under Public Health Response Authorization under the US Common Rule.

Study Details

Study Site: The State of São Paulo (23°3′S, 46°4'W) is the most populous state in Brazil: an estimated population of 46,289,333 in 2020. São Paulo State has 645 municipalities and its capital, São Paulo city, has 12 million inhabitants. São Paulo State reported 2,827,833 COVID-19 cases (cumulative incidence rate: 6,109 per 100,000 population) and 92,548 deaths (cumulative mortality: 200 per 100,000 population), by 24/04/2021. The State Secretary of Health of Sao Paulo (SES-SP) initiated its COVID-19 vaccination campaign on 17 January 2021 and is administering two vaccines, CoronaVac and ChAdOx1. As of 24 April 2021, 10.7 million doses (6.9 million first doses and 3.8 million second doses) have been administered in the State.

Data Sources and Integration: We will identify eligible cases and controls from the State of São Paulo who test positive and negative, respectively, from the *state laboratory testing registry* of public health laboratory network; 2) Determine vaccination status from *state vaccination registries*; and 3) Extract information from *national healthcare and surveillance databases* that will be used to define outcomes, match controls to cases, determine vaccination status, serve as covariates for post-stratification and provide a source for cross-validation of information from databases. Registries are not available which enables constructing a cohort of people eligible for vaccination in the general population. Data sources for this study will include:

- State laboratory testing registry (**GAL**) of the network of public health laboratories
- State COVID-19 vaccination registry (**Vacina Já**)
- National surveillance database of severe acute respiratory illnesses (**SIVEP-Gripe**) created by Ministry of Health Brazil in 2009
- National surveillance system of suspected cases of COVID-19 (**e-SUS**) from mild to moderate "influenza like illness", created by the Ministry of Health Brazil in 2020

The databases will be integrated by the São Paulo State Government – PRODESP - using CPF numbers (Brazilian citizens' unique identifier code) and send to the VEBRA-COVID group anonymized. The database will be updated on a bi-weekly basis.

Study Population

Inclusion criteria:

- Has a residential address in the State of São Paulo,
- Eligible to receive a COVID-19 vaccine based on age,
- With complete information, which is consistent between databases, on age, sex, and residential address
- With consistent vaccination status and dates for those who were vaccinated.

Exclusion criteria:

- Does not have a residential address in the State of São Paulo,
- Not eligible to receive a COVID-19 vaccine based on age,
- With missing or inconsistent information on age, sex, or city of residence
- With existing but inconsistent vaccination status or dates.

Case definition and eligibility: We will use information from integrated GAL/SIVEP-Gripe/e-SUS databases to identify cases that are defined as eligible members of the study population (as defined above, Study Population) who:

- Had a sample with a positive SARS-CoV-2 RT-PCR, which was collected between January 17, 2021 and 7 days prior to database extraction of information
- Did not have a positive RT-PCR test in the 90 day period preceding the index positive RT-PCR result
- Have complete and consistent data on SARS-CoV-2 RT-PCR test results

Control definition and eligibility: We will use integrated GAL/SIVEP-Gripe/e-SUS databases to identify eligible controls. Controls are defined as eligible members of the study population who:

- Had a sample with a negative SARS-CoV-2 RT-PCR result, which was collected after January 17, 2021,
- Did not have a positive RT-PCR test in the 90 day period preceding the index positive RT-PCR result
- Did not have a subsequent positive RT-PCR test in the 7-day period following the index positive RT-PCR result
- Have complete and consistent data on SARS-CoV-2 PCR test result

When studying each vaccine, individuals that received another vaccine are eligible for selection as a case and/or control until the day they receive their vaccine, i.e. we will consider test positive and test negative cases for RT-PCR collected before the day of receipt of the other vaccine.

Matching: Test-negative controls will be matched 1:1 to the cases. We chose the matching factors to balance the ability to reduce bias and to enroll sufficient case-control pairs. Matching factors will include variables that are anticipated to be causes of the likelihood of receiving the vaccine, risk of infection and likelihood of receiving PCR testing for SARS-CoV-2 (see Figures 1-5):

- Age, categorized as 5-years age bands (e.g., 70-74, 75-79 years),
- Sex,
- Municipality,
- Self-reported race,
- Window of ±3 days between collection of RT-PCR positive respiratory sample for cases and collection of RT-PCR negative respiratory sample for controls. If the date of respiratory sample collection is missing, the date of notification of testing result will be used.

We will use the standard algorithms to conduct matching which include: 1) setting a seed, 2) locking the database, 4) creating a unique identifier for matching after random ordering, 5) implementing exact matching based on matching variables, sampling controls at random if more than one available per case within strata.

An individual who fulfils the control definition and eligibility and later has a sample tested that fulfils the case definition and eligibility can be included in the study as both a case and a control. An individual who fulfils the control definition for multiple different sample collection dates can be included in the study as a control for each collection date, up to a maximum of three times.

Exposure definition:
CoronaVac vaccination:

- Received the first vaccine dose, and not having received a second dose, in the following time periods relative to sample collection for their PCR test:
  - 0-13 days
  - ≥14 days
- Received the second dose in the following time periods relative to sample collection for their PCR test:
  - 0-13 days
  - ≥14 days

ChAdOx1vaccination:

- Received the first vaccine dose, and not having received a second dose, in the following time periods relative to sample collection for their PCR test:

  - 0-13 days
  - 14-27 days
  - ≥28 days

- Received the second dose in the following time periods relative to sample collection for their PCR test:
  - 0-13 days
  - ≥14 days

Statistical Analyses: We will evaluate the effectiveness of CoronaVac and ChAdOx1for the following SARS-CoV-2 infection outcomes:

- Primary: Symptomatic COVID-19, defined as one or more reported COVID-19 related symptom with onset within 0-10 days before the date of their positive RT-PCR test

- Secondary:
  - COVID-19 associated hospitalization within 21 days of the symptom onset
  - COVID-19 associated ICU admission within 21 days of the symptom onset
  - COVID-19 associated respiratory support
  - COVID-19 associated death within 28 days of symptom onset

We will evaluate vaccine effectiveness for the primary outcome according to the test-negative design. Table 1 shows a list of all planned analyses in the test-negative design. The test-negative design may introduce bias when evaluating outcomes of hospitalizations and deaths during an epidemic. We will therefore perform time to event/logistic regression analysis of test positive cases to evaluate the association of vaccination status and the risk for hospitalization, ICU admission, COVID-19 respiratory support, and death after infection.

Our initial analyses will focus on estimating vaccine effectiveness in the population with age ≥70 years of age who were the initial priority group of the COVID-19 vaccination campaign.

Case-control analysis: Analyses of the primary outcome will be restricted to case and control pairs who are matched based on the presence of a COVID-19 related symptom before or at the time of testing.

We will use conditional logistic regression to estimate the odds ratio (OR) of vaccination among cases and controls, accounting for the matched design, where 1-OR provides an estimate of vaccine effectiveness under the standard assumptions of a test-negative design. For the CoronaVac analysis, the reference group will be individuals who have not received a first dose of CoronaVac by the date of respiratory sample collection. For the ChAdOx1 analysis, the reference group will be individuals who have not received a first dose of ChAdOx1by the date of respiratory sample collection. Date of notification of the testing result will be used if the date of respiratory sample collection is missing. To evaluate potential biases and the timing of vaccine effectiveness after administration, we will evaluate the windows of vaccination status corresponding: A) 0-13 days and ≥14 days after the 1st dose and 0-13 days and ≥14 days after the 2nd dose of CoronaVac; and B) 0-13 days, 14-27 days and ≥28 after the 1st dose and0-13 days and ≥14 days after the 2nd dose of ChAdOx1.

We will include the following covariates in the adjusted model, which we hypothesize are predictive of vaccination, the risk of SARS-CoV-2 infection and COVID-19 severity and healthcare access and utilization:

- Age as continuous variable
- Comorbidities (None, 1-2, ≥3 comorbidities)
- Evidence of prior SARS-CoV-2 infection (defined as positive PCR test, antigen test or rapid antibody test)

Although data on comorbidities is available through e-SUS and SIVEP-Gripe, this data may have different degrees of missingness between databases and between cases and control groups. Adjusting for comorbidities using complete case data will likely introduce bias. We will explore the feasibility of multiple imputation of comorbidity in a sensitivity analysis. Additional sensitivity analyses will evaluate potential effect modification of the vaccine effectiveness by history of a positive RT-PCR, antigen or serological test result prior to the vaccination campaign and age subgroups.

Survival/logistic regression analysis of hospitalization, ICU, respiratory support and death: We will perform additional analyses for hospitalization and death amongst individuals who test positive and estimate the hazards according to vaccination status at the date of positive test, adjusting for covariates described in the case-control analyses. Sensitivity analyses will be conducted to evaluate the association of influence of a positive RT-PCR, antigen or serological test result prior to the vaccination campaign.

Sample size calculations and timing of analyses: The power of a matched case-control study depends on the assumed odds ratio and the number of discordant pairs (i.e. pairs in which the case is exposed and the control is unexposed, or vice versa), which is a function of the assumed odds ratio and the expected prevalence of exposure among controls. Moreover, the estimate of the odds ratio for one level of a categorical variable compared to baseline is determined by the distribution of all discordant pairs. As vaccine coverage and incidence are changing over time, the latter in ways we cannot predict, and there is no power formula for this analysis, we will simulate power and enroll individuals until we have reached a target power, which we can assess without analyzing the data. In particular, after determining the number of discordant case-control pairs for each combination of exposure categories, we will randomly assign one of each pair to each relevant exposure type according to a Bernoulli distribution, with the probability determined by the assumed odds ratio comparing the two categories. We will run an unadjusted conditional logistic regression on the simulated dataset to determine the p-value, and estimate the power as the proportion of N=1,000 simulations that return $p<0.05$. Code to perform the power calculation can be found at https://github.com/mhitchings/VEBRA_COVID-19.

Timing of final analyses: We will perform an analysis of the primary outcome upon reaching simulated 80% power to detect vaccine effectiveness of 40% ≥14 days after the second dose for the CoronaVac. For the ChAdOx1, we will perform an analysis of effectiveness of at least one dose upon reaching simulated 80% power to detect vaccine effectiveness of 40% ≥28 days after the first dose. In addition, we will perform an analysis of effectiveness of two doses upon reaching simulated 80% power to detect vaccine effectiveness of 40% ≥14 days after the second dose. We chose a vaccine effectiveness of 40% to address the question of whether vaccination with CoronaVac and ChAdOx achieved a threshold of real-world effectiveness, below which the public health value of vaccination may need to be reconsidered.

Privacy: Only SES-SP, São Paulo State data management had access to the identified dataset to linkage the datasets by name, date of birth, mother's name and CPF. After the linkage, the CPF was encrypted and the de-identified dataset was sent to the team for analysis.

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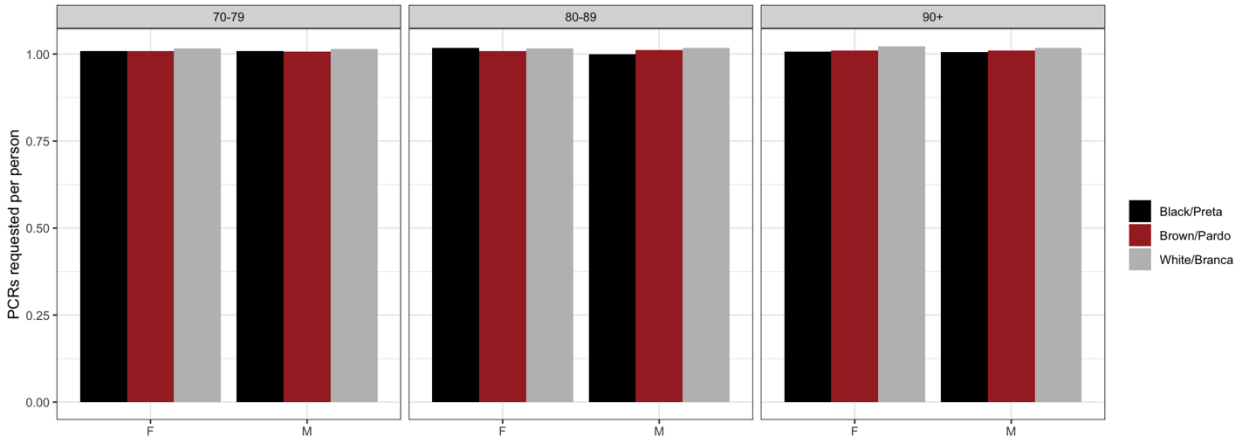


Figure 1: PCR testing rate by age, sex and self-reported race (from data extracted on April 07, 2021)

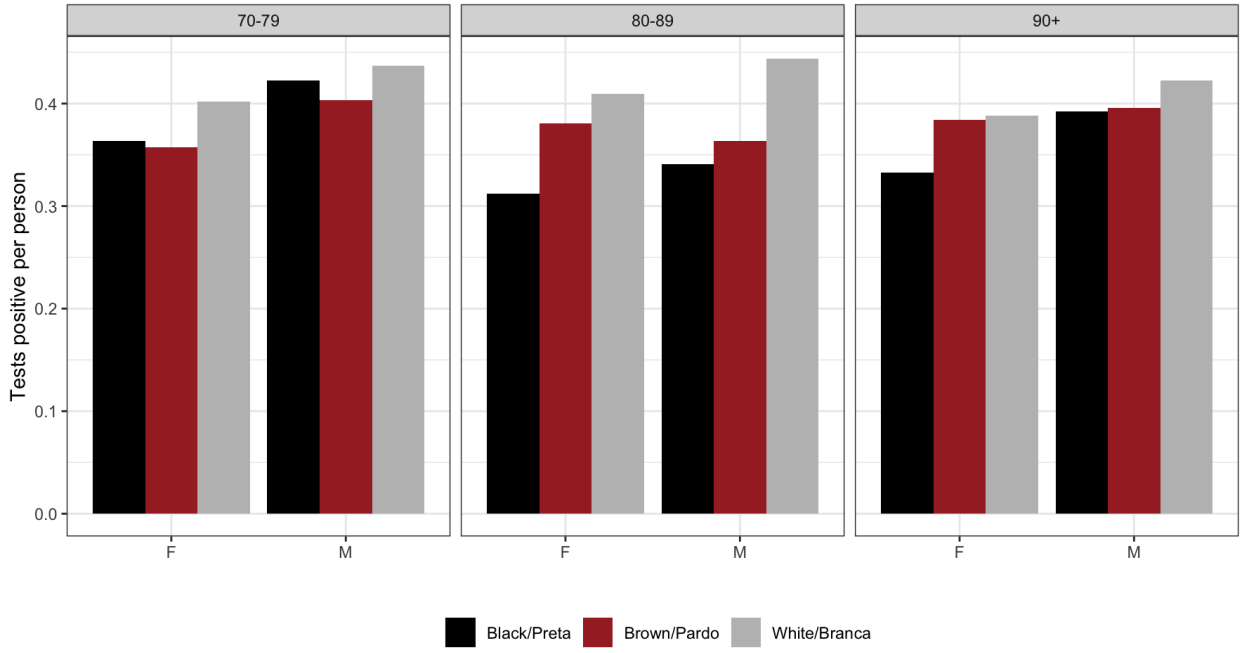


Figure 2: PCR positive testing rate by age, sex and self-reported race (from data extracted on April 07, 2021)

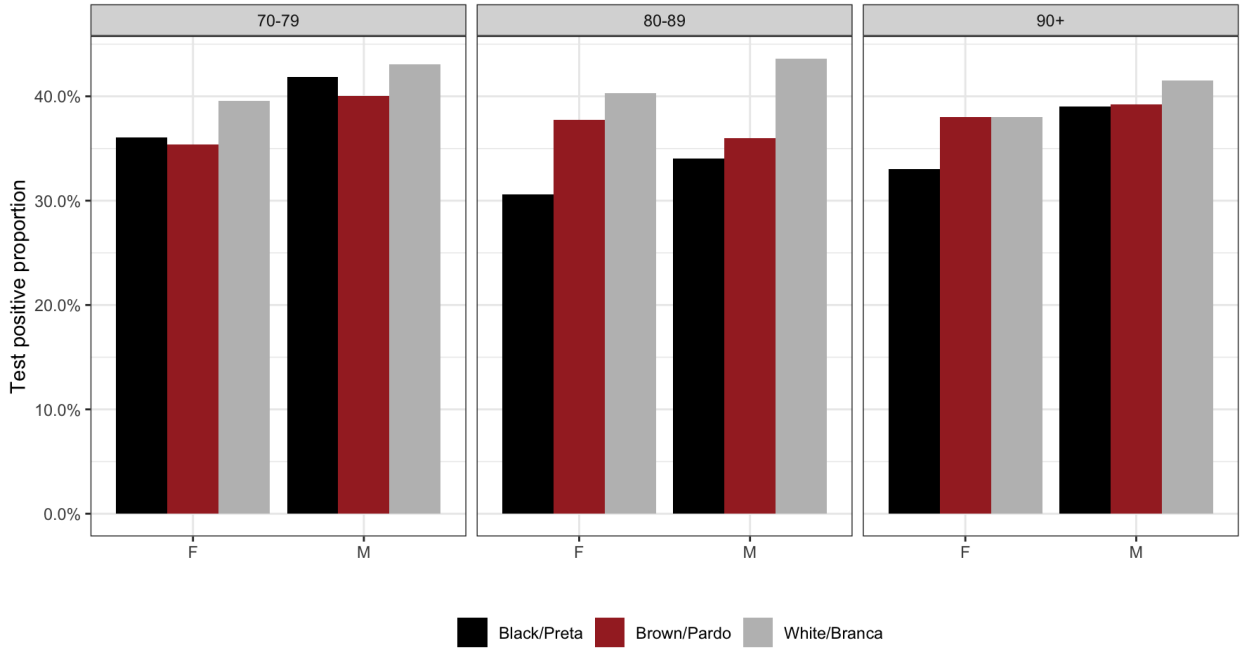


Figure 3: PCR positive proportion by age, sex and self-reported race (from data extracted on April 07, 2021)

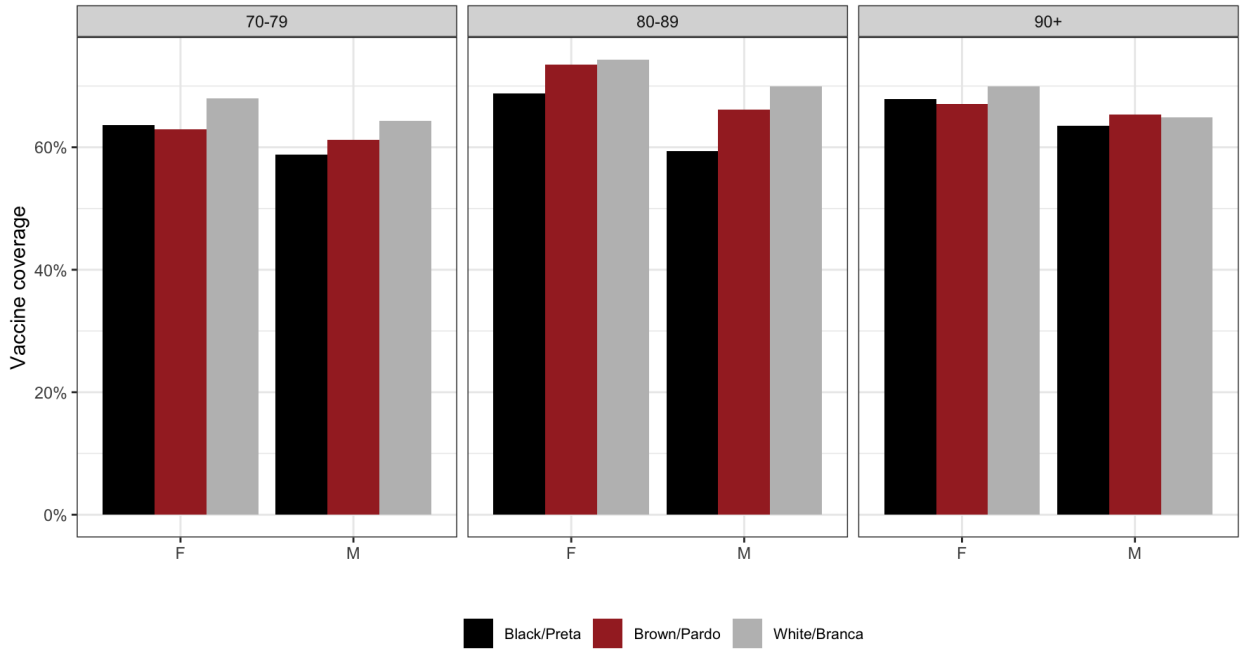
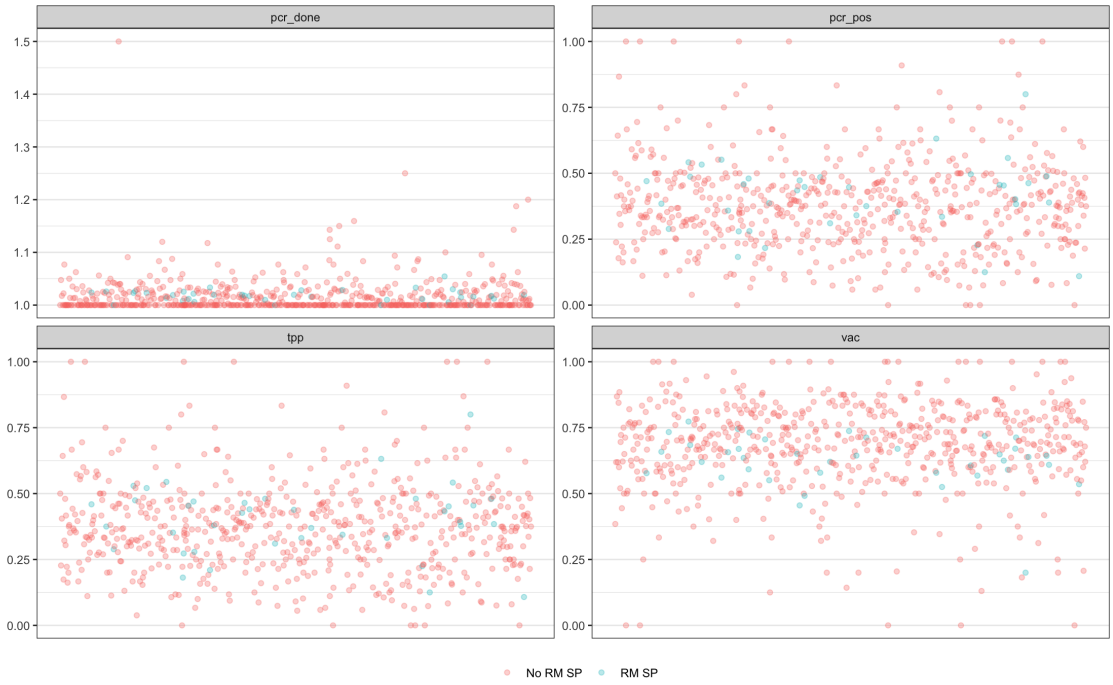


Figure 4: Vaccine coverage by age, sex and self-reported race (from data extracted on April 07, 2021)

Panel A. Indicators by Municipality



Panel B. Indicators by Municipality and Race

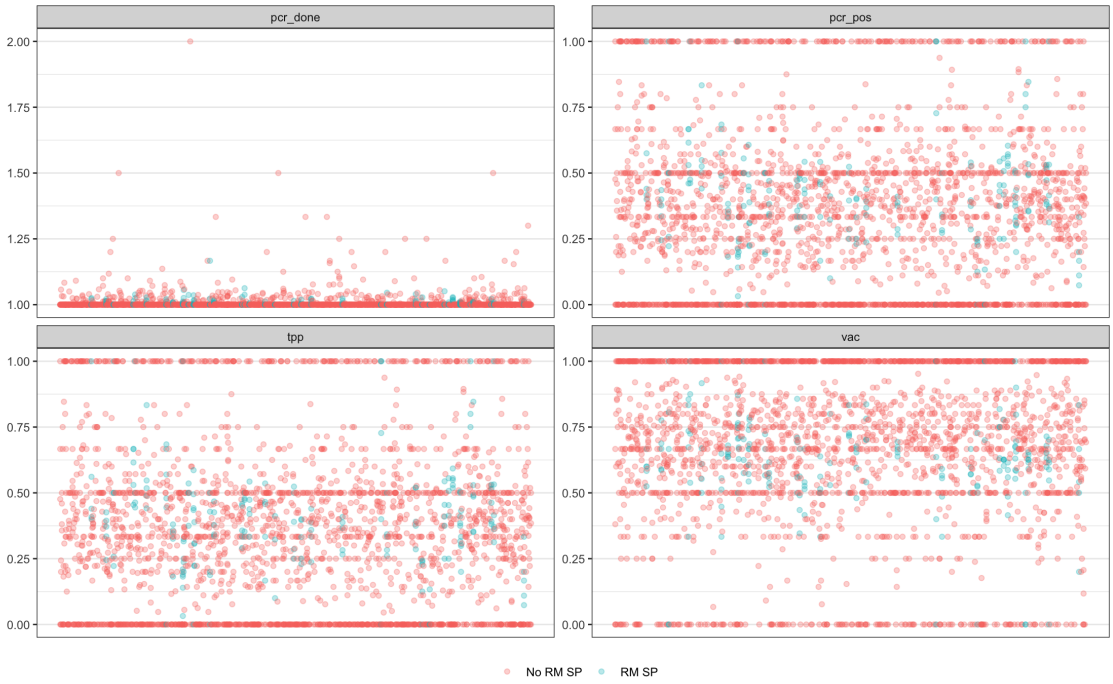
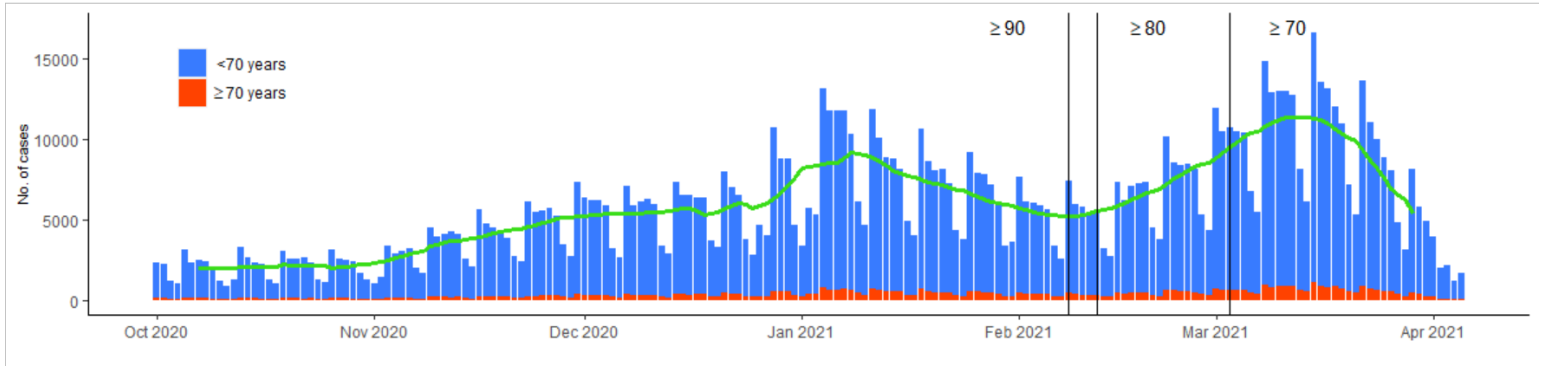


Figure 5: PCR testing rate (pcr_done), PCR positive testing rate (pcr_pos), positivity proportion (tpp) and vaccine coverage (vac) by each municipality (A) and municipality and race (B). RM SP denotes metropolitan area of São Paulo city (from data extracted on April 07, 2021)

Supplementary Figure 1. Reported RT-PCR or Antigen confirmed COVID-19 in the general population of the São Paulo State, Brazil from October 2020 to April 7, 2021. Lines depict moving 14-day averages for case. Vertical lines represent vaccine eligibility by age.



Supplementary Figure 2. Reported RT-PCR or Antigen confirmed COVID-19 rates in the general population of the São Paulo State, Brazil from October 2020 to April 7, 2021. Lines depict rolling averages. Vertical lines represent vaccine eligibility by age.

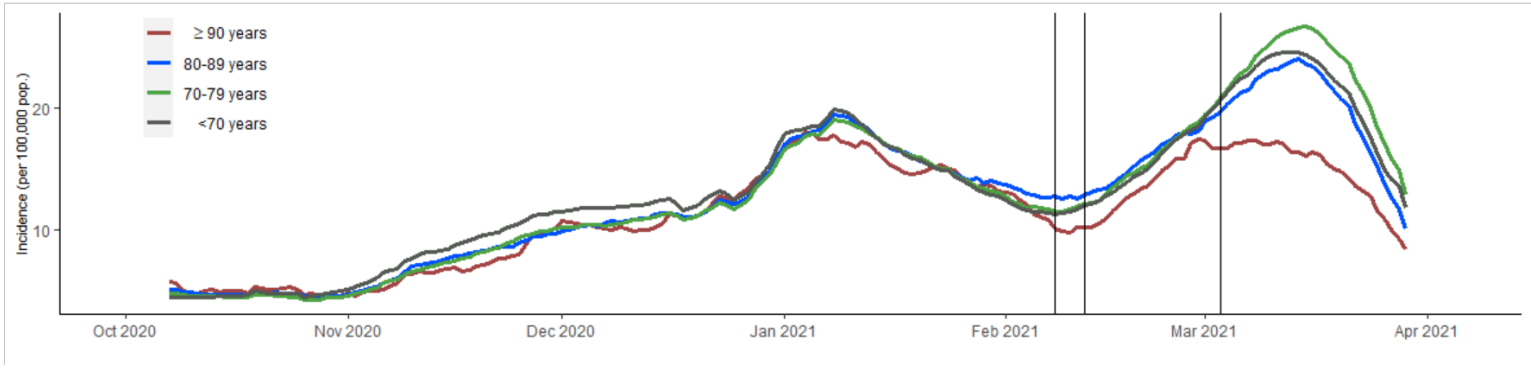


Table 1: Table of planned analyses

Analysis	Exposure	Outcome
CoronaVac		
Primary outcome, primary exposure	Two-dose regimen of CoronaVac in the period starting 14 days after administration of the 2nd dose	Positive test for SARS-CoV-2, with at least one COVID-19 symptom reported 0-10 days before sample collection date
Primary outcome, secondary exposure (2-dose)	Two-dose regimen of CoronaVac in the period 0-13 days after administration of the 2nd dose	
Primary outcome, secondary exposure (1-dose)	One-dose regimen of CoronaVac, in the period starting 14 days after administration of the 1st dose	
Primary outcome, bias indicator	One-dose regimen of CoronaVac, in the period 0-13 days after administration of the 1st dose	
ChAdOx1		
Primary outcome, primary exposure	One-dose regimen of ChAdOx1 in the period starting 28 days after administration of the 1st dose	Positive test for SARS-CoV-2, with at least one COVID-19 symptom reported 0-10 days before sample collection date
Primary outcome, secondary exposure (2-dose)	Two-dose regimen of ChAdOx1 in the period ≥14 days after administration of the 2nd dose	
Primary outcome, secondary exposure (1-dose)	One-dose regimen of ChAdOx1 in the period 0-13 days after administration of the 1st dose	
Primary outcome, secondary exposure (1-dose)	One-dose regimen of ChAdOx1, in the period starting 14-27 days after administration of the 1st dose	
Primary outcome, secondary exposure (2-dose)	Two-dose regimen of ChAdOx1, in the period starting 0-13 days after administration of the 2nd dose	
Primary outcome, bias indicator	One-dose regimen of ChAdOx1, in the period 0-13 days after administration of the 1st dose	