BNT162b2 (Pfizer–BioNTech) and Coronavac (Sinovac) Vaccine Effectiveness in adolescents and children from Brazil

Statistical Analysis Plan (SAP)

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1. Background

Brazil's COVID-19 immunization campaign began to vaccinate adolescents between 12 to 17 years old in October 2021 and children in January 2022 with BNT162b2 (Pfizer-BioNTech). Next, still in January, Coronavac (Sinovac) was approved for use in the 5 to 17 years old population. Vaccine Effectiveness (VE) in the general Brazilian adult population was previously well documented (1). However, there is still no information on VE in Brazilian adolescents and children. Therefore, real-world COVID-19 epidemiological monitoring is essential for public health policy decision-making. Although children and teenagers present a lower risk of developing severe COVID-19 when compared to adults, there is evidence that these groups become infected and can spread the virus to others (2).

2. Objectives

2.1. General Objective

Our main goal is to evaluate the vaccine effectiveness (VE) of BNT162b2 and Coronavac against COVID-19 in adolescent and children populations using the Brazilian National database.

2.2. Specific Objectives

- To estimate **VE** of BNT162b2 against symptomatic COVID-19 among adolescents and children.
- To estimate **VE** of BNT162b2 and Coronavac against severe COVID-19, including hospitalization and death.
- Assess if **VE** differs through time since complete vaccination, age group (5-11; 12-17), and sex.

3. Methods

3.1. Study design

We will conduct a **test-negative design** (TND) study, including those who tested positive for SARS-CoV-2 and controls who tested negative for SARS-CoV-2 among the under 18-year population. VE will be estimated for BNT162b2 and Coronavac vaccine against confirmed symptomatic SARS-CoV-2 infection and severe COVID-19. Cases and controls will be identified and selected from COVID-19 testing records. Information on vaccination will be extracted from registries of the Brazilian immunization campaign.

3.2. Setting

Brazil.

3.3. Population

Children and adolescent residents in Brazil between 5 and 17 years have presented COVID-like symptoms and tested with RT-PCR or antigen for SARS-Cov2.

3.4. Selection criteria

The eligible study population will be individuals aged between 5 to 17 years in Brazil who presented COVID-19-like symptoms and were tested with RT-PCR or antigen for SARS-CoV-2.

We will exclude (i) individuals older than 17 years and younger than 5 years at the date of testing; (ii) individuals who did not present COVID-19-like symptoms; (iii) individuals whose time interval between the first and second doses was less than 21 days; (iv) tests with missing information on age, sex, city of residence, or sample collection date; (v) consecutive negative tests less than 14 days apart; (vi) negative tests followed by a positive test up to 7 days; (vii) any test after a positive test up to 90 days; (viii) tests with a symptom onset date greater than notification date.

3.5. Cases and controls for analyzing confirmed symptomatic SARS-CoV-2 infection

Cases: individuals who had COVID-19-like symptoms presented a positive RT-PCR or antigen test result for SARS-CoV-2 from a sample collected within 10 days of symptoms onset.

Controls: individuals who had COVID-19-like symptoms presented a negative RT-PCR or antigen test result for SARS-CoV-2 from a sample collected within 10 days of symptoms onset.

3.6. Cases and controls for analyzing severe COVID-19

Cases: individuals who had COVID-19-like symptoms presented a positive RT-PCR or antigen test result for SARS-CoV-2 within 10 days of symptoms onset and experienced COVID-19 related hospitalization within 28 days of sample collection or death up to 28 days of sample collection.

Controls: individuals who had COVID-19-like symptoms presented a negative RT-PCR or antigen test result for SARS-CoV-2 from a sample collected within 10 days of symptoms onset.

3.7. Valid RT-PCR or antigen test result

An RT-PCR or antigen test result will be considered valid if:

There have been no positive test results in the previous 90 days to the current positive test result. In addition, there is no positive test result in the 7 days after a negative test result. Also, there have been no negative tests in the past 14 days.

3.8. Outcomes

The outcomes of interest will be: (i) Confirmed symptomatic SARS-CoV-2 infection; (ii) Severe COVID-19, defined as COVID-19 related hospitalization or death.

3.9. Exposures

To estimate CoronaVac or BNT162b2 VE, we will include the following exposure categories: unvaccinated individuals as the reference group, partially vaccinated

individuals with less than 14 days post 2nd dose, and fully vaccinated with at least 14 days post 2nd dose. Also, we will include individuals with the first dose from 0 to 6 days and 7 to 13 days. For temporal trends, vaccination status will be established according to the status at the time of RT–PCR test collection: unvaccinated and grouped in periods (days) after each dose: first dose (0–6, 7–13, and ≥14), second dose (0–13, 14–27, 28–41, 42–55, 56–69, 70–83, 84–97 and ≥98).

3.10. Potential confounders

The analyses will be adjusted for potential confounders such as age, sex, ethnicity, temporal trend, state of residence, previous infection, Brazilian index of deprivation, and comorbidities. These confounders were identified based on previous studies (1,3). In addition, the temporal trend will be estimated using the time elapsed, in weeks, between the study start and the date of symptoms onset.

3.11. Potential effect modifiers

To perform subgroup analysis, stratification by age (5-11;12-17 years) will be considered. State or region may also be considered if adequate numbers are available for deriving significant statistical differences.

4. Data

4.1. Data sources

Our study will use 3 administrative datasets which presents national coverage:

1) *Programa Nacional de Imunizações* (PNI) - holds records of all vaccines administered.

2) *e-SUS Notifica* - holds records of clinical and laboratory testing of COVID-19 suspected cases.

3) *Sistema de Informação da Vigilância Epidemiológica da Gripe* (SIVEP-Gripe) - holds records of COVID-19-related hospitalizations and deaths.

The 3 datasets described will be deterministically linked using a unique identifier available across all 3-health databases in a secure data-management environment

within FIOCRUZ. As a result, researchers will have only access to anonymized data during the study period.

Table 1 displays all variables grouped by category available for this study in each data source. Exposure data are described in the vaccination category. Outcome data are described in secondary care, mortality, and laboratory testing. The remaining categories contain data on potential confounding factors or effect modifiers.

Data category	Data item	Data source
Socio-demographic	Age	PNI or eSUS Notifica or SIVEP-Gripe
	Sex	PNI or eSUS Notifica or SIVEP-Gripe
Geographic	State of residence	PNI or eSUS Notifica or SIVEP-Gripe
Vaccination	Vaccine type	PNI
	Vaccine dose	PNI
	Vaccination date	PNI
Laboratory testing	RT-PCR test result	eSUS Notifica or SIVEP-Gripe
	Rapid antigen test result	eSUS Notifica or SIVEP-Gripe
	Date of symptoms onset	eSUS Notifica or SIVEP-Gripe
	Date of sample collection	eSUS Notifica or SIVEP-Gripe
Secondary care	Date of COVID-19 hospital admission	SIVEP-Gripe
Mortality	Date of COVID-19 death	SIVEP-Gripe
Comorbidities	Cardiac disease, diabetes mellitus, obesity, immunosuppression, and chronic kidney disease	eSUS Notifica or SIVEP-Gripe
Pregnancy	Pregnancy indicator and postpartum period	eSUS Notifica or SIVEP-Gripe

Table 1. Variables that are available for this study.

4.2. Consistency and error checking

We will examine the patterns of missingness and check for implausible values (e.g., the date of the second vaccine dose being earlier than the first) for all analytical variables being used. If a variable of interest presents excessive missing data, we may consider

using another closely related variable as an alternative for these missing data. A record will accompany excluded values or variables from the analysis with the criteria used for exclusion.

4.3. Sample size

We anticipate having over 9M individuals vaccinated with two doses based on previous descriptive explorations.

5. Statistical analyses

5.1. Analytical procedures

We will conduct descriptive analyses of the COVID-19 vaccine among the under 18 population, including assessing the number of outcome events in groups receiving Coronavac or BNT162b2 vaccines. Groups with at least 100 outcome events will be considered for VE analyses.

The odds ratio (OR) will be estimated using generalized logistic regression to compare the vaccination probability between cases and control and the associated 95% confidence interval.

This regression analysis will be adjusted for potential confounders such as age, sex, ethnicity, social-economic status, temporal trend, region of residence, previous infection, and comorbidities. We will compare the standard errors of the VE effect estimates from the fully adjusted model to those from the basic model, adjusted only for age and epidemiological week, to check for multicollinearity (4). The temporal trend will be modeled as cubic regression spline smooth functions. VE will be estimated as 1-OR and expressed as a percentage.

5.2. Subgroup analysis

Suppose an adequate number of outcome events is available among vaccine and age groups. Then, the analytical procedures described in the above section will be applied to conduct subgroup analyses by age, with models being estimated for each group.

5.3. Sensitivity analysis

We will include SARS-CoV-2 tests based on antigen detection and RT-PCR tests. Even though the antigen test presents a lower accuracy than RT-PCR, they progressively replace the RT-PCR test.

5.4. Corrections for multiple testing

Following previous epidemiological recommendations (5), we will not correct multiple testing since we focus on effect estimation rather than hypothesis testing.

5.5. Missing data

We will examine the quantity and patterns of missing data in all covariates. We may use records with no item missingness (complete case analysis) or include a missing category. When possible, missing data will be reported as percentages of total or absolute numbers.

5.6. Statistical software

Analyses will be conducted using the R statistical software.

6. Reporting results

6.1. Reporting guidelines and conventions

Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of Studies Conducted using Observational Routinely collected Data (RECORD) guidelines. P-values will be quoted to two decimal places unless they are less than 0.001 (whereby the p-value will be given as <0.001) or between <0.005 and >0.001, in which case they will be stated to three decimal places. Measures of the association will be interpreted based on 95% CIs.

6.2. Dissemination

The analyses will be written in a manuscript and submitted to a peer-reviewed journal. We will also seek to provide feedback to relevant COVID-19 advisory bodies (e.g., the Brazilian Ministry of Health). All codes used in the analyses will be publicly available via a GitHub repository.

7. Reference

1 - Cerqueira-Silva T, Oliveira V de A, Pescarini J, Júnior JB, Machado TM, Ortiz RF, et al. The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19). 2021. Preprint.

2 - Mustafa NM, L AS. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. *J Clin Virol*. 2020. 128:104395.

3 - Katikireddi SV, Cerqueira-Silva T, Vasileiou E, Robertson C, Amele S, Pan J, et al.Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. Lancet. 2022. 399(10319):25–35.

4 - Greenland S, Daniel R, Pearce N. Outcome modeling strategies in epidemiology: traditional methods and basic alternatives. *Int J Epidemiol*. 2016. 45(2):565–75.

5 - Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990.1(1):43–6.