Effectiveness of the CoronaVac vaccine in prevention of symptomatic and progression to severe Covid-19 in pregnant women in Brazil

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Abstract

Background

The effectiveness of Covid-19 inactivated vaccines in pregnant women is unknown. We estimated vaccine effectiveness (VE) of CoronaVac against symptomatic and severe Covid-19 and in preventing progression from symptomatic to severe Covid-19 in pregnant women in Brazil.

Methods

We conducted a test-negative design study in all pregnant women aged 18 to 49 years in Brazil, linking records of negative and positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) tests to national vaccination records. We also linked records of test positive cases with notification of severe, hospitalized or fatal Covid-19. Using logistic regression, we estimated adjusted odds and VE against symptomatic Covid-19 by comparing vaccine status in test positive (confirmed cases) to that in subjects with a negative test result. We also calculated the odds/VE against progression by comparing vaccine status in symptomatic cases to that in severe Covid-19 cases.

Findings

Of 19838 tested pregnant women, 7424 (37.4%) tested positive for Covid-19 and 588 (7.9%) had severe disease. Only 83% of pregnant women who received a first dose of CoronaVac completed the vaccination scheme. A single dose of the CoronaVac vaccine was not effective at preventing symptomatic Covid-19. Effectiveness of two doses of CoronaVac was 41% (95% CI 27.1- 52.2) against symptomatic Covid-19, 85% (95% CI 59.5-94.8) against severe Covid-19 and (75%; 95% CI 27.9- 91.2) in preventing progression to severe Covid-19 among those infected.

Interpretation

A complete regimen of CoronaVac in pregnant women was effective in preventing symptomatic Covid-19, and highly effective against severe illness in a setting that combines high disease burden and elevated Covid-19 related maternal deaths.

Research in Context

Evidence before this study

We searched PubMed for articles published "pregnant women" AND "vaccine" AND "SARS-CoV-2" AND “CoronaVac” AND “effectiveness” no results were found. Additionally, we repeated the search using "pregnant women" AND "vaccine" AND "SARS-CoV-2" AND “effectiveness”. Although pregnant women are at elevated risk of Covid-19 complications, they were excluded from most Covid-19 vaccine trials. The observational studies of vaccine effectiveness (VE) recently conducted were restricted to mRNA vaccines.

Added value of this study

This study observed that a single dose of the CoronaVac vaccine offered no protection against symptomatic Covid-19; a complete regimen of CoronaVac was 41% effective in preventing symptomatic Covid-19, and 85% effective in preventing severe Covid-19 disease; it was 75% effective in preventing severe outcomes in those who had been infected.

Implications of all the available evidence

A complete regimen of CoronaVac in pregnant women was effective in preventing symptomatic Covid-19, and highly effective against severe illness in a setting that combines high disease burden and elevated Covid-19 related maternal deaths.

Introduction

Cardiopulmonary and immune changes during pregnancy induce shifts in immune responses, increasing pregnant women's susceptibility to some infectious-related adverse outcomes.[1] Although pregnant women have higher a risk of Covid-19 complications, need intensive care and mechanical ventilation more often, and have higher fatality,[2] they were excluded from most Covid-19 vaccine trials.[3] There is considerable interest on establishing the safety and efficacy/effectiveness of Covid-19 vaccines in this population.[4] A number of observational studies of vaccine effectiveness (VE) were recently conducted[5,6,7,8], but those studying pregnant women were restricted to mRNA vaccines.[9,10,11,12,13]

Many low- and middle-income countries are conducting vaccination campaigns using CoronaVac,[5] an inactivated-virus vaccine; some countries, like Brazil, offer CoronaVac to pregnant women. On January 17, 2021, the Brazilian Ministry of Health initiated Covid-19 vaccination with two CoronaVac doses with two to four weeks interval between doses. The policy followed internationally agreed priorities.[14] On March 15, 2021, pregnant women with co-morbidities and in occupations considered, on balance, to be at high risk, became eligible to receive Covid-19 vaccine.[15] On April 26, this recommendation was expanded to include all pregnant women.[16] Although the exact figures for pregnant women are unclear, we anticipated that enough pregnant women would have been vaccinated to make it possible to evaluate vaccine effectiveness in pregnant women: Brazil combines a sufficient vaccine coverage (more than 50% of the population with two doses),[17] more than 21 million cases and 600,000 deaths (October 2021),[18] and a considerable number of maternal deaths.[19,20]

In this observational study of routine data in Brazil we estimated the VE of CoronaVac vaccine against symptomatic Covid-19 and in preventing progression from symptomatic to severe Covid-19 disease in pregnant women.

Methods

Objectives and study design

The primary objective of this study was to estimate VE of CoronaVac vaccine against symptomatic cases of Covid-19 in a test negative design (TND) in all pregnant women who had a RT-PCR test. We also estimated the effectiveness of vaccine the against developing severe Covid-19 (comparing severe, hospitalized or fatal Covid-19 with test negatives). As a further consistency check, we estimated VE against progression from symptomatic Covid-19 disease to severe Covid-19 (severe, hospitalized or fatal) by comparing the vaccine status of

those who developed severe disease with those who tested positive but did not develop severe disease.

Data sources

All data used was abstracted from 3 routinely collected sources: the national surveillance system for RT-PCR test for Covid-19 (e-SUS Notifica); the information system for severe acute respiratory illness (SIVEP-Gripe) and the national immunisation system (SI-PNI).

e-SUS Notifica: This database contains information on suspected cases of Covid-19 recorded in the country. It includes all positive and negative RT-PCR test results, and information on residence, demographic and clinical data of individuals, such as presence of comorbidities and pregnancy status (so we can identify women registered during pregnancy) and presence of symptoms, with acute respiratory diseases defined as presence of at least two of the following signs and symptoms: fever (even if referred), chills, sore throat, headache, cough, runny nose, loss or change to a sense of smell or taste.[21] Asymptomatic individuals with a positive RT-PCR test confirming by Covid-19 infection are registered but were not included in this study.

SIVEP-Gripe is the national registration for severe acute respiratory syndrome (SARS) in Brazil, created after the Influenza pandemic of 2009. In 2020, it was expanded to include Covid-19. All Covid-19 hospitalisations and deaths are meant to be registered in this system.[22] In SIVEP-Gripe, severe acute respiratory illness is defined as an individual with acute respiratory disease who presents dyspnea/respiratory discomfort, persistent pressure or pain in the chest, oxygen saturation less than 95% without oxygen, or cyanosis of the lips or face.[22] Individuals who died with severe acute respiratory illness independent of hospitalisation are also registered. By linking these data with e-SUS Notifica, we identified which pregnant women in e-SUSNotify with a positive RT-PCR test progressed to severe disease.

SI-PNI contains data on all vaccines administered in Brazil. Covid-19 vaccines are administered by health services and recorded in point-of-care applications.[23] From SI-PNI, we extracted information on which Covid-19 vaccine was received with dates of first and second doses. By linking these data with the data on pregnant women in the other files, we were able to determine: (i) which pregnant women who tested negative for Covid-19 had been vaccinated (ii) which pregnant women with confirmed symptomatic Covid-19 infections had been vaccinated and (ii) which pregnant women with severe Covid-19 associated severe case had been vaccinated. We assumed that pregnant women whose record did not link to a SI-PNI vaccination record were not vaccinated.

All data were extracted on October 05, 2021 and made available by the Brazilian Ministry of Health. The information technology bureau of the Brazilian Ministry of Health provided pseudo-anonymised data with a common unique identifier that were used to link individual-level records from the three databases (more details about linkage procedures are available at https://vigivac.fiocruz.br/).

Study population

All pregnant women with symptoms suggesting Covid-19, aged between 18 and 49 years in Brazil with a record of a RT-PCR test between March 15, 2021, and October 03, 2021, registered in e-SUS Notifica. Testing for Covid-19 in Brazil is accessible to anyone through the universal public health system (SUS). Subjects who received any Covid-10 Vaccine were excluded: ChAdOx1 nCoV-19 or Ad26.COV2.S (Janssen/Johnson & Johnson) because these are not indicated for pregnant women in Brazil and BNT162b2 because numbers of women with complete regimen were too small to allow evaluation given they were included in the Brazilian program more recently and the long interval between doses. So, the study is restricted to evaluating CoronaVac vaccine effectiveness. The population consisted of symptomatic pregnant women who were tested with RT-PCR for Covid-19 classified into 3 groups: RT-PCR test negative, RT-PCR test positive with Covid-19 symptoms and RT-PCR test positive with severe Covid-19. The study population in the TND included all symptomatic women with a RT-PCR irrespective of test result. For the nested case control study only women in the first study who had a positive RT-PCR test for Covid-19.

Definition of outcome, cases, and controls

In the TND, the primary outcome was a positive RT-PCR test in a symptomatic subject. Cases were defined as all symptomatic women in the study population with a RT-PCR test result from a respiratory sample collected within 10 days after the onset of symptoms and who did not have a positive RT-PCR test result in the preceding 90 days. We also conducted an additional analysis for the subgroup of cases with severe Covid-19, identified through notification to SIVEP-Gripe or with a register of hospitalization or death in e-SUS record. Controls were defined as all women in the study population with a negative RT-PCR test result, and no positive RT-PCR test in the previous 90 days or in the subsequent 14 days. The test date was defined as either the date of collecting a respiratory specimen or the date of the case registration (when the test date was missing).

As a further consistency check, we estimated VE against progression from symptomatic Covid-19 disease to severe Covid-19 (severe, hospitalized or fatal) by comparing the vaccine status of those who developed severe disease with those who tested positive but did not develop

severe disease. Cases were defined as all women with severe Covid-19, identified through notification to SIVEP-Gripe or with a register of hospitalization or death in e-SUS record. Controls were defined as all confirmed cases of Covid-19 in e-SUS not notified to SIVEP-Gripe and with no registration of hospitalisation nor deaths in e-SUS.

Exposure definition

The exposure studied was vaccination with CoronaVac. This was classified into partially vaccinated (≥14 days after the first dose and before receipt of the second dose at time of RT-PCR testing) and fully vaccinated (≥14 days after the second dose at time of RT-PCR testing). We also calculated effectiveness in the period <14 days since vaccination as the vaccine is expected to have no or limited effectiveness in the first 13 days since vaccination. This was used as a test as high effectiveness or increased risk during this period might serve as an indicator of unmeasured bias or confounding. The reference group for vaccination status was the women who did not received a first vaccine dose before the date of sample collection.

Covariates

A number of risk factors may be associated with both the likelihood of the exposure (i.e., receiving a vaccine) and the likelihood of receiving an RT-PCR SARS-CoV-2 test. These include age, ethnicity, comorbidities status, geography location, index of deprivation,[24] and time (reflecting changes in vaccination policy and disease circulation) and presence of a previous Covid-19 positive RT-PCR as this may both related with vaccination and the risk of a second Covid-19 infection. We extracted information on these potential confounders from the e-SUS Notifica.

Statistical analyses

The test negative design is a type of case-control study, in which the study population consist of the population tested, and controls are selected from those who have a negative test. [25] Accordingly, both the test negative design and the additional comparison of severe cases with non-severe cases were analysed using the standard methods for case-control studies.[25,26] Logistic regression was used to estimate the odds of vaccination with CoronaVac in RT-PCR test confirmed cases compared with those who tested negative, and the odds of vaccination in the severe cases compared to those who tested negative; finally, we also estimated the odds of progression from symptomatic to severe Covid-19, by comparing the odds of vaccination in the severe cases to that in the non-severe cases. Individuals only contributed their first positive test result from March 15, 2021 (when the vaccination programme was recommended for pregnant women nationally). Week of RT-PCR test was included in the regression models because of the variations over time in both Covid-19 incidence and vaccine delivery in Brazil.

We also adjusted for age (<20, 20-34, ≥35), ethnicity (white, mixed brown, black and others), presence of registered comorbidities, geography (region), index of deprivation (quintile). We estimated the VE as one minus the corresponding odds ratio (OR), obtained from a model including the described covariates, expressed as a percentage.

Data analyses were performed in Stata version 17.0.

This study analysed de-identified data and was approved by the National Ethics committee (CONEP) (CAAE registration no. 50199321.9.0000.0040).

Results

During the study period, 95,738 symptomatic suspected cases of Covid-19 among pregnant women were registered in the Brazilian surveillance system e-SUS Notify. Of those, 50,819 (53.1%) had an RT-PCR SARS-CoV-2 test, and the results were available for 30,947 (60.9%) samples. After exclusions, 19838 subjects were included in the analysis; 7424 (37.4%) were test-positive, and 12414 (62.6%) test-negative. Of the 7424 with a positive test, 588 (7.9%) were severe and 84 (1.1%) died (Figure1). Table 1 shows the characteristics of cases and controls.

Figure 2 shows the number of cases and controls by time since the first and second vaccination doses among vaccinated pregnant women. After the first doses of CoronaVac, the proportion of positive tests does not seem to change. Notably, 165 (16.6%) out of all women with a single dose of CoronaVac had not received a second dose after the recommended interval between doses (4 weeks).

The odds of testing positive among vaccinated women during the 13 days after the first dose, was 1.35 (95% CI 1.09 to 1.68) compared with those unvaccinated, indicating an unexpected small increase in risk of Covid-19 among the vaccinated during this initial period. VE among those receiving only the first dose with at least 14 days between the first dose and the date of RT-PCR) was low and not statistically significant 5.02 (95% CI -18.22- 23.69). The estimated adjusted VE in the fully vaccinated group against symptomatic Covid-19 was 41.0% (95% CI 27.1 to 52.2) (Table 2). The corresponding estimate for severe Covid-19 was 67.7 (95% CI 20.0-87.0) for those partially vaccinated and 85.4 (95% CI 59.4- 94.8) for fully vaccinated women (Table 3).

The estimated adjusted VE of CoronaVac against progression from symptomatic to severe Covid-19 was 67.4% (95% CI 17.7 to 87.1) among partially vaccinated pregnant women and 74.7% (95% CI 28.0 to 91.2) among fully vaccinated women (Table 3). No deaths occurred

among partially or fully vaccinated pregnant women when four would have been expected if mortality was the same as in unvaccinated.

Discussion

In this investigation of CoronaVac VE in pregnant women, we found that a single dose of the CoronaVac vaccine offered no protection against symptomatic Covid-19; two doses were 41% effective against symptomatic Covid-19 and 85% effective against severe Covid-19. Those who were fully vaccinated and went on to have symptoms had a 75% lower risk of progressing to severe Covid-19 than those unvaccinated. No deaths occurred among partially or fully vaccinated women, when 4 were expected. About 17% of vaccinated women did not get a second dose as prescribed by the time they were tested.

Although the findings from this study suggest that the complete CoronaVac vaccine regimen was effective against symptomatic Covid-19 among pregnant women, the magnitude of estimated effectiveness was lower than reported previously in studies in the general population conducted in Brazil,[8] Chile,[5] and Turkey.[27] Pregnancy promotes resistance to generating proinflammatory antibodies compared to non-pregnant women, suggesting that pregnant women may not respond to some vaccines as effectively.[28,29] We did not investigate biological mechanisms; further investigation is required to establish whether the lower effectiveness found is due to immunological changes during pregnancy. In contrast with other Covid-19 vaccines such as the BNT162b2 which confers protection after the first dose,[30] CoronaVac was effective against symptomatic Covid -19 only after a complete regimen. This was also found is in older people in Brazil.[31]

This study has strengths and limitations. As a strength, it used rich, routinely collected data from Brazil, recognised to be of high-quality.[32] By using the TND, we have minimised bias related to access to health care, the occurrence of symptoms and health-seeking behaviour. In most populations strong pressures have influenced who got tested for Covid-19. These biases can mean that those who get tested, and test positive for SARS-CoV-2 may not be a random sample of all cases in the population. The assumption that underlies the TND is that people who seek testing and manage to get tested would be influenced by similar pressures regardless of vaccine status and the test outcome,[26] thus biases will 'cancel out' and relatively unbiased estimates of effect can be obtained.[25,26]

However, as observational designs are vulnerable to confounding and bias. The fact that the risk of Covid-19 increased in vaccinated women in the 2 weeks after the first dose is not biological plausible and may be an indication of residual bias/confounding, which in this

case could lead to an underestimation of VE. A potential explanation for this would be if vaccinated subjects feel safer than unvaccinated subjects, such that unvaccinated subjects are more likely to seek testing for a symptom (not caused by Covid-19) that would not lead a vaccinated subject to test. This would result in a higher proportion of negative tests among the unvaccinated, leading to an apparent estimated increase in risk in the vaccinated, underestimating VE. Other potential explanations are that the process of vaccination itself increases the risk of infection, such travelling to or from a vaccination site, and finally, that after being vaccinated, believing themselves to be protected, women undergo a period of 2 weeks of contacts and reduced protective measures, leading to a peak of infection shortly after vaccination.

A limitation intrinsic to the use and availability of secondary data is the limited choice of covariates and the potential for misclassifying vaccine status due to linkage failure. Finally, we did not assess vaccination safety as data necessary for this assessment was not available. However, it is reassuring that CoronaVac contains an adjuvant that is commonly used in many other vaccines, such as against Hepatitis B and Tetanus, with a well-documented safety profile among pregnant women.[34] Previous evidence of safety of inactivated vaccines for other pathogens and using this adjuvant is reassuring.[34]

We note that an alarming 17% of the study sample with a single dose of CoronaVac did not take the second dose after the recommended maximum interval (4 weeks). This has important repercussions for public health authorities, highlighting the importance of actively searching those delaying the second doses and promoting opportunities to vaccinate these women during regular prenatal care appointments.

In conclusion, this study involved pregnant women in a setting that combines high disease burden and elevated Covid-19 related maternal related deaths. In this setting, we found that a complete regimen of CoronaVac was 41% effective in preventing symptomatic Covid-19, and 85% effective in preventing severe Covid-19 disease; it was 75% effective in preventing severe outcomes in those who had been infected.

Contributors
ESP, NP, MLB, MBN developed the study concept. VAO, TCS, JBJ, TMM, GP, MBN acquired, treated and linked the data. KLMW, FJOA, EPPJ, VO, GLW, LCR contributed to the data analyses and interpretation of results. VAO, KLMW vouched for the data analyses. ESP wrote the first draft. All authors decided to publish and revised the manuscript and approved the final version.

Declarations
We declare no competing interests. VO, VB, MB, and MB-N are employees from Fiocruz, a federal public institution, which manufactures Vaxzevria in Brazil, through a full technology transfer agreement with AstraZeneca. Fiocruz allocates all its manufactured products to the Ministry of Health for the public health service (SUS) use.

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References

1. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal immunological adaptation during normal pregnancy. Frontiers in Immunology 2020,11, 2627.
2. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis.Bmj 2020, 370.
3. BioNTech, S. E. Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older.2021
4. Duarte G, Coutinho CM, Rolnik DL, Quintana SM, Rabelo e Silva AC,Poon LC et al..Perspectives on administration of COVID-19 vaccine to pregnant and lactating women: a challenge for low-and middle-income countries. AJOG Global Reports 2021: 100020.
5. Jara A, Undurraga EA, González C J, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med 2021;385:875-884
6. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med 2021;385:1355-1271.
7. Lopez Bernal J, Andrews N, Gower C, Robertson C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021 May 13;373:n1088. doi: 10.1136/bmj.n1088. PMID: 33985964; PMCID: PMC8116636.
8. Ranzani O T, Hitchings M D T, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ 2021; 374 :n2015 doi:10.1136/bmj.n2015
9. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med. 2021 Oct;27(10):1693-1695. doi: 10.1038/s41591-021-01490-8. Epub 2021 September 07. PMID: 34493859.
10. Goldshtein I, Nevo D, Steinberg DM, et al. Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. JAMA. 2021 August 24;326(8):728-735. doi: 10.1001/jama.2021.11035. PMID: 34251417; PMCID: PMC8276131.
11. Bleicher I, Kadour-Peero E, Sagi-Dain L, Sagi S. Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study. Vaccine. 2021 Oct 22;39(44):6535-6538. doi: 10.1016/j.vaccine.2021.09.043. Epub 2021 September 25. PMID: 34600749; PMCID: PMC8463327.
12. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest. 2021 Oct 6:e153662. doi: 10.1172/JCI153662. Epub ahead of print. PMID: 34618693.
13. Dagan N, Barda, Biron-Shental N et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nature Medicine 27.10 (2021): 1693-1695.
14. Brazilian Ministry of Health. Campanha Nacional de Vacinação contra a Covid-1. Décimo oitavo informe técnico.(https://www.conasems.org.br/wp-content/uploads/2021/04/20adistribuic%CC%A7a%CC%83o_Campanha_Nacional_de_Vacinacao_contra_a_Covid_19.pdf)
15. Brazilian Ministry of Health. Nota Técnica Nº 1/2021-DAPES/SAPS/MS - Vaccination for pregnant and postpartum women with comorbities.2021(https://portaldeboaspraticas.iff.fiocruz.br/wpcontent/uploads/2021/03/NT-vacinacao-gestantes-peurperas-e-lactantes.pdf)

16. Brazilian Ministry of Health. Nota Técnica Nº 467/2021-CGPNI/DEIDT/SVS/MS - Vaccination for pregnant and postpartum women without comorbidities.2021(https://portaldeboaspraticas.iff.fiocruz.br/wpcontent/uploads/2021/04/nota-tecnica-467-2021-cgpni-deidt-svs-ms.pdf)
17. Brazilian Ministry of Health. COVID-19 Vacinação Doses Aplicadas. (https://qsprod.saude.gov.br/extensions/demas_c19vacina/demas_c19vacina.html)
18. Worldmeters. Coronavirus update (Live) COVID-19 virus pandemic. 2021. (https://www.worldometers.info/coronavirus/)
19. de Carvalho, RC, Costa MCN, Teixeira MG, et al. "Impact of COVID-19 pandemic on time series of maternal mortality ratio in Bahia, Brazil: analysis of period 2011–2020." BMC Pregnancy and Childbirth 2021, 21.1: 1-7.
20. Takemoto MLS, Menezes MO, Andreucci CB, Nakamura-Pereira M, Amorim MMR, Katz L, Knobel R. The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. Int J Gynaecol Obstet. 2020 Oct;151(1):154-156. doi: 10.1002/ijgo.13300. Epub 2020 July 29. PMID: 32644220.
21. Brazilian Ministry of Health. e-SUS Notifica. https://datasus.saude.gov.br/notifica/(accessed october, 2021)
22. Brazilian Ministry of Health. Opendatasus. https://opendatasus.saude.gov.br/dataset/bd-srag-2021. (accessed october, 2021)
23. Brazilian Ministry of Health. SI-PNI - Sistema de Informação do Programa Nacional de Imunizações. http://pni.datasus.gov.br/. (accessed october, 2021)
24. Allik M, Ramos D, Agranonik M et al. Developing a Small-Area Deprivation Measure for Brazil. Technical Report. Cidacs/University of Glasgow. 2020. https://cidacs.bahia.fiocruz.br/ibp/wp-content/uploads/2020/12/technical-report_compressed.pdf
25. Vandenbroucke JP, Pearce N. Test-Negative Designs: Differences and Commonalities with Other Case-Control Studies with "Other Patient" Controls. Epidemiology. 2019 Nov;30(6):838-844. doi: 10.1097/EDE.0000000000001088. PMID: 31430265.
26. Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, Pearce N. A Test-Negative Design with Additional Population Controls Can Be Used to Rapidly Study Causes of the SARS-CoV-2 Epidemic. Epidemiology. 2020 Nov;31(6):836-843. doi: 10.1097/EDE.0000000000001251. PMID: 32841988; PMCID: PMC7523580.
27. Tanriover, M D, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey.The Lancet.2021: 398.10296: 213-
28. Atyeo, C, DeRiso EA, Davis C et al. COVID-19 mRNA vaccines drive differential Fc-functional profiles in pregnant, lactating, and non-pregnant women. *bioRxiv* 2021.
29. Saeed Z, Greer O, Shah NM. Is the Host Viral Response and the Immunogenicity of Vaccines Altered in Pregnancy? Antibodies (Basel). 2020 Aug 4;9(3):38. doi: 10.3390/antib9030038. PMID: 32759839; PMCID: PMC7551810.
30. Roest S, Hoek RAS, Manintveld OC. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 May 20;384(20):1968-1970. doi: 10.1056/NEJMc2104281. Epub 2021 April 21. PMID: 33882226.
31. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, Villela EFM, Torres MSS, de Oliveira SB, Schulz W, Almiron M, Said R, de Oliveira RD, Vieira da Silva P, de Araújo WN et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021 Aug 20;374:n2015. doi: 10.1136/bmj.n2015.

32. Jorge MH P M, Laurenti R, Gotlieb SLD. Análise da qualidade das estatísticas vitais brasileiras: a experiência de implantação do SIM e do SINASC. *Ciência & Saúde Coletiva* 12. 2007
33. MHPM Jorge, R Laurenti, SLD Gotlieb. Análise da qualidade das estatísticas vitais brasileiras: a experiência de implantação do SIM e do SINASC. Ciência & Saúde Coletiva, v. 12, p. 643-654, 2007.
34. WHO. The Sinovac-CoronaVac COVID-19 vaccine: What you need to know. September 2021 (https://www.who.int/news-room/feature-stories/detail/the-sinovac-covid-19-vaccine-what-you-need-to-know)

Figure 1: Flowchart of the study population from surveillance system and final sample of cases and controls

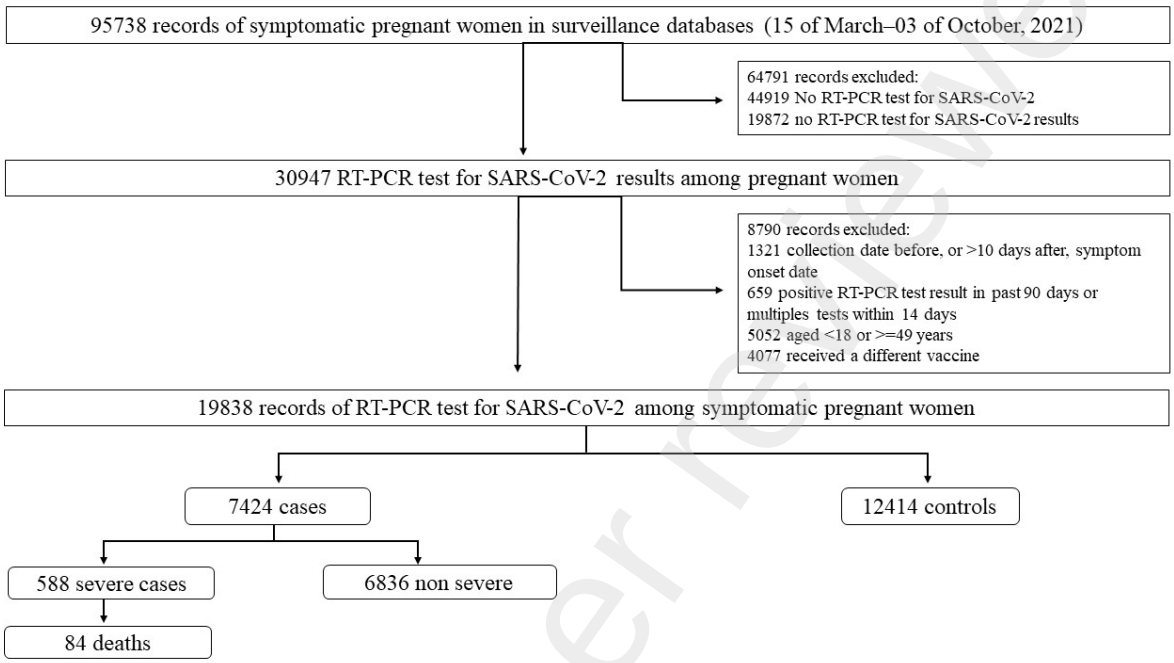

Figure 2: Number of cases and controls by interval since first and second vaccination

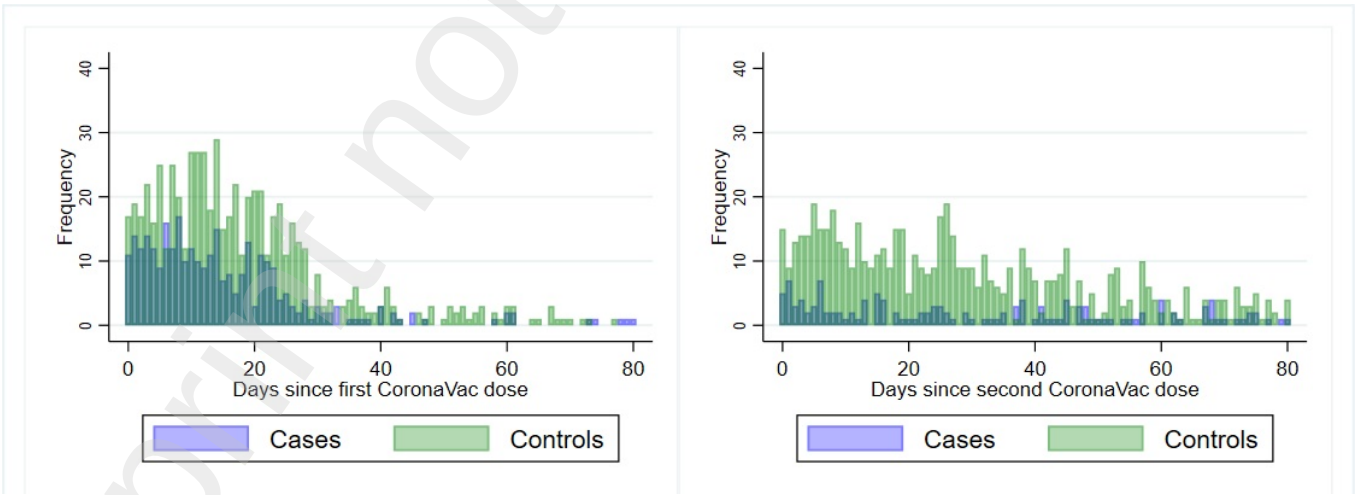

Table 1: Characteristics of cases and controls in pregnant women aged 18-49 years in Brazil.

Characteristics	Test positive	Test negative
Vaccination status		
Not vaccinated	6886 (92.75)	10919 (87.96)
Single dose, within 0-13 days	169 (2.28)	284 (2.29)
Single dose, ≥14 days	156 (2.10)	386 (3.11)
Two doses, within 0-13 days	45 (0.61)	192 (1.55)
Two doses, ≥14 days	168 (2.26)	633 (5.10)
Age group		
< 20	406 (5.47)	940 (7.57)
20-34	5606 (75.51)	9629 (77.57)
35+	1412 (19.02)	1845 (14.86)
Missing	-	-
Self-reported race		
White	2787 (43.75)	5226 (47.93)
Mixed Brown	3085 (48.43)	4830 (44.30)
Black	390 (6.12)	689 (6.32)
Others	108 (1.70)	158 (1.45)
Missing	1054	1511
Reported co-morbidities		
Yes	554 (7.46)	767 (6.18)
No	6870 (92.54)	11647 (93.82)
Missing*	-	-
Previous events notified to surveillance		
Yes	2447 (32.96)	5145 (41.45)
No	4977 (67.04)	7269 (58.55)
Missing	-	-
Brazilian Deprivation Index		
1	1940 (26.13)	3634 (29.29)
2	1638 (22.07)	2949 (23.77)
3	1502 (20.23)	2269 (18.29)
4	1293 (17.42)	2039 (16.43)
5	1050 (14.15)	1518 (12.23)
Missing	1	5
Region of residence		
North	349 (4.70)	623 (5.02)
Northeast	1663 (22.40)	2244 (18.08)
South	734 (9.89)	2136 (17.21)
Southeast	3981 (53.62)	6444 (51.92)
Midwest	697 (9.39)	965 (7.77)
Missing	-	2

* those who reported only pregnancy as condition were considered without co-morbidities

Table 2: Effectiveness of -CoronaVac against symptomatic and severe Covid-19, among pregnant women aged 18-49 years in Brazil (comparison of symptomatic and severe cases with test-negative controls)

	Unadjusted Odds Ratio (95% CI)	Unadjusted# Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Adjusted* VE% (95% CI)	p-value
Vaccination status					
Symptomatic Covid-19			**Sinovac-CoronaVac**		
Unvaccinated	Ref	Ref	Ref	Ref	
One dose <13 days	0.94 (0.77-1.14)	1.35 (1.10-1.66)	1.35 (1.09-1.68)	-	0.006
Partially vaccinated (One dose ≥14 days)	0.64 (0.53-0.77)	1.00 (0.82-1.22)	0.94 (0.76-1.18)	5.02 (-18.22- 23.69)	0.645
Two doses ≥14 days	0.42 (0.35-0.50)	0.69 (0.57-0.83)	0.59 (0.47-0.72)	40.97 (27.07- 52.22)	<0.001
Severe Covid-19					
Unvaccinated	Ref	Ref	Ref	Ref	
One dose <13 days	1.38 (0.87-2.19)	1.64 (1.01-2.65)	1.42 (0.83-2.43)	-	0.192
Partially vaccinated (One dose ≥14 days)	0.30 (0.13-0.69)	0.38 (0.16-0.87)	0.32 (0.13-0.80)	67.74 (20.00-87.00)	0.015
Two doses ≥14 days	0.15 (0.06-0.37)	0.20 (0.08-0.50)	0.14 (0.05-0.40)	85.39 (59.44- 94.80)	<0.001

Table 3: Effectiveness of Sinovac-CoronaVac against symptomatic Covid-19 and progressing to severe forms (comparing severe, hospitalized or fatal Covid-19 with test negative), among pregnant women aged 18-49 years in Brazil (comparison of severe cases with non-severe cases)

	Unadjusted Odds Ratio (95% CI)	Unadjusted# Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Adjusted* VE% (95% CI)	p-value
Vaccination status					
Symptomatic Covid-19			**Sinovac-CoronaVac**		
Severe Covid-19					
Unvaccinated	Ref	Ref	Ref	Ref	
One dose <13 days	1.52 (0.95-2.45)	1.16 (0.70-1.93)	1.02 (0.58-1.78)	-	0.932
Partially vaccinated (One dose ≥14 days)	0.45 (0.20-1.04)	0.34 (0.15-0.80)	0.32 (0.12-0.82)	67.46 (17.66- 87.14)	0.018
Two doses ≥14 days	0.35 (0.14-0.86)	0.27 (0.10-0.69)	0.25 (0.08-0.72)	74.69 (27.95-91.20)	0.001

Supplementary material

Table S1: Vaccination plan for pregnant and postpartum women in Brazil

Date	Technical notes issued by the Ministry of Health	Recommendations
15/03/2021	**NOTA TÉCNICA Nº 1/2021-DAPES/SAPS/MS -** Vaccination for pregnant and postpartum women with comorbities	- Vaccination for pregnant and lactating women with comorbidities - Vaccine can be offered to pregnant and postpartum women without comorbidities after evaluating the risks and benefits, especially considering the professional activity performed by the woman.
26/04/2021	**NOTA TÉCNICA Nº 467/2021-CGPNI/DEIDT/SVS/M**S - Vaccination for pregnant and postpartum women without comorbidities	Phase I- Pregnant and postpartum women with comorbidities, regardless of age Phase II- Pregnant and postpartum women, regardless of comorbidities
14/05/2021	**NOTA TÉCNICA nº 627/2021-CGPNI/DEIDT/SVS/MS -** Temporary suspension of vaccination	- Temporary suspension of vaccination with the vaccine AstraZeneca/Oxford/Fiocruz in pregnant and postpartum women
19/05/2021	**NOTA TÉCNICA Nº 651/2021 - CGPNI/DEIDT/SVS/MS - C**ontinued vaccination in pregnant and postpartum women with comorbidities	- Vaccination of pregnant and postpartum women with comorbidities after benefit risk evaluation and medical prescription (Vaccines without viral vector -SINOVAC/Butantan or Pfizer-BioNTech BNT162b2) - Pregnant and postpartum women (including those without additional risk factors) who have already received the first dose of the AstraZeneca/Oxford/Fiocruz vaccine must wait for the end of the gestation and postpartum period (up to 45 days after delivery) for the administration of the second dose of the vaccine - Pregnant and postpartum women (including those without additional risk factors) who have already received the first dose of another COVID-19 vaccine that does not contain a viral vector (Sinovac/Butantan or Pfizer-BioNTech BNT162b2) should complete the regimen with the same vaccine at the usual intervals - Pregnant and postpartum women of other priority groups (health workers or other essential services workers, for example) may be vaccinated after an individual risk and benefit evaluation
06/07/2021	**NOTA TÉCNICA Nº 2/2021 - SECOVID/GAB/SECOVID/MS -** Continued vaccination in pregnant and postpartum women without comorbidities	- Vaccination of pregnant and postpartum women aged 18 years and over, regardless of risk factors - Pregnant of any gestational age - Needs for Medical evaluation and Prescription
23/07/2021	**NOTA TÉCNICA Nº 6/2021-SECOVID/GAB/SECOVID/MS** - Interchangeability between vaccines for pregnant and postpartum women who	- Vaccination of pregnant and postpartum women aged 18 years and over, regardless of risk factors - Pregnant of any gestational age

	took the oxford astrazeneca vaccine in the first dose	- Need for Medical evaluation and Prescription - To pregnant and postpartum women who received the first dose of the AstraZeneca/Fiocruz vaccine, at time of the second dose, preferably, the Pfizer-BioNTech BNT162b2 /Wyeth vaccine should be offered. If this immunising agent is not available locally, Sinovac/Butantan vaccine may be used