Effectiveness of the SARS-CoV-2 mRNA Vaccines in Pregnant Women

Adeel Butt (aabutt@HAMAD.QA)
Hamad Medical Corporation
Abdul-Badi Abou-Samra
Hamad Medical Corporation
Hiam Chemaitelly
Weill Cornell Medicine-Qatar https://orcid.org/0000-0002-8756-6968
Abdullatif Al Khal
Hamad Medical Corporation
Peter Coyle
Hamad Medical Corporation
Huda Saleh
HMC
Anvar Hassan Kaleeckal
Hamad Medical Corporation
Ali Nizar Latif
Hamad Medical Corporation
Roberto Bertollini
MOPH Qatar
Laith Abu-Raddad
Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Doha
https://orcid.org/0000-0003-0790-0506

Article

Keywords: SARS-CoV-2, COVID-19, vaccine, pregnancy, pregnant, Qatar

DOI: https://doi.org/10.21203/rs.3.rs-622782/v1

Abstract

Pregnancy may increase the risk of adverse maternal and neonatal outcomes in SARS-CoV-2 infection. Effectiveness of SARS-CoV-2 vaccines in pregnant women is not known. Using a test-negative case-control study, we determined the vaccine effectiveness of mRNA vaccines in preventing confirmed SARS-CoV-2 infection in pregnant women at a national referral hospital, which handles > 75% of the deliveries in Qatar. Among 2,020 pregnant women who met the study criteria, 397 had a positive SARS-CoV-2 RT-PCR and 1,623 had a negative test. Vaccine effectiveness ≥ 14 days after the second dose was 67.7% (95%CI 30.5–86.9), while vaccine effectiveness ≥ 14 days after the first dose but before the second dose was 40.3% (95%CI 0.0-80.4). There were nine severe/critical disease cases, and no deaths in the PCR-positive pregnant women, all among unvaccinated. The mRNA vaccines provide high level of protection against documented SARS-CoV-2 infection, which supports including pregnant women in vaccination campaigns.

Introduction

Several vaccines for the SARS-CoV-2 infection have received emergency use authorization across the globe. The earliest vaccines to obtain such authorization were the BNT-162b2 (Pfizer) and the mRNA-1273 (Moderna) vaccines. Early randomized clinical trials using these vaccines reported an efficacy of 94-95% in preventing confirmed SARS-CoV-2 infection or symptomatic COVID-19 disease.[1,2] Subsequent effectiveness studies in the real-world settings have reported similarly high rates of effectiveness in preventing confirmed infection and nearly 100% effectiveness in preventing severe disease or death.[3,4] SARS-CoV-2 infection in pregnant women is often asymptomatic, though maternal infection in pregnancy is associated with higher rates of neonatal respiratory distress and hospitalization.[5,6] However, no mortality difference in infants born to mothers with SARS-CoV-2 infection in pregnancy has been observed.[6] When maternal infection occurs >60 days prior to delivery, efficient transfer of maternal SARS-CoV-2 antibodies has been reported with up to 38% of infants demonstrating positive IgG antibodies at 13-28 weeks.[7] Despite being at a potentially high risk of more severe disease and adverse outcomes, pregnant women were excluded from the vaccine efficacy trials.[8] Hence, other than very limited data in women who were inadvertently enrolled in clinical trials, no robust data are available regarding the effectiveness of SARS-CoV-2 vaccines in pregnant women. We undertook this study to determine the effectiveness of SARS-CoV-2 mRNA vaccines in pregnant women at a national level in Qatar.

Results

Between December 20, 2020 and May 30, 2021, we identified 4,534 with confirmed pregnancy. We excluded 2,087 without any SARS-CoV-2 testing during the study period and 427 who were tested before pregnancy onset. **(Figure)** Among the remaining 2,020 pregnant women, 397 had a positive SARS-CoV-2 RT-PCR and 1,623 had a negative test. For 393 RT-PCR positive pregnant women, we found 1,074 matched RT-PCR negative controls using an algorithm to find up to 3 controls for each case. Our final

study groups consisted of 23 vaccinated and 370 unvaccinated cases (“test-positive” group) and 109 vaccinated and 753 unvaccinated controls (“test-negative” group).

The median age was 31 years for the cases and controls. Age group distribution and nationalities of the cases and controls are presented in **table 1.** Vaccine effectiveness ≥14 days after the second dose was 67.7% (95% CI 30.5-86.9), while vaccine effectiveness ≥14 days after the first dose but before the second dose was 40.3% (95% CI 0.0-80.4). **(Table 2)**

Table 1. Demographic characteristics of cases (PCR-positive) and controls (PCR-negative).

Characteristics*	Cases† (PCR positive) *N=393*	Controls† (PCR negative) *N=862*	p-value
Median age (IQR) — years	31 (27-34)	31 (28-35)	0.144
Age group — no. (%)			
15-19 years	8 (2.0)	14 (1.6)	0.317
20-24 years	36 (9.2)	96 (11.1)	
25-29 years	98 (24.9)	245 (28.4)	
30-34 years	137 (34.9)	295 (34.2)	
35-39 years	94 (23.9)	159 (18.5)	
40-44 years	19 (4.8)	50 (5.8)	
45+ years	1 (0.3)	3 (0.3)	
Nationality‡			
Bangladeshi	9 (2.3)	9 (1.0)	<0.001
Egyptian	39 (9.9)	55 (6.4)	
Filipino	26 (6.6)	51 (5.9)	
Indian	43 (10.9)	122 (14.2)	
Nepalese	0 (0.0)	4 (0.5)	
Pakistani	28 (7.1)	40 (4.6)	
Qatari	82 (20.9)	272 (31.6)	
Sri Lankan	6 (1.5)	8 (0.9)	
Sudanese	23 (5.9)	40 (4.6)	
Other nationalities§	137 (34.9)	267 (31.0)	

†Cases and controls were matched one-to-five by 5-year age group and reason for polymerase chain reaction (PCR) testing.

‡Nationalities were chosen to represent the most populous groups in Qatar.

§These comprise 30 other nationalities in Qatar among Cases, 41 other nationalities among controls.

Table 2. Effectiveness of the mRNA Covid-19 vaccines against SARS-CoV-2 infection among pregnant women ≥14 days after the first dose and ≥14 days after the second dose.

	Cases: PCR positive	Controls: PCR Negative	Vaccine effectiveness in % (95% CI)
≥14 days after first dose and no second dose			
Vaccinated	6	22	40.3 (0.0-80.4)
Unvaccinated	331	724	
≥14 days after second dose			
Vaccinated	8	52	67.7 (30.5-86.9)
Unvaccinated	318	667	

Discussion

To our knowledge, this is the first large scale study of SARS-CoV-2 vaccine effectiveness in pregnant women. We found the vaccine effectiveness to be 68.5% in preventing any documented infection.

Pregnant women with SARS-CoV-2 infection are at a higher risk of adverse maternal and neonatal outcomes. They are more likely to experience premature rupture of membranes, venous thrombotic events, severe pre-eclampsia, pre-term birth, and fetal death.[9,10] Early studies have not shown any obvious safety issues with the mRNA vaccines in pregnant women,[11] while maternal vaccination with the BNT162b2 vaccine has been shown to induce a robust humoral response in pregnant women with effective transfer to the fetus.[7,12] These data coupled with reasonably high effectiveness in preventing SARS-CoV-2 infection provides strong rationale for including pregnant women in SARS-CoV-2 vaccination campaigns using the mRNA vaccines.

While the mRNA vaccines against SARS-CoV-2 infection appear to be safe and effective, equivalent data for vaccines using other platforms (e.g. adenovirus vector based vaccines, inactivated vaccines) are not yet available. Urgent clinical trials and real-world safety and effectiveness studies are needed to advocate use of other vaccines in pregnant women.

Strengths of our study include a large national population of pregnant women, with robust testing and vaccination data and availability of data on variants of concern. Of all infections diagnosed on these pregnant women, 74 were alpha variant (previously known as the B1.1.7 variant), 163 were beta variant (previously known as the B1.351 variant), and 156 were variants of unknown status. Our previous work has shown that the Pfizer-BNT162b2 vaccine is 89.5% effective against the alpha variant (previously known as the B1.1.7 variant) and 75% effective against the beta variants (previously known as the B1.351 variant).[4] The predominant variant in Qatar during the first half of the study was the alpha variant, while beta variant accounted for over 75% of the infections during the second half of the study. Due to the very small number of outcome events, we were not able to accurately determine vaccine effectiveness against severe disease and death. However, there were 8 COVID-19 severe disease cases, one critical disease case, and no deaths in the PCR-positive pregnant women, all of which were among those unvaccinated and none among those vaccinated. We did not assess the individual effectiveness of the Pfizer-BNT162b2 and Moderna-mRNA-1273 vaccines. However, key clinical trials have shown them to be equally efficacious.[1,2]

In conclusion, the mRNA vaccines are associated with a 67.7% effectiveness against documented infection $\geq$14 days after the second dose. While lower than the effectiveness observed in non-pregnant persons, the extremely low number of more severe outcome events among the vaccinated group provides strong supporting evidence to include pregnant women in SARS-CoV-2 vaccination campaigns.

Methods

Study Setting and Participants

The study was carried out at Hamad Medical Corporation in Qatar, which provides approximately 85% of the hospital bed capacity in Qatar. A specialty care hospital for women caters to more than 75% of the deliveries in Qatar. SARS-CoV-2 vaccination campaign began in Qatar in December 2020, prioritizing high risk individuals early in the campaign due to limited global supplies of the vaccine. The earliest persons to be vaccinated included those >70 years old, those with comorbidities, and frontline healthcare workers. Vaccination was rapidly expanded to younger age groups in a stepwise fashion. Pregnancy itself was not a priority condition, though pregnant women were encouraged to get vaccinated based on age and comorbidity criteria.

All women who presented to Hamad Medical Corporation between December 20, 2020 and May 30, 2021 with confirmed pregnancy were eligible to be included for the current study. Pregnant women were identified from the centralized hospital electronic medical records. Pregnancy was ascertained by presence of diagnostic codes for pregnancy in women attending antenatal clinics. We excluded those who were tested for SARS-CoV-2 by RT-PCR on a nasopharyngeal swab prior to pregnancy and those who had no SARS-CoV-2 testing done between December 20, 2020 and May 30, 2021. For each woman who tested among the vaccinated group, we identified up to 3 RT-PCR negative controls matched on age and reason for testing.

Statistical Analyses

We used test-negative case control design to determine the effectiveness of vaccination against confirmed SARS-CoV-2 infection. This design is a widely accepted standard to determine vaccine effectiveness in a population after the introduction of a vaccine.[13-15] Vaccine effectiveness was determined using the following formula:

$$Vaccine\ effectiveness = 1 - \frac{(\text{tested positive among vaccinated x tested negative among unvaccinated})}{(\text{tested negative among vaccinated x tested positive among unvaccinated})}$$

The test-negative design is predicated on negative controls getting tested for symptoms compatible with the outcome of intertest (in this case, SARS-CoV-2 infection). In a real-world setting, those getting tested for a specific disease or infection approximate this population and the above formula can be applied.[13] We have used the same design to report overall effectiveness of the Pfizer-BNT162b2 vaccine against the B1.1.7 and B1.351 variants in Qatar.[4] We used STATA SE 16.1 (Stata Corporation, College Station TX) for statistical analyses.

Outcomes

We determined overall vaccine effectiveness ≥14 days after the second dose of the vaccine as our primary outcome of interest. We also determined vaccine effectiveness ≥14 days after the first dose up to the date of the second dose. For all point estimates of vaccine effectiveness, we calculated the corresponding 95% confidence intervals.[16,17]

Declarations

Data Availability Statement

Requests for deidentified and aggregate data must be directed to the Ministry of Public Health in the State of Qatar. Any request must fulfil all requirements for data sharing according the existing laws, regulations, and policies of the State of Qatar. Any data sharing will be at the sole discretion of the relevant legal authorities in the State of Qatar.

Code Availability

Statistical code can be provided upon request made to the authors.

Acknowledgement and disclaimer:

The authors are grateful for the leadership and assistance provided by the Ministry of Public Health in Qatar, the System-Wide Incident Command and Control Center and the Business Intelligence Unit at Hamad Medical Corporation, and all the dedicated frontline healthcare workers who have selflessly served and provided care and comfort to all patients in Qatar. The views expressed in this article are those of the authors and do not necessarily represent official government views or policy of the State of Qatar or Hamad Medical Corporation.

Author contributions:

Concept and study design: AAB, LJA, HC

Drafting of the manuscript: AAB

Data acquisition: AHK, ANL

Data analysis: AAB, HC, LJA

Data interpretation: AAB, LJA

Critical appraisal and review: AAB, LJA, HC, AAK, PC, AHK, HS, ANL, RB, AA

Competing interests/Disclosures: Dr. Butt has received investigator initiated grant funding (to the institution, Veterans Health Foundation of Pittsburgh) which is unrelated to the work presented here. Other authors declare no financial conflict of interest regarding the content of this article.

References

1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021;384(5):403-416.

2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020;383(27):2603-2615.

3. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med.* 2021;384(15):1412-1423.

4. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med.* 2021:DOI: 10.1056/NEJMc2104974.

5. Crovetto F, Crispi F, Llurba E, Figueras F, Gómez-Roig MD, Gratacós E. Seroprevalence and presentation of SARS-CoV-2 in pregnancy. *Lancet.* 2020;396(10250):530-531.

6. Norman M, Navér L, Söderling J, et al. Association of Maternal SARS-CoV-2 Infection in Pregnancy With Neonatal Outcomes. *JAMA.* 2021;325(20):2076-2086.

7. Song D, Prahl M, Gaw SL, et al. Passive and active immunity in infants born to mothers with SARS-CoV-2 infection during pregnancy: Prospective cohort study. *medRxiv.* 2021.

8. Wang EW, Parchem JG, Atmar RL, Clark EH. SARS-CoV-2 Vaccination During Pregnancy: A Complex Decision. *Open forum infectious diseases.* 2021;8(5):ofab180.

9. Cruz Melguizo S, de la Cruz Conty ML, Carmona Payán P, et al. Pregnancy Outcomes and SARS-CoV-2 Infection: The Spanish Obstetric Emergency Group Study. *Viruses.* 2021;13(5).

10. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol.* 2021.

11. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med.* 2021.

12. Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *J Clin Invest.* 2021.

13. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine.* 2013;31(17):2165-2168.

14. Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls C, 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;31(6):836-843.

15. Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol.* 2016;184(5):345-353.

16. Hightower AW, Orenstein WA, Martin SM. Recommendations for the use of Taylor series confidence intervals for estimates of vaccine efficacy. *Bull World Health Organ.* 1988;66(1):99-105.

17. Austin PC. Type I error rates, coverage of confidence intervals, and variance estimation in propensity-score matched analyses. *Int J Biostat.* 2009;5(1):Article 13.

Figures

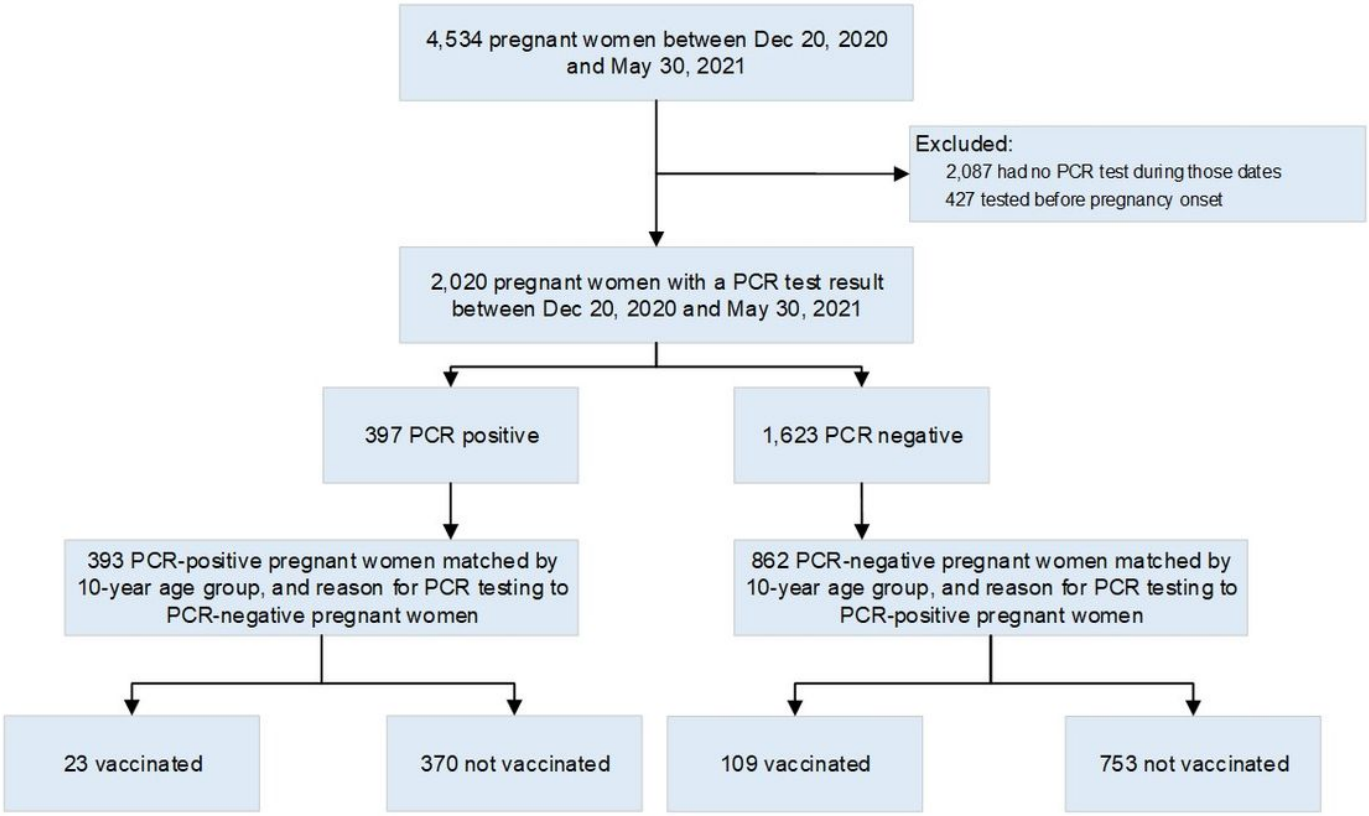

Figure 1

Flowchart of dataset creation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx
- flatButtepc.pdf