# SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women

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**BACKGROUND.** SARS-CoV-2 infection in pregnancy is associated with a higher risk of pregnancy-related complications and neonatal respiratory distress and hospitalization. Effectiveness of SARS-CoV-2 vaccines in pregnant women is not known.

**METHODS.** All women with confirmed pregnancy who presented to the national referral hospital in Qatar between December 20, 2020, and May 30, 2021, with at least 1 SARS-CoV-2 test and not testing prior to pregnancy were included. We determined the vaccine effectiveness of mRNA vaccines in preventing confirmed SARS-CoV-2 infection during pregnancy using both cohort and test-negative case-control designs. Analyses were adjusted for age group, nationality, and gestational age.

**RESULTS.** Among 4534 pregnant women, there were 407 vaccinated and 407 unvaccinated women in the matched cohort analysis. Vaccine effectiveness was 87.6% (95%CI 44.1%–97.2%) at least 14 days after the second dose. There were 386 test-positive and 834 matched women in the test-negative case control analysis. Vaccine effectiveness was 86.8% (95%CI 47.5%–98.5%) at least 14 days after the second dose. Adjustment for age, nationality, and gestational age yielded similar results for both designs. In the test-negative analysis, vaccine effectiveness at least 14 days after the first dose but before the second dose was 40.8% (95% CI 0.0%–80.4%). Of the 386 test-positive pregnant women, 74 cases were Alpha variant, 163 cases were Beta variant, and 156 cases were variants of unknown status. There were 9 severe or critical disease cases and no deaths in the test-positive pregnant women, all of whom were unvaccinated.

**CONCLUSION.** The mRNA vaccines provide a high level of protection against documented SARS-CoV-2 infection, which supports the inclusion of pregnant women in vaccination campaigns.

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## Introduction

Several vaccines for the SARS-CoV-2 infection have received emergency use authorization around the globe. The earliest vaccines to obtain such authorization were the BioNTech-162b2 (Pfizer) and the mRNA-1273 (Moderna) vaccines, with the BioNTech-162b2 vaccine receiving a full formal approval from the US Food and Drug Administration in August 2021. Early randomized clinical trials using these vaccines reported an efficacy of 94% to 95% in preventing confirmed SARS-CoV-2 infection or symptomatic COVID-19 disease (1, 2). Subsequent 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, hospitalization, and pregnancy loss before 24 weeks (5–7). When maternal infection occurs more than 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 to 28 weeks (8). Despite being at a potentially high risk of more severe disease and adverse outcomes, pregnant women were excluded from the vaccine efficacy trials (9). Other than a recent study from Israel, which reported an absolute difference of 1.31% (95% CI, 0.89%–1.74%) with an adjusted hazard ratio of 0.22 (95% CI, 0.11–0.43) among vaccinated versus unvaccinated pregnant women (10), there are very limited data 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

*Cohort design analyses.* Among the 4534 women with confirmed pregnancy identified between December 20, 2020, and May 30, 2021, we identified 407 vaccinated pregnant

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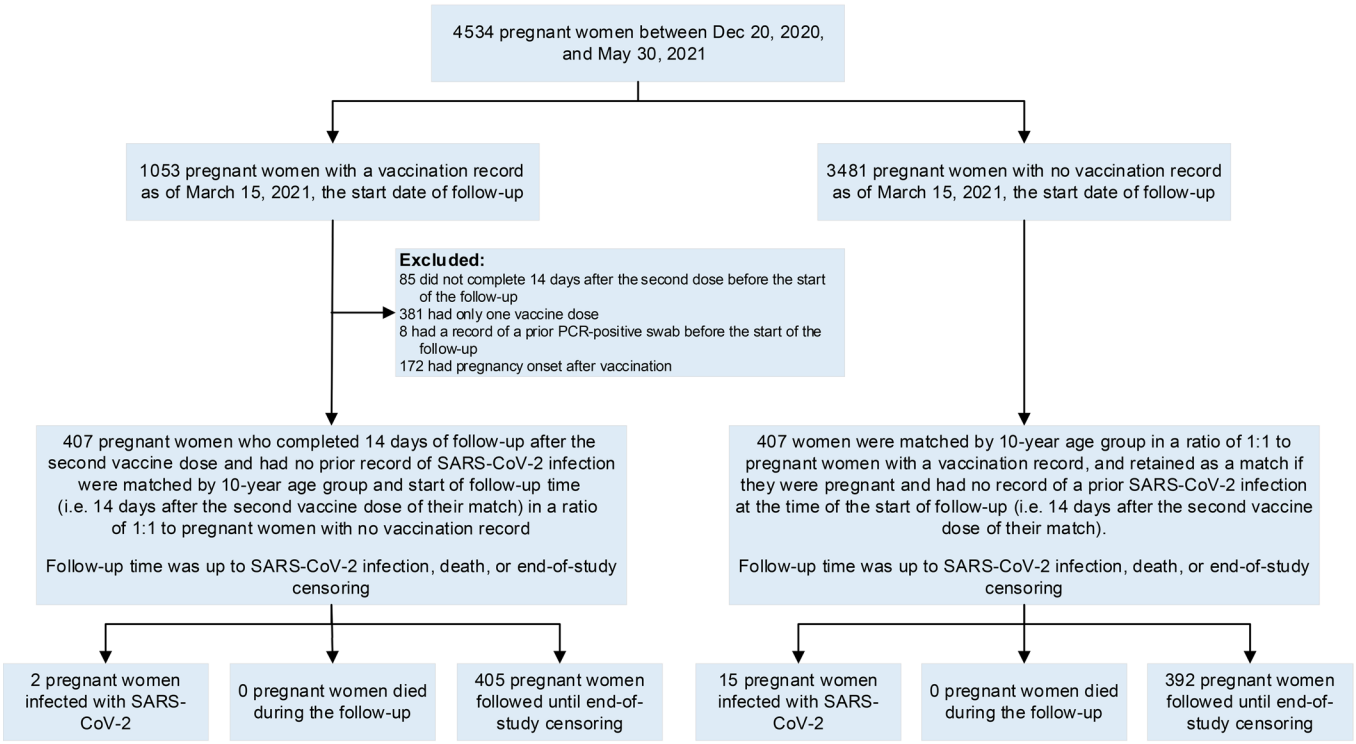



**Figure 1. Flowchart of data set creation for the cohort design.**

**Table 1. Baseline characteristics of the matched cohorts of fully vaccinated and of unvaccinated pregnant women**

| Characteristics[A] | Vaccinated, *n* = 407 | Unvaccinated, *n* = 407 | *P* |
|---|---|---|---|
| Median age (IQR), years | 32 (29–36) | 32 (28–36) | 0.180 |
| Age group, no. (%) | | | 1.000 |
| 15–24 years | 26 (6.4) | 26 (6.4) | |
| 25–34 years | 238 (58.5) | 238 (58.5) | |
| 35–44 years | 141 (34.6) | 141 (34.6) | |
| 45+ years | 2 (0.5) | 2 (0.5) | |
| Nationality[A] | | | 0.061 |
| Bangladeshi | 3 (0.7) | 4 (1.0) | |
| Egyptian | 47 (11.6) | 26 (6.4) | |
| Filipino | 28 (6.9) | 19 (4.7) | |
| Indian | 75 (18.4) | 73 (17.9) | |
| Nepalese | 2 (0.5) | 1 (0.3) | |
| Pakistani | 15 (3.7) | 30 (7.4) | |
| Qatari | 78 (19.2) | 88 (21.6) | |
| Sri Lankan | 4 (1.0) | 8 (2.0) | |
| Sudanese | 14 (3.4) | 20 (4.9) | |
| Other nationalities[B] | 141 (34.6) | 138 (33.9) | |
| Gestational age | | | 0.002 |
| <12 weeks | 63 (15.5) | 43 (10.6) | |
| 12–15 weeks | 122 (30.0) | 89 (21.9) | |
| 16–19 weeks | 110 (27.0) | 140 (34.4) | |
| 20–24 weeks | 112 (19.8) | 135 (33.2) | |

[A]Nationalities were chosen to represent the most populous groups in Qatar. [B]These comprise 30 other nationalities in Qatar among fully vaccinated women and 29 other nationalities among unvaccinated women.

women with at least 14 days of follow-up after the second vaccine dose, after excluding those with a record of prior SARS-CoV-2 infection and those who had at least 1 dose of vaccine before pregnancy onset. Vaccinated pregnant women were matched by 10-year age group in a ratio of 1:1 to pregnant women with no vaccination record and no record of a prior SARS-CoV-2 infection at the time of the start of follow-up. Time of follow-up started from 14 days after the second vaccine dose for each vaccinated woman and on the same date for her unvaccinated match. That is, each pair of vaccinated and unvaccinated pregnant women was followed starting from the same day (Figure 1). Median age was 32 years (IQR 29–36 years) for the vaccinated group and 32 years (IQR 28–36 years) for the unvaccinated group. Age groups, nationality, and gestational age data for the 2 groups are provided in Table 1. Of the 407 vaccinated women, 323 (79.4%) received their first vaccine dose during the first trimester, while the other 84 (20.6%) received their first vaccine dose during the second trimester. There were a total of 127 tests conducted 14 days after the second vaccine dose and up to May 30, 2021, among the 407 vaccinated women, of which a total of 3 tests (for 2 cases) were positive. There were in total 75 tests conducted among the 407 unvaccinated women, of which a total of 17 tests were positive (for 15 cases).

The total follow-up time was 1891.0 person-weeks for the vaccinated group and 1816.4 person-weeks for the unvaccinated group. Cumulative incidence of SARS-CoV-2 infection was 0.96% (95% CI 0.24%–3.78%) for the vaccinated group and 6.57% (3.82%–10.87%) for the unvaccinated group. Unadjusted vaccine effectiveness was 87.1% (95% CI 43.4%–97.1%) using the matched

**Table 2. Effectiveness of the mRNA SARS-CoV-2 vaccines against confirmed SARS-CoV-2 infection in pregnant women using the matched cohort study design**

| Measure | Fully vaccinated[A] | Unvaccinated[A] |
|---|---|---|
| Cumulative incidence (95% CI) at 50 days after follow-up | 0.96% (0.24%–3.78%) | 6.57% (3.82%–10.87%) |
| Total follow-up time in person-weeks | 1891.0 | 1816.4 |
| Incidence rate (95% CI) per 10,000 person-weeks[B] | 10.58 (2.65–42.29) | 82.58 (49.78–136.98) |
| Unadjusted hazard ratio (95% CI)[C] | 0.13 (0.03–0.57) | |
| Unadjusted vaccine effectiveness | 87.1% (43.4%–97.1%) | |
| Adjusted hazard ratio (95% CI)[D] | 0.12 (0.03–0.56) | |
| Adjusted vaccine effectiveness (95% CI) | 87.6% (44.1%–97.2%) | |
| Adjusted hazard ratio, BNT162b2 (95% CI)[E] | 0.12 (0.03–0.56) | |
| Adjusted vaccine effectiveness, BNT162b2 (95% CI)[E] | 87.7% (43.5%–97.3%) | |
| Adjusted hazard ratio, mRNA-1273 (95% CI)[F] | 0.00 (0.0–1.0) | |
| Adjusted vaccine effectiveness, mRNA-1273 (95% CI)[F] | 100.0% (0.0%–100.0%) | |

[A]Matched by 10-year age group and vaccination date. [B]Using Poisson model. [C]Using Cox regression. [D]Using Cox regression adjusting for 10-year age group, nationality (see Table 3), and gestational age (see Table 3). [E]Sample included 299 pregnant women who completed at least 14 days of follow-up after the second BNT162b2 vaccine dose and 299 matched pregnant women with no vaccination record and no prior infection. Follow-up for these women was 1652.6 and 1578.1 person-weeks, respectively. [F]Sample included 108 pregnant women who completed at least 14 days of follow-up after the second mRNA-1273 vaccine dose and 108 matched pregnant women with no vaccination record and no prior infection. Follow-up for these women was 238.4 and 238.3 person-weeks, respectively. Given zero events among the vaccinated women, hazard ratio was estimated with no ties, and the upper bound for the confidence interval used the rule of 3 method.

cohorts by 10-year age group and vaccination time. After additionally adjusting for age group, nationality, and gestational age in Cox regression, the vaccine effectiveness was 87.6% (95% CI 44.1-97.2%) (Table 2). Kaplan-Meier curves showing the incidence of infection show a very early divergence in the cohorts of vaccinated and unvaccinated pregnant women (Figure 2).

*Test-negative case control design analyses*. Between December 20, 2020, and May 30, 2021, we identified 4534 women with confirmed pregnancy. We excluded 2087 women without any SARS-CoV-2 testing during the study period, 427 women who were tested before pregnancy onset, and 74 women who had at least 1 dose of vaccine before pregnancy onset (Figure 3). Among the remaining 1946 pregnant women, 389 had a positive SARS-CoV-2 RT-PCR and 1557 had a negative test. For 386 pregnant women who tested positive for SARS-CoV-2 by RT-PCR, we found 834 matched controls who tested negative by RT-PCR using an algorithm to find up to 3 controls for each case. Three women who tested positive by PCR analysis were at least 45 years of age and were tested because of appearance of symptoms. We could not match them to women who tested negative by PCR in this age group and who were tested because of presence of symptoms.

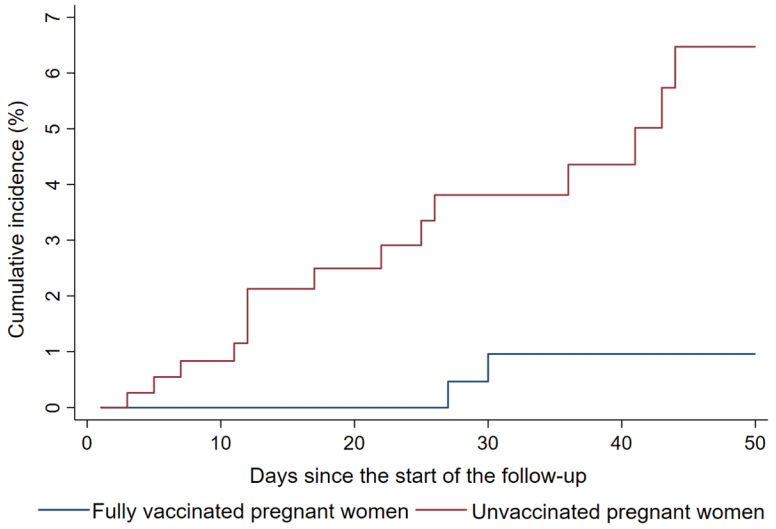
Our final study groups consisted of 16 vaccinated and 370 unvaccinated cases (test-positive group) and 87 vaccinated and 747 unvaccinated controls (test-negative group). Of the 1946 pregnant women, 433 had a vaccination record; 337 (77.8%) received the Pfizer-BNT-162b2 vaccine and 96 (22.2%) received the Moderna-mRNA-1273 vaccine; 255 (58.9%) had received 2 vaccine doses. Of the 16 vaccinated women who were PCR-positive for SARS-CoV-2, 13 were infected after the first dose, 1 was infected within the first 14 days after the second dose, and 2 were infected at least 14 days after the second dose.

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 3. Vaccine effectiveness at least 14 days after the second dose was 86.8% (95% CI 47.5%–98.5%), while vaccine effectiveness at least 14 days after the first dose but before the second dose was 40.8% (95% CI 0.0%–80.5%) (Table 4). Of all infections diagnosed in the pregnant women, 74 were Alpha variant (previously known as the B.1.1.7 variant), 182 were Beta variant (previously known as the B.1.351 variant), and 130 were variants of unknown status. 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 cases of COVID-19 severe disease, 1 case of critical disease, and no deaths in the pregnant women who were PCR-positive for SARS-CoV-2, all of which were among those who were unvaccinated and none among those who were vaccinated. The woman with critical disease was in her second trimester. Of the 8 women with severe disease, 6 were in their first trimester and 2 were in their second trimester (Supplemental Table 1).

## Discussion

To our knowledge, this is the first large-scale study of SARS-CoV-2 vaccine effectiveness in pregnant women that uses both cohort and test-negative case control designs to calculate vaccine effectiveness in a real-world setting. We found the vaccine effectiveness of the SARS-CoV-2 mRNA vaccine to be approximately 87% in preventing any documented infection in pregnant women in a real-world setting.

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 preeclampsia, preterm birth, and fetal death (11, 12). Early studies have not shown any obvious safety issues with the mRNA vaccines in pregnant women (13), 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 (8, 14). In an exploratory analysis of a convenience sample of 30 pregnant, 16 lactating, and 57 nonpregnant, nonlactating women who received either the Moderna mRNA-1273 or Pfizer BNT162b2 vaccine, immunogenicity was demonstrated in pregnant women and vaccine-elicited antibodies were transported to infant cord blood and breast milk (15). In another study that prospectively enrolled 131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, and 16 nonpregnant women), mRNA vaccines generated robust humoral immunity in




| Time, days | 0 | 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|---|
| **No. at risk** | | | | | | |
| Fully vaccinated | 407 | 326 | 254 | 201 | 158 | 103 |
| Unvaccinated | 407 | 323 | 247 | 192 | 150 | 93 |
| **Cumulative no. of events** | | | | | | |
| Fully vaccinated | 0 | 0 | 0 | 2 | 2 | 2 |
| Unvaccinated | 0 | 3 | 8 | 11 | 12 | 15 |

**Figure 2. Flowchart of data set creation for the test-negative case control design.**

pregnant and lactating women, which was similar to that observed in nonpregnant women (16). These data coupled with high effectiveness in preventing SARS-CoV-2 infection provide 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. Furthermore, newer variants of concern have emerged, with the Delta variant being the predominant strain in the United States, the United Kingdom, Qatar, and many other countries since May 2021. It has been suggested that the Delta variant is more infectious and associated with reduced vaccine effectiveness and poorer clinical outcomes compared with the earlier variants of concern (17, 18).

Vaccinations for various infectious diseases are recommended in pregnant women to reduce the risk of infections and their consequences in the mother as well as the newborn. However, vaccine efficacy and effectiveness studies in pregnant women have often been limited by variable study design, lack of uniform outcomes measures, and heterogeneity of participants in terms of gestational age. When indicated, vaccination in pregnancy has been associated with widely varying estimates of effectiveness (19–21). These variations may be ascribed to the physiologic changes in pregnancy, including altered total body weight and volume of distribution, and an immunosuppressed state. Whether alternate vaccination strategies in pregnant women, such as higher or more frequent doses, may affect outcomes is not known.

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 diag-

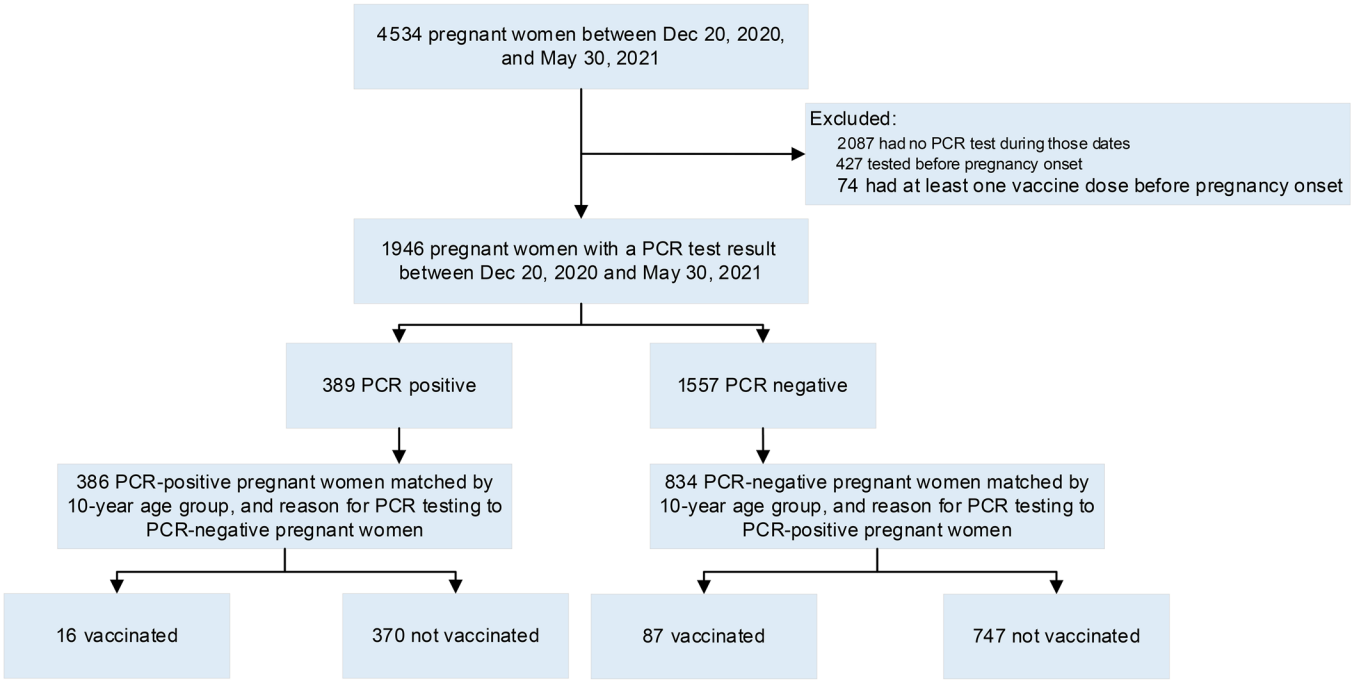



**Figure 3. Kaplan-Meier curves showing the incidence of infection in the matched cohorts of vaccinated and unvaccinated pregnant women.**

**Table 3. Demographics of cases and controls**

| Characteristics | Cases[A] (PCR positive), *n* = 386 | Controls[A] (PCR negative), *n* = 834 | *P* |
|---|---|---|---|
| Median age (IQR), years | 31 (28–35) | 31 (27–34) | 0.107 |
| Age group, no. (%) | | | |
| 15–24 years | 44 (11.4) | 110 (13.2) | 0.285 |
| 25–34 years | 228 (59.1) | 519 (62.2) | |
| 35–44 years | 113 (29.3) | 202 (24.2) | |
| 45+ years | 1 (0.3) | 3 (0.4) | |
| Nationality[B] | | | |
| Bangladeshi | 9 (2.3) | 9 (1.1) | 0.002 |
| Egyptian | 38 (9.8) | 51 (6.1) | |
| Filipino | 25 (6.5) | 51 (6.1) | |
| Indian | 42 (10.9) | 111 (13.3) | |
| Nepalese | 0 (0.0) | 4 (0.5) | |
| Pakistani | 28 (7.3) | 38 (4.6) | |
| Qatari | 80 (20.7) | 251 (30.1) | |
| Sri Lankan | 6 (1.6) | 8 (1.0) | |
| Sudanese | 21 (5.4) | 32 (3.8) | |
| Other nationalities[C] | 137 (35.5) | 279 (33.5) | |
| Gestational age | | | 0.098 |
| <12 weeks | 20 (5.2) | 71 (8.5) | |
| 12–15 weeks | 84 (21.8) | 164 (19.7) | |
| 16–19 weeks | 141 (36.5) | 328 (39.3) | |
| 20–24 weeks | 141 (36.5) | 271 (32.5) | |
| Reason for PCR testing | | | 0.001 |
| Clinical suspicion | 188 (48.7) | 297 (35.6) | |
| Contact tracing | 51 (13.2) | 100 (12.0) | |
| Survey | 90 (23.3) | 266 (31.9) | |
| Port of entry | 19 (4.9) | 57 (6.8) | |
| Individual request | 15 (3.9) | 45 (5.4) | |
| Healthcare routine testing | 17 (4.4) | 51 (6.1) | |
| Before travel | 6 (1.6) | 18 (2.2) | |

[A]Cases and controls were matched by 10-year age group and reason for PCR testing (up to 3 controls per case). [B]Nationalities were chosen to represent the most populous groups in Qatar. [C]These comprise 29 other nationalities in Qatar among cases, 37 other nationalities among controls.

nosed on the pregnant women in our study, 74 were Alpha variant, 182 were Beta variant, and 130 were variants of unknown status. Our previous work has shown that the Pfizer-BNT162b2 vaccine is 89.5% effective against the Alpha variant and 75% effective against the Beta variant (4). The predominant variant in Qatar during the first half of the study was the Alpha variant, while the 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, all cases of severe or critical disease were among the unvaccinated women and there were no deaths. The vaccine effectiveness at least 14 days after the first dose but before the second dose was 40.8%. Due to the small number of events, the confidence interval is wide, and these results should be interpreted with caution. We assessed the individual effectiveness of the Pfizer-BNT162b2 and Moderna-mRNA-1273 vaccines, but again, the number of events was small, particularly in those who received the mRNA-1273 vaccine, yielding very wide 95% confidence intervals. Previously published key clinical trials have shown the vaccines to be equally efficacious (1, 2). While our study provides robust estimates of vaccine effectiveness in pregnant women, we did not determine the safety or reactogenicity of the vaccines. An additional limitation is the lack of information on comorbidities, which may affect the risk of infection and/or outcomes after infection. However, the burden of comorbidities in this otherwise young population is expected to be small and unlikely to affect the main results of our study. Finally, we did not match the cases and controls for the time of testing, which can be an important factor in determining the risk and level of exposure in a community.

In conclusion, the mRNA vaccines are associated with an 87% effectiveness against documented infection at least 14 days after the second dose. While slightly lower than the effectiveness observed in nonpregnant persons, the extremely low number of 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, the Women's Wellness and Research Center, part of Hamad Medical Corporation, caters to more than 75% of the deliveries in Qatar and was the setting for the current study. The 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 over 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 in the present 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. For the cohort design, we identified women with and without vaccination from among all pregnant women. Among the vaccinated group we excluded those with fewer than 14 days of follow-up after the second vaccine dose, those who received only a single vaccine dose, those with prior SARS-CoV-2 infection, and those with pregnancy onset after vaccination. Among the unvaccinated, we excluded those with prior SARS-CoV-2 infection. For the test-negative case control analyses, we excluded those women who were tested for SARS-CoV-2 by RT-PCR on a nasopharyngeal swab prior to pregnancy and those women who had no SARS-CoV-2 testing done between December 20, 2020, and May 30, 2021, as well as those who had at least 1 dose of vaccination before pregnancy onset. For each woman who tested positive, we identified up to 3 RT-PCR negative controls matched on age and reason for testing.

**Table 4. Effectiveness of the mRNA SARS-CoV-2 vaccines against confirmed SARS-CoV-2 infection among pregnant women at least 14 days after the first dose and at least 14 days after the second dose using the test-negative case control design**

| | Cases (PCR positive) | | Controls (PCR negative) | | Effectiveness, % (95% CI) |
|---|---|---|---|---|---|
| | Vaccinated | Unvaccinated | Vaccinated | Unvaccinated | |
| **Matching in a 1:3 ratio by 10-year age group and reason for PCR testing** | | | | | |
| ≥14 days after first dose and no second dose | 6 | 336 | 22 | 729 | 40.8 (0.0–80.5) |
| ≥14 days after second dose | 2 | 312 | 32 | 661 | 86.8 (47.5–98.5) |
| **Adjusting for 10-year age group, nationality, and gestational age in logistic regression** | | | | | |
| ≥14 days after first dose and no second dose | 6 | 336 | 22 | 729 | 46.3 (0.0–78.8) |
| ≥14 days after second dose | 2 | 312 | 32 | 661 | 88.1 (49.4–97.2) |

*Outcomes*. Our primary outcome was overall vaccine effectiveness in preventing confirmed infection at least 14 days after the second dose of the vaccine. For all point estimates of vaccine effectiveness, we calculated the corresponding 95% confidence intervals (22, 23).

*Cohort design*. Among the vaccinated group we excluded those with fewer than 14 days of follow-up after the second vaccine dose, those who received only a single vaccine dose, and those who had at least 1 dose of vaccine before pregnancy onset. Vaccinated pregnant women were matched by age group in a 1:1 ratio to women with no vaccination record but who were pregnant and had no record of a prior infection at the time of the start of follow-up, set at 14 days after the second vaccine dose for those vaccinated and their vaccinated matches. Vaccinated women and their unvaccinated matches were thus followed from the same date up to SARS-CoV-2 infection, death, or end-of-study censoring (set at May 30, 2021).

*Statistics*. Cumulative incidence of confirmed SARS-CoV-2 infection in the matched cohorts of vaccinated and unvaccinated women were estimated using the Kaplan-Meier estimator method, and incidence rates per 10,000 person-weeks were estimated using Poisson regression. Unadjusted and adjusted (for age, nationality, and gestational age) Cox regression analyses were used to calculate vaccine effectiveness among pregnant women using 1 minus the hazard ratio. We used STATA SE 16.1 (Stata Corporation) for statistical analyses.

*Test-negative case control design*. The test-negative case control design is a widely accepted standard to determine vaccine effectiveness in a population after the introduction of a vaccine (24–26). Vaccine effectiveness was determined using the following formula: vaccine effectiveness = 1 – odds (test + vaccinated) / odds (test + non-vaccinated). We used the same design to report overall effectiveness of the Pfizer-BNT162b2 vaccine against the B1.1.7 and B1.351 variants in Qatar and among US veterans in the United States (4, 27).

*Study approval*. The study was approved by the Hamad Medical Corporation IRB. A waiver of informed consent was granted for the study because no actual patient contact occurred.

## Author contributions

AAB, HC, and LJAR conceived and designed the study. AAB drafted the manuscript. AHK and ANL acquired the data. HC, AAB, and LJAR analyzed the data. AAB and LJAR interpreted the data. AAB, LJAR, HC, AAK, PVC, AHK, HS, ANL, RB, and ABAS critically appraised and reviewed the manuscript.

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