



Evaluation of immunogenicity and reactogenicity of COVID-19 vaccines in pregnant women

H. BLAKEWAY¹, Z. AMIN-CHOWDHURY², S. PRASAD¹, E. KALAFAT^{3,4}, M. ISMAIL¹, F. N. ABDALLAH¹, A. REZVANI¹, G. AMIRTHALINGAM², K. BROWN², K. LE DOARE⁵, P. T. HEATH⁵, S. N. LADHANI^{2,5#} and A. KHALIL^{1,6#}

¹Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK; ²Immunisation and Vaccine Preventable Diseases Division, UK Health Security Agency, London, UK; ³Koc University, School of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey; ⁴Department of Statistics, Faculty of Arts and Sciences, Middle East Technical University, Ankara, Turkey; ⁵Centre for Neonatal and Paediatric Infection and Vaccine Institute, Institute of Infection and Immunity, St George's University of London, London, UK; ⁶Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

KEYWORDS: adverse event; antibody; COVID-19; immunogenicity; maternal immunization; pandemic; pregnancy; reactogenicity; SARS-CoV-2; vaccine

CONTRIBUTION

What are the novel findings of this work?

Antibody responses after vaccination were lower in pregnant compared with non-pregnant women. Very high antibody titers were elicited by one dose in previously infected women. Pregnant women experienced fewer adverse events than non-pregnant women after the first and second doses of vaccine.

What are the clinical implications of this work?

This study provides valuable data on the immunogenicity and reactogenicity of mRNA vaccines in pregnancy using the extended-interval dosing schedule recommended in the UK. Prior infection was associated with very high antibody levels after the first mRNA vaccine dose. A single dose of vaccine may be sufficient for previously infected pregnant women.

ABSTRACT

Objective Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pregnancy is associated with increased risk of adverse maternal and perinatal outcomes. Vaccines are highly effective at preventing severe coronavirus disease 2019 (COVID-19), but there are limited data on COVID-19 vaccines in pregnancy. This study aimed to investigate the reactogenicity and immunogenicity of COVID-19 vaccines in pregnant women when

administered according to the 12-week-interval dosing schedule recommended in the UK.

Methods This was a cohort study of pregnant women receiving COVID-19 vaccination between April and September 2021. The outcomes were immunogenicity and reactogenicity after COVID-19 vaccination. Pregnant women were recruited by phone, e-mail and/or text and were vaccinated according to vaccine availability at their local vaccination center. For immunogenicity assessment, blood samples were taken at specific timepoints after each dose to evaluate nucleocapsid protein (N) and spike protein (S) antibody titers. The comparator group comprised non-pregnant female healthcare workers in the same age group who were vaccinated as part of the national immunization program in a contemporaneous longitudinal cohort study. Longitudinal changes in serum antibody titers and association with pregnancy status were assessed using a two-step regression approach. Reactogenicity assessment in pregnant women was undertaken using an online questionnaire. The comparator group comprised non-pregnant women aged 18–49 years who had received two vaccine doses in primary care. The association of pregnancy status with reactogenicity was assessed using logistic regression analysis.

Results Overall, 67 pregnant women, of whom 66 had received a mRNA vaccine, and 79 non-pregnant women, of whom 50 had received a mRNA vaccine, were included in the immunogenicity study. Most (61.2%) pregnant

Correspondence to: Prof. A. Khalil, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK (e-mail: asmakhalil79@googlemail.com; akhalil@sgul.ac.uk)

#S.N.L. and A.K. are joint last authors.

Accepted: 29 July 2022

women received their first vaccine dose in the third trimester, while 3.0% received it in the first trimester and 35.8% in the second trimester. SARS-CoV-2 S-antibody geometric mean concentrations after mRNA vaccination were not significantly different at 2–6 weeks after the first dose but were significantly lower at 2–6 weeks after the second dose in infection-naïve pregnant compared with non-pregnant women. In pregnant women, prior infection was associated with higher antibody levels at 2–6 weeks after the second vaccine dose. Reactogenicity analysis included 108 pregnant women and 116 non-pregnant women. After the first dose, tiredness and chills were reported less commonly in pregnant compared with non-pregnant women ($P=0.043$ and $P=0.029$, respectively). After the second dose, feeling generally unwell was reported less commonly ($P=0.046$) in pregnant compared with non-pregnant women.

Conclusions Using an extended 12-week interval between vaccine doses, antibody responses after two doses of mRNA COVID-19 vaccine were found to be lower in pregnant compared with non-pregnant women. Strong antibody responses were achieved after one dose in previously infected women, regardless of pregnancy status. Pregnant women reported fewer adverse events after both the first and second dose of vaccine. These findings should now be addressed in larger controlled studies. © 2022 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has impacted both maternal and perinatal mortality and morbidity. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy is associated with increased risk of stillbirth, preterm birth, pre-eclampsia and Cesarean delivery^{1–3}. Furthermore, pregnant women are at particularly high risk of severe complications from COVID-19, with an increased risk of hospitalization, admission to an intensive care unit and death, compared with non-pregnant women⁴. The most effective method of reducing disease burden in pregnancy is vaccination⁵.

In December 2020, the UK became the first country⁶ to implement a national immunization program against COVID-19. Contrary to the 3–4-week interval between the first and second doses used in clinical trials, the UK government recommended a longer interval of up to 12 weeks to allow more rapid rollout of the first dose, which was estimated to provide up to 90% protection within 2 weeks of administration⁷. At the time of writing, adults in the UK, including pregnant women, are being offered a third dose to improve protection against circulating and emerging SARS-CoV-2 variants⁸. In April 2021, the UK Joint Committee on Vaccination and Immunisation advised that pregnant women should

be offered the vaccine at the same time as that in non-pregnant people in the same age group⁹. Since then, the Royal College of Obstetricians and Gynaecologists and the Royal College of Midwives have called repeatedly for pregnant women to be vaccinated against COVID-19; in January 2022, around 59% of pregnant women had been vaccinated against COVID-19 in the UK^{10,11}.

A COVID-19 vaccine is recommended and considered safe at any point during pregnancy¹². Research has documented the presence of maternal antibodies against SARS-CoV-2 at delivery regardless of the timing of vaccination during pregnancy, with maternal and umbilical cord antibody levels increasing with gestational age at vaccination up to 34 weeks^{13,14}.

There are limited data on the immunogenicity and reactogenicity of COVID-19 vaccines in pregnant women. Reactogenicity data from Israel and a large database study in the USA are reassuring^{15,16}, although these countries use a 3–4-week interval between COVID-19 vaccine doses. An extended 8–12-week two-dose schedule is recommended in the UK^{7,17} on the basis that it elicits higher antibody levels and stronger cellular responses after the second dose, compared with shorter-interval schedules¹⁷.

Following the UK decision to recommend COVID-19 vaccination for pregnant women, the UK Health Security Agency (UKHSA, formerly Public Health England) and St George's University Hospitals NHS Foundation Trust (SGUH), London, UK initiated rapidly an evaluation of pregnant women receiving COVID-19 vaccines as part of the national immunization program. The objective of this study was to investigate the immunogenicity and reactogenicity of COVID-19 vaccines in pregnant compared with non-pregnant women receiving two doses according to the 12-week extended-interval schedule.

METHODS

Study population and design

The UKHSA is responsible for the evaluation of the national immunization program. This was a prospective cohort study of women who received COVID-19 vaccination during pregnancy, undertaken in partnership with SGUH. Participants were identified from the hospital electronic records and invited to participate in the COVID-19 Vaccination in Pregnancy (COVIP) study by phone, email and/or text. Participants provided online consent and completed a short questionnaire about their pregnancy, complications, antenatal appointments and pregestational comorbidities using a secure online Snap Survey platform. The comparator group for antibody response assessment comprised non-pregnant women in the same age group who were vaccinated as part of the national immunization program in a contemporaneous longitudinal cohort study of healthcare workers in England (the ESCAPE study)¹⁸. The comparator group for reactogenicity assessments comprised non-pregnant women aged 18–49 years who had received two doses of the BNT16B2b2 (Comirnaty, Pfizer–BioNTech) vaccine in primary care under the

South West London Clinical Commissioning Group and were identified using the National Immunisation Management System database on 21 July 2021.

The women were vaccinated at their local COVID-19 vaccination center as part of the national immunization program. The administered vaccine depended on what was available at the time. Most pregnant women received BNT16B2b2, a mRNA vaccine containing 30 mg of spike-protein mRNA. Some received mRNA-1273 (Spikevax, Moderna), another mRNA vaccine containing 100 mg of spike-protein mRNA, or ChAd-Ox1/nCoV-19 (Vaxzevria, AstraZeneca), an adenovirus vector-based vaccine. With a stronger international evidence base supporting the safety of mRNA vaccines in pregnancy, and emerging reports of vaccine-induced thrombosis and thrombocytopenia following ChAd-Ox1/nCoV-19 administration, a recommendation was issued in April 2021 to vaccinate young adults and pregnant women with mRNA vaccines only^{9,19}.

Immunogenicity and reactogenicity assessment

To assess immunogenicity in pregnant women, the study protocol aimed to collect blood samples at the following timepoints: within 72 h (up to 7 days) after the first dose, at 6 ± 2 weeks after the first dose, within 72 h (up to 7 days) after the second dose and at 3 ± 2 weeks after the second dose. However, as this was a pragmatic evaluation of a national immunization program, the protocol did not restrict blood sampling outside the stated intervals. Serum samples were tested for nucleocapsid protein (N) antibodies using the Elecsys Anti-SARS-CoV-2 total antibody assay (Roche Diagnostics, Basel, Switzerland) and spike protein (S) antibodies using the Elecsys Anti-SARS-CoV-2 S total antibody assay (Roche Diagnostics: positive ≥ 0.8 arbitrary units/mL)^{18,20}. N-antibody positivity provided immunological confirmation of prior SARS-CoV-2 infection, whilst S-antibody positivity indicated previous infection and/or vaccination.

To assess reactogenicity in pregnant and non-pregnant women, data were collected on vaccine type, timing and solicited as well as unsolicited adverse events during the first 7 days after each vaccine dose using an online questionnaire hosted by Snap Survey (Appendix S1).

Statistical analysis

SARS-CoV-2 antibody geometric mean concentrations (GMCs) with 95% CI were calculated and compared between pregnant and non-pregnant women at each visit. GMCs were calculated by fitting interval regression models to correct for right-censored data, as there were instances in which antibody titers exceeded the limit of assay detection and further dilution was not performed to obtain true values. Left censoring, where antibody titers were below the assay's limit of detection, was rare and only affected the first timepoint, so was not corrected for in the models. Blood samples that were indeterminate or insufficient for testing were excluded from GMC

comparisons. Baseline characteristics of the pregnant and control groups were compared using the Wilcoxon signed-rank test or chi-square test. Changes in paired categorical data were assessed using McNemar's test.

Longitudinal changes in serum antibody levels were assessed using a two-step approach. First, the change in the antibody levels with respect to blood collection intervals (centered on the second dose) was modeled with mixed-effects polynomial regression. The likelihood-ratio test was used to determine the model fit and the random effects from the best model were extracted. In the second step, the association of random effects from individual patients with pregnancy status was assessed using linear regression analysis. Longitudinal changes in serum antibody levels were depicted using spaghetti plots and adverse events following vaccination were depicted using Likert plots. The association of pregnancy status with postvaccination reactogenicity was assessed using logistic regression analysis. *P*-values < 0.05 were considered statistically significant. All analyses were conducted using R for Statistical Computing Software and STATA version 15.1 (StataCorp., College Station, TX, USA).

RESULTS

Between April and September 2021, 270 pregnant women were approached to participate in the study, of whom 86 consented to take part in immunogenicity studies and 113 agreed to complete an online reactogenicity questionnaire.

Immunogenicity

In total, blood samples were taken from 67 pregnant women within the prespecified time intervals following each vaccine dose, including 66 women who received two doses of the same mRNA vaccine (64 BNT16B2b2, two mRNA-1273) and one who received two doses of ChAd-Ox1/nCoV-19. The woman receiving ChAd-Ox1/nCoV-19 vaccine was excluded from the statistical analysis. Of the participants, two (3.0%) received their first vaccine dose in the first trimester, 24 (35.8%) in the second trimester and 41 (61.2%) in the third trimester. In the control group of 79 non-pregnant female healthcare workers in the same age group who were vaccinated as part of the national immunization program, 50 received a mRNA vaccine (49 BNT16B2b2, one mRNA-1273) and 29 received ChAd-Ox1/nCoV-19. The baseline characteristics of pregnant and non-pregnant women are summarized in Table 1. Pregnant women were significantly older than controls ($P < 0.001$). The proportion of pregnant and non-pregnant women with evidence of prior COVID-19 infection (as determined by N-antibody positivity) was similar (16.4% vs 17.7%, $P = 0.83$).

Immunogenicity analysis was performed at the following timepoints: (1) within 2 weeks after the first dose, (2) 2–6 weeks after the first dose, (3) within 2 weeks after the second dose and (4) 2–6 weeks after the second dose. The medians and interquartile ranges for the time from vaccination to immunological assessment, as well

as the SARS-CoV-2 S-antibody GMCs, in pregnant women receiving a mRNA vaccine compared with non-pregnant women receiving a mRNA or ChAd-Ox1/nCoV-19 vaccine, are reported in Table 2. S-antibody GMCs after mRNA vaccination were not significantly different at 2–6 weeks after the first dose, but were significantly lower at 2–6 weeks after the second dose, in infection-naïve pregnant compared with non-pregnant women. In pregnant women, prior infection was associated with higher antibody levels at all timepoints; GMC

ratios between previously infected and infection-naïve pregnant women were 72.7 at 2–6 weeks after dose one, 18.1 within 2 weeks after dose two and 2.8 at 2–6 weeks after dose two, although the latter was not statistically significant. Comparing previously infected pregnant and non-pregnant women, S-antibody GMCs were significantly higher at 2–6 weeks after the first and second doses of mRNA vaccine in the latter cohort, although data were only available for one previously infected non-pregnant woman at 2–6 weeks after the second dose.

Table 1 Baseline characteristics of pregnant and non-pregnant women for whom immunogenicity data were available after second COVID-19 vaccine dose

Characteristic	Pregnant women (n = 67)	Non-pregnant women (n = 79)	P
Age			< 0.001
< 30 years	4 (6.0)	44 (55.7)	
30–34 years	33 (49.3)	18 (22.8)	
35–39 years	27 (40.3)	17 (21.5)	
≥ 40 years	3 (4.5)	0 (0)	
Vaccine type			< 0.001
mRNA	66 (98.5)	50 (63.3)	
Viral vector	1 (1.5)	29 (36.7)	
Previous COVID-19 infection	11 (16.4)	14 (17.7)	0.83
Gestational age at vaccination			
First trimester	2 (3.0)	—	—
Second trimester	24 (35.8)	—	—
Third trimester	41 (61.2)	—	—

Data are given as n (%).

Longitudinal changes in S-antibody levels 1 month following the first and second doses of vaccine were also assessed (Figure S1). Antibody titers rose sharply following the second dose and this increase was not significantly different between pregnant and non-pregnant women receiving mRNA vaccines ($P = 0.172$). Pregnancy outcomes are presented in Table S1.

Reactogenicity

A total of 108 pregnant women received at least one dose of mRNA vaccine and completed an online questionnaire on postvaccination reactogenicity. Those who did not return the questionnaire were excluded. The comparator group comprised 116 non-pregnant women aged 18–49 years who had received two doses of the BNT16B2 vaccine in primary care in South West London, UK. Tiredness (25% vs 38%), headache (16% vs 24%), joint ache (11% vs 20%), feeling generally unwell (11% vs 19%), chills (4% vs 12%) and fever (4% vs 9%) after the first dose were less commonly reported in

Table 2 Geometric mean anti-spike-protein (S) antibody concentration in infection-naïve and previously infected pregnant and non-pregnant women after COVID-19 vaccination

Timepoint	Pregnant women vaccinated with mRNA vaccine		Non-pregnant women					
	Days from dose to sampling	n	Anti-S antibody concentration (AU/mL)	Days from dose to sampling	n	Anti-S antibody concentration (AU/mL)	n	Anti-S antibody concentration (AU/mL)
N-antibody negative								
< 2 weeks after dose one	5	16*	0.70 (0.24–2.05)	12	11	12.00 (4.48–32.16)	3	1.07 (0.22–5.16)
2–6 weeks after dose one	33	17	160.61 (48.03–537.08)	28	50	102.10 (74.14–140.61)	29	32.26 (20.58–50.59)
< 2 weeks after dose two	4	33	625.76 (287.38–1362.59)	5	24	2617.60 (652.56–10 500.03)	9	132.70 (40.26–437.43)
2–6 weeks after dose two	18	17	5198.92 (2366.63–11 420.79)	22	20	17 306.87 (13 732.77–21 811.16)	7	1662.97 (1215.25–2275.62)
N-antibody positive								
< 2 weeks after dose one	5	5	618.60 (86.34–4432.08)	2	1	161.00	1	2500.00†
2–6 weeks after dose one	29	3	11 683.86 (6775.38–20 148.36)	29	13	29 217.12 (20 965.55–40 715.74)	8	17 992.12 (8568.68–37 779.05)
< 2 weeks after dose two	5.5	6	11 324.36 (6464.22–19 838.60)	12	4	9902.47 (4327.68–22 658.49)	2	21 506.98 (4301.01–107 544.50)
2–6 weeks after dose two	19	2	14 395.44 (7608.78–27 235.59)	14	1	39 014.00	2	16 435.09 (2198.98–122 835.34)

Data are presented as median [interquartile range] or geometric mean (95% CI), unless stated otherwise. Blood samples were not obtained from all participants at all timepoints, and those that were indeterminate or insufficient for testing were excluded. *15/16 observations were below assay's limit of detection at < 0.4 arbitrary units (AU)/mL. †Right-censored observation. N-antibody, nucleocapsid protein antibody.

pregnant compared with non-pregnant women, although only chills ($P = 0.029$) and tiredness ($P = 0.043$) reached statistical significance (Figure 1, Table 3). Reactogenicity was generally similar after the first and second doses in pregnant women ($P > 0.10$ for all symptoms). Although adverse events after the second dose remained less common in pregnant women compared with non-pregnant women (Figure 2), only feeling generally unwell was significantly less common ($P = 0.046$) (Table 3).

DISCUSSION

Summary of main findings

Among infection-naïve individuals, SARS-CoV-2 immunoglobulin-G (IgG) antibody levels against the S

protein were similar after the first dose but significantly lower after the second dose of mRNA COVID-19 vaccine in pregnant *vs* non-pregnant women. SARS-CoV-2 infection prior to vaccination was associated with very high antibody levels irrespective of vaccine type or pregnancy status. Pregnant women experienced fewer symptoms after each dose of mRNA vaccine compared with non-pregnant women, although only chills and tiredness after the first dose, and feeling generally unwell after the second dose, reached statistical significance.

Interpretation of study findings and comparison with published literature

Pregnant women developed robust antibody responses after mRNA vaccination and, while antibody titers do not predict protection against disease, postimplementation surveillance of immunization programs indicates that protection against severe COVID-19 in vaccinated pregnant women is high²¹. Contrary to our results, other studies have found similar antibody responses among pregnant and non-pregnant women after COVID-19 vaccination^{15,22}, highlighting the need for large, multicenter, randomized controlled trials in pregnant women.

Since the extended-interval dosing schedule provides greater antibody responses and potentially longer protection, pregnant women in the UK may be better protected than those in countries that use shorter-interval schedules^{23,24}. Ultimately, further studies are needed to determine the vaccine type, dose, schedule and timing that provide optimal protection pre- and postnatally. Two

Table 3 Comparison of reported adverse events between pregnant and non-pregnant women after first and second doses of mRNA COVID-19 vaccine

Symptom	After first dose		After second dose	
	OR (95% CI)	P	OR (95% CI)	P
Fever	0.37 (0.10–1.11)	0.094	0.57 (0.16–1.68)	0.340
Chills	0.28 (0.08–0.81)	0.029	0.63 (0.19–1.71)	0.390
Headache	0.59 (0.29–1.14)	0.120	0.66 (0.27–1.47)	0.320
Generally unwell	0.54 (0.24–1.13)	0.110	0.38 (0.13–0.93)	0.046
Tiredness	0.55 (0.31–0.98)	0.043	0.78 (0.38–1.56)	0.490
Joint ache	0.50 (0.23–1.06)	0.076	0.43 (0.14–1.12)	0.100
Nausea and vomiting	0.53 (0.07–2.79)	0.470	0.23 (0.01–1.32)	0.180

OR, odds ratio.

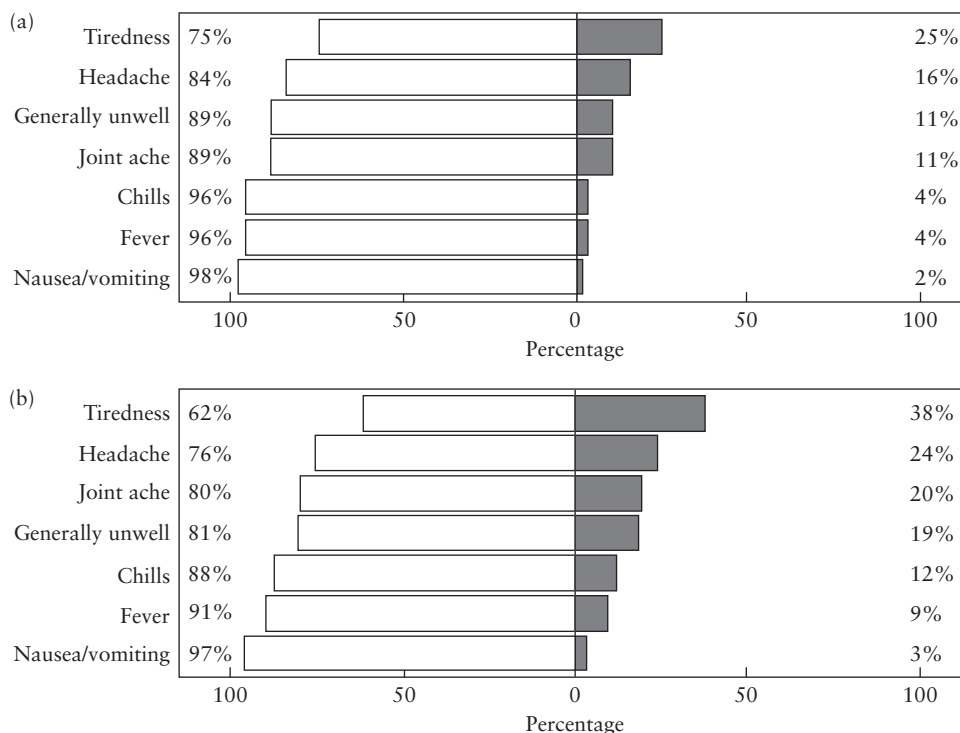


Figure 1 Likert plot of vaccine-related adverse events in pregnant (a) and non-pregnant (b) individuals after first dose of mRNA COVID-19 vaccine. □, no; ■, yes.

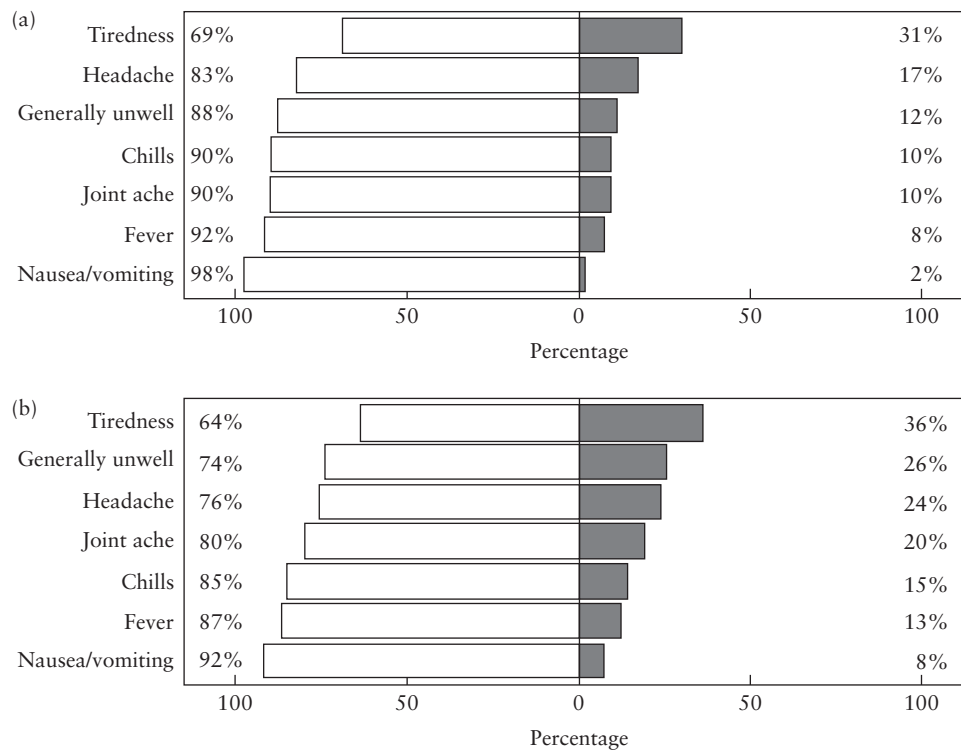


Figure 2 Likert plot of vaccine-related adverse events in pregnant (a) and non-pregnant (b) individuals after second dose of mRNA COVID-19 vaccine. □, no; ■, yes.

doses with a shorter interval may provide more rapid protection early in pregnancy, and although protection may wane by the third trimester, this could be mitigated by a third dose later in pregnancy, which may provide better postnatal protection for the mother and infant¹³.

Consistent with reported literature in non-pregnant populations²³, prior infection in pregnant women was associated with very high antibody levels after one mRNA vaccine dose, more than 2-fold higher than those elicited by two doses in infection-naïve pregnant women. Additionally, compared with infection-naïve pregnant women, previously infected pregnant women had only a modest increase in antibody levels after their second dose, consistent with studies in non-pregnant women²⁵. Therefore, a single dose of vaccine may be sufficient for previously infected pregnant women. This could have important implications globally, especially for countries in which vaccine supply is limited, and may also help to improve vaccine uptake in pregnant women.

Postvaccination symptoms were less prevalent in pregnant compared with non-pregnant women. Some of the reported symptoms, however, are experienced commonly during pregnancy. For example, the lower prevalence of feeling generally unwell or tired could be because tiredness is common throughout pregnancy²⁶ and as such, pregnant women may not attribute such symptoms to vaccination. Furthermore, non-pregnant women in the comparison group may be more likely to complete the questionnaire if they suffered a negative experience after vaccination.

Our findings are consistent with published data on the reactogenicity of COVID-19 vaccines in pregnancy.

An observational case-control study of pregnant women receiving two doses of the BNT16B2b2 vaccine 3 weeks apart found a similar rate of adverse events post vaccination in pregnant women and in age-matched, non-pregnant women¹⁵. The only exceptions were paresthesia, which was more common among pregnant women (4.6%) compared with non-pregnant women (1.2%) after the second dose, and myalgia, arthralgia and headache, which were significantly less common in pregnant women after both doses. Importantly, the study found very low rates of short-term obstetric complications, such as uterine contractions and vaginal bleeding, after the first or second dose of vaccine, and of later obstetric outcomes, such as preterm birth, low birth weight, requirement for neonatal care and fetal/neonatal death (none reported). The study also reported lower IgG antibody levels against the receptor-binding domain of the SARS-CoV-2 spike protein at 2 weeks to 2 months after the second dose in pregnant compared with non-pregnant women¹⁵, which differs from our findings.

Another large cohort study of over 35 000 women also reported no safety signals after two doses given 3 weeks apart; pregnant women reported injection-site pain more frequently, and headache, myalgia and chills less frequently, than did non-pregnant women¹⁶. Additionally, reactogenicity rates are higher in younger compared with older individuals²⁷. Overall, reactogenicity rates after mRNA vaccination in pregnant women are generally lower than or similar to those in non-pregnant adults, including after the extended-interval dosing schedule recommended in the UK²⁸.

Clinical and research implications

This study adds to the increasing body of evidence supporting the immunogenicity and safety of mRNA vaccines in pregnancy. Pregnant women are at increased risk of severe COVID-19⁴ and adverse pregnancy outcome^{1–3,29–31}. This study differs from other publications in that we assessed an extended-interval vaccination schedule in both infection-naïve and previously infected pregnant women. Vaccine uptake in pregnant women remains low and most pregnant women hospitalized with severe COVID-19 are unvaccinated. These cases are potentially preventable through vaccination^{14,29}. A recent survey found that 57% of pregnant women in the USA were still hesitant to accept COVID-19 vaccines during pregnancy³². In the UK, only 54% of pregnant women were vaccinated¹¹ by December 2021. Improving COVID-19 vaccine uptake in pregnancy is critical, especially with the arrival of the more transmissible and immune-evasive Omicron variant³³, which may require three doses of mRNA vaccine for protection³⁴. An important reason for vaccine hesitancy among pregnant women is safety concerns³⁵, especially because pregnant women were excluded from prelicensure COVID-19 vaccine trials. In the UK, the Preg-CoV trial aims to provide robust data on the optimum vaccine type, dose and dosing interval for COVID-19 vaccination during pregnancy^{36–38}.

Strengths and limitations

We implemented real-world monitoring rapidly to assess the immunogenicity and reactogenicity of COVID-19 vaccines in pregnant women at the height of the pandemic, when there were limited data regarding vaccine outcome in pregnant women, especially those receiving the extended-interval schedule recommended in the UK. A limitation of this study was the relatively small sample size, which was because local vaccine uptake was low, especially in light of concerns about vaccine-induced thrombosis and thrombocytopenia. Additionally, because this was a real-world study, the timing of recruitment and blood sampling varied between participants, so not all samples could be included in the final analysis. Consequently, some of our results lack power, which limits our conclusions. For reactogenicity analysis studies, non-pregnant women who responded to the invitation to participate may not be representative of the population at large; those with negative experiences after vaccination, for example, may have been more likely to take part. Finally, since nucleocapsid antibodies can wane post infection, some infected participants may have been misclassified as infection-naïve; however, in our cohort, previously infected women had much higher antibody responses than infection-naïve women.

Conclusions

This study adds to the currently limited data on the immunogenicity and reactogenicity of COVID-19 vaccines in pregnancy, especially when administered with an

extended interval between doses. Whilst acknowledging the small sample size of our cohort, our findings, along with emerging international literature showing favorable pregnancy, birth and neonatal outcomes after vaccination, should help to reassure and improve vaccine uptake among pregnant women.

REFERENCES

- Chmielewska B, Barratt I, Townsend R, Kalafat E, van der Meulen J, Gurol-Urganci I, O'Brien P, Morris E, Draycott T, Thangaratnam S, Le Doare K, Ladhani S, von Dadelszen P, Magee L, Khalil A. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health* 2021; 9: e759–772. Erratum in: *Lancet Glob Health* 2021; 9: e758.
- Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ* 2021; 193: E540–548.
- DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, Ellington SR. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization - United States, March 2020–September 2021. *MMWR Morb Mortal Wkly Rep* 2021; 70: 1640–1645.
- Zambrano LD, Ellington S, Strid P, Galang RR, Oduyabo T, Tong VT, Woodworth KR, Nahabedian JF 3rd, Azziz-Baumgartner E, Gilboa SM, Meaney-Delman D; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1641–1647.
- Viana J, van Dorp CH, Nunes A, Gomes MC, van Boven M, Kretzschmar ME, Veldhoen M, Rozhnova G. Controlling the pandemic during the SARS-CoV-2 vaccination rollout. *Nat Commun* 2021; 12: 3674.
- Baraniuk C. Covid-19: How the UK vaccine rollout delivered success, so far. *BMJ* 2021; 372: n421.
- Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, Gallagher E, Chand M, Brown K, Ladhani S, Ramsay M, Bernal J. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. *N Engl J Med* 2022; 386: 340–350.
- Coronavirus (COVID-19) booster vaccine. 2021. <https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/>.
- GOV.UK. JCVI issues new advice on COVID-19 vaccination for pregnant women. 2021. <https://www.gov.uk/government/news/jcvi-issues-new-advice-on-covid-19-vaccination-for-pregnant-women>.
- RCOG. Pregnant women eligible for the COVID-19 booster vaccine urged to take up offer. 2021. <https://www.rcog.org.uk/news/pregnant-women-eligible-for-the-covid-19-booster-vaccine-urged-to-take-up-offer/>.
- UK Health Security Agency. Over half of pregnant women have now had one or more doses of COVID-19 vaccines. 2022. <https://www.gov.uk/government/news/over-half-of-pregnant-women-have-now-had-one-or-more-doses-of-covid-19-vaccines>.
- RCOG. Covid-19 Vaccines – Pregnancy and breastfeeding. 2021. <https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/covid-19-vaccines-and-pregnancy/covid-19-vaccines-pregnancy-and-breastfeeding/>.
- Yang YJ, Murphy EA, Singh S, Sukhu AC, Wolfe I, Adurty S, Eng D, Yee J, Mohammed I, Zhao Z, Riley LE, Prabhu M. Association of Gestational Age at Coronavirus Disease 2019 (COVID-19) Vaccination, History of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, and a Vaccine Booster Dose With Maternal and Umbilical Cord Antibody Levels at Delivery. *Obstet Gynecol* 2022; 139: 373–380.
- Kalafat E, O'Brien P, Heath PT, Le Doare K, von Dadelszen P, Magee L, Ladhani S, Khalil A. Benefits and potential harms of COVID-19 vaccination during pregnancy: evidence summary for patient counseling. *Ultrasound Obstet Gynecol* 2021; 57: 681–686.
- Bookstein Peretz S, Regev N, Novick L, Nachshol M, Goffer E, Ben-David A, Asraf K, Doolman R, Levin EG, Regev Yochay G, Yinon Y. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. *Ultrasound Obstet Gynecol* 2021; 58: 450–456.
- Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyabo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Gee JM, Meaney-Delman DM; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med* 2021; 384: 2273–2282. Erratum in: *N Engl J Med* 2021; 385: 1536.
- Parry H, Bruton R, Stephens C, Bentley C, Brown K, Brown K, Amirthalingam G, Hallis B, Otter A, Zuo J, Moss P. Extended interval BNT162b2 vaccination enhances peak antibody generation. *NPJ Vaccines* 2022; 7: 14.
- Harris RJ, Whitaker HJ, Andrews NJ, Aiano F, Amin-Chowdhury Z, Flood J, Borrow R, Linley E, Ahmad S, Stapley L, Hallis B, Amirthalingam G, Höschler K, Parker B, Horsley A, Brooks TJG, Brown KE, Ramsay ME, Ladhani SN. Serological surveillance of SARS-CoV-2: Six-month trends and antibody response in a cohort of public health workers. *J Infect* 2021; 82: 162–169.
- Mahase E. COVID-19: UK offers under 40s alternative to AstraZeneca vaccine to boost confidence. *BMJ* 2021; 373: n1185.
- Public Health England. Evaluation of Roche Elecsys AntiSARS-CoV-2 serology assay for the detection of anti-SARS-CoV-2 antibodies. 2020. <https://assets.publishing>

- .service.gov.uk/government/uploads/system/uploads/attachment_data/file/989460/Evaluation_of_Roche_Elecsys_anti_SARS-CoV-2_S_assay_PHE.pdf.
21. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N, Linster M, Chia WN, Chen MI, Wang LF, Ooi EE, Kalimuddin S, Tambyah PA, Low JG, Tan YJ, Bertoletti A. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* 2020; 584: 457–462.
 22. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Baez AM, Shook LL, Cvrk D, James K, De Guzman R, Brigida S, Diouf K, Goldfarb I, Bebell LM, Yonker LM, Fasano A, Rabi SA, Elovitz MA, Alter G, Edlow AG. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol* 2021; 225: 303.e1–17.
 23. Amirthalingam G, Bernal JL, Andrews NJ, Whitaker H, Gower C, Stowe J, Tessier E, Subbarao V, Ireland G, Baawuah F, Linley E, Warriner L, O'Brien M, Whillock C, Moss P, Ladhani S, Brown K, Ramsay M. Higher serological responses and increased vaccine effectiveness demonstrate the value of extended vaccine schedules in combatting COVID-19 in England. *medRxiv* 2021. DOI: 10.1101/2021.07.26.21261140.
 24. Francis AI, Ghany S, Gilkes T, Umakanthan S. Review of COVID-19 vaccine subtypes, efficacy and geographical distributions. *Postgrad Med J* 2022; 98: 389–394.
 25. Kent, Stephen J, Juno, JA. Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots. *EBioMedicine* 2021; 72: 103586.
 26. Cox R, Granne I. Common symptoms in pregnancy. *InnovAiT* 2020; 13: 409–413.
 27. Xiong X, Yuan J, Li M, Jiang B, Lu ZK. Age and Gender Disparities in Adverse Events Following COVID-19 Vaccination: Real-World Evidence Based on Big Data for Risk Management. *Front Med (Lausanne)* 2021; 8: 700014.
 28. Powell AA, Power L, Westrop S, McOwat K, Campbell H, Simmons R, Ramsay ME, Brown K, Ladhani SN, Amirthalingam G. Real-world data shows increased reactivity in adults after heterologous compared to homologous prime-boost COVID-19 vaccination, March–June 2021, England. *Euro Surveill* 2021; 26: 2100634. *Erratum in: Euro Surveill* 2022; 27.
 29. Vouga M, Favre G, Martinez-Perez O, Pomar L, Acebal LF, Abascal-Saiz A, Hernandez MRV, Hcini N, Lambert V, Carles G, Sichertu J, Salomon L, Stirnemann J, Ville Y, de Tejada BM, Gonc e A, Hawkins-Villarreal A, Castillo K, Solsona EG, Trigo L, Cleary B, Geary M, Bartels H, Al-Kharouf F, Malone F, Higgins M, Keating N, Knowles S, Poncellet C, Ribeiro-do-Valle CC, Surita F, Dantas-Silva A, Borrelli C, Luz AG, Fuenzalida J, Carvajal J, Canales MG, Hernandez O, Grechukhina O, Ko AI, Reddy U, Figueiredo R, Moucho M, Pinto PV, De Luca C, De Santis M, de Campos DA, Martins I, Garabedian C, Subtil D, Bohrer B, Da Rocha Oppermann ML, Wender MCO, Schuler-Faccini L, Sanseverino MTV, Giugliani C, Friedrich L, Scherer MH, Mottet N, Ducarme G, Pelerin H, Moreau C, Breton B, Quibel T, Rozenberg P, Giannoni E, Granado C, Monod C, Mueller D, Hoesli I, Bassler D, Heldstab S, K oblle NO, Sentilhes L, Charvet M, Deprest J, Richter J, Van der Veeken L, Egel-Hort B, Plantefeve G, Derouich M, Calvache AJN, Lopez-Giron MC, Burgos-Luna JM, Escobar-Vidarte MF, Hecher K, Tallarek AC, Hadar E, Haratz KK, Amikam U, Malinge G, Maymon R, Yoge Y, Sch affer L, Toussaint A, Rossier MC, De Sa RAM, Grawe C, Aebi-Popp K, Radan AP, Raio L, Surbek D, B ockenhoff P, Strizek B, Kaufmann M, Bloch A, Boulvain M, Johann S, Heldstab SA, Bernasconi MT, Grant G, Feki A, Brochut AM, Giral M, Sedille L, Papadia A, Brugger RC, Weber B, Fischer T, Kahlert C, Saines KN, Cambou M, Kanellos P, Chen X, Yin M, Haessig A, Ackermann S, Baud D, Panchoad A. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. *Sci Rep* 2021; 11: 13898.
 30. Ciapponi A, Bardach A, Comand e D, Berrueta M, Argento FJ, Rodriguez Cairoli F, Zamora N, Santa Maria V, Xiong X, Zarea S, Mazzoni A, Buekens P. COVID-19 and pregnancy: An umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes. *PLoS One* 2021; 16: e0253974.
 31. Vousden N, Ramakrishnan R, Bunch K, Morris E, Simpson NAB, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ, Knight M. Severity of maternal infection and perinatal outcomes during periods of SARS-CoV-2 wildtype, alpha, and delta variant dominance in the UK: prospective cohort study. *BMJ Medicine* 2022; 1: e000053.
 32. Simmons LA, Whipps MDM, Phipps JE, Satish NS, Swamy GK. Understanding COVID-19 vaccine uptake during pregnancy: 'Hesitance', knowledge, and evidence-based decision-making. *Vaccine* 2022; 40: 2755–2760.
 33. Torjesen I. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear *BMJ* 2021; 375: n2943.
 34. Pfizer. Pfizer and Biontech provide update on omicron variant. 2021 <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant>.
 35. Skjefte M, Ngirbabul M, Akeju O, Escudero D, Hernandez-Diaz S, Wyszynski DF, Wu JW. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. *Eur J Epidemiol* 2021; 36: 197–211.
 36. Pfizer. Pfizer and BioNTech commence global clinical trial to evaluate COVID-19 vaccine in pregnant women. 2021. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate>.
 37. GOV.UK New study into COVID-19 vaccine dose interval for pregnant women. 2021. <https://www.gov.uk/government/news/new-study-into-covid-19-vaccine-dose-interval-for-pregnant-women>.
 38. St George's Vaccine Institute. Preg-CoV trial. 2021. <https://vaccine.ac.uk/research/preg-cov-trial/>.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Appendix S1 COVID-19 Vaccination in Pregnancy (COVIP) participant questionnaire

Figure S1 Longitudinal change in serum SARS-CoV-2 anti-spike-protein antibody levels in pregnant (orange line) and non-pregnant (green line) women, 1 month following the first dose of mRNA vaccine. The increase in antibody levels was not significantly different between pregnant and non-pregnant women ($P = 0.172$).

Table S1 Pregnancy outcome of 67 women who received COVID-19 vaccine during pregnancy