Boosting maternal and neonatal anti SARS-CoV-2 humoral immunity using a third mRNA vaccine dose

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Abstract

Importance: To minimize COVID-19 pandemic burden and spread, third booster dose vaccination campaigns commenced worldwide. Since pregnant patients are at increased risk for severe disease, they were recently included in that policy despite the lack of available evidence regarding the impact of a third boosting dose during pregnancy; underscoring the urgent need for relevant data.

Objective: We aimed to characterize the effect on anti-SARS-CoV-2 antibody titers of the third, boosting dose of mRNA Pfizer BNT162b2 vaccine in pregnancy, and profile its most common side effects.

Design: Prospective cohort study of anti-SARS-CoV-2 antibody titers measured at the time of delivery in maternal and cord blood, and dedicated side effect questionnaire.

Setting: Labor and delivery ward and virology laboratory of a large, urban, university-affiliated medical center.

Participants: Gravidae (N=216) without history of COVID-19 disease, presenting for delivery were divided to two groups by vaccination status: parturients who received a third boosting dose of Pfizer BNT162b2 mRNA vaccine, were compared to those vaccinated with the 2-dose regimen.

Main Outcomes: Anti-SARS-CoV-2 antibody titers measured in maternal and cord blood samples collected at delivery and side effect profile.

Results: We found a robust surge in maternal and cord blood levels of anti-SARS-CoV-2 titers at the time of delivery: parturients that received a third boosting dose had titers 4.7-fold higher as compared to 2-dose vaccinated parturients. The effect of the third boosting dose remained significant when controlling for the trimester of most recent vaccine dose, suggesting additive immunity extends beyond that obtained after the second dose. Efficient transplacental transfer was observed. Neonatal (cord blood) anti-SARS-CoV-2 antibody titers positively correlated with ($r= 0.745$; $P< .0001$) and were significantly higher than maternal levels ($p<0.0001$). Overall, fewer side effects were reported following the third dose as compared to the second vaccine dose among the 2-dose group, with lower rates of injection site pain and swelling, myalgia, and general malaise.

Conclusions and relevance: The third, boosting dose of mRNA Pfizer BNT162b2 vaccine augmented maternal and neonatal immunity with mild side effects. These data provide essential evidence to bolster clinical and public health guidance, reassure patients, and increase vaccine uptake among pregnant patients.

Key Points

Question: What is the effect of a third, boosting dose of Pfizer BNT162b2 mRNA vaccine in pregnancy on anti-SARS-CoV-2 antibody titers at delivery, in parturients and cord blood, compared to vaccinated parturients who received the 2-dose regimen?

Findings: A third vaccine dose yielded significantly higher anti-SARS-CoV-2 antibody levels in maternal and cord blood, with mild reported side effects. Effect remained significant when controlling for trimester of exposure to last vaccine dose.

Meaning: A third, boosting dose of mRNA Pfizer BNT162b2 vaccine significantly augments maternal and neonatal humoral immunity, beyond that achieved with the 2-dose regimen, with mild side effects.

Introduction

As the COVID19 pandemic continues to evolve[1], waning in anti-SARS-CoV-2 antibody titers[2] and the appearance of novel variants challenge immunity acquired following primary infection or vaccination[3]. Data from non-pregnant patients shows that boosting waning immunity via a single boosting dose of an mRNA vaccine greatly enhances protection against reinfection and novel variants, including the B.1.617.2 (delta)[4] and the B.1.1.529 (omicron)[5] variants.

Increased risk for severe illness, mechanical ventilation, and death from COVID19 has been reported in pregnant individuals compared to properly matched non-pregnant cohorts[6–16]. Maternal COVID19 morbidity and pregnancy related complications also significantly affect fetal and neonatal health[17].

Maternal anti-SARS-CoV-2 antibodies are an important module of maternal anti-viral immunity. Additionally, vertical transport of maternal IgG across the human placenta provides significant maternal titers in fetal circulation, hence providing the first line of defense for neonatal humoral immunity. Importantly, recent reports clearly show the protective effect of COVID-19 vaccination during pregnancy, in reducing maternal infection and severe illness[18–20].

In an attempt to stop the COVID-19 pandemic burden and spread, third booster dose vaccination campaigns commenced worldwide. Israel was the first country (July 2021) that launched an unprecedented third dose booster vaccination campaign, using a single dose of Pfizer BNT162b2 mRNA vaccines. Since pregnant patients are at increased risk for severe disease, they were urged to attend for inoculation despite the lack of available evidence regarding the impact of a third boosting dose during pregnancy[21]. Similar recommendations were recently adopted by the American Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG)[22,23]. These recommendations were based on the best available evidence, extrapolating data from non-pregnant populations. Nevertheless, pregnancy is a time of immune system modulation, affecting many aspects of the maternal immune response, including the humoral response[24,25]. Lack of relevant data creates conditions amenable to the dissemination of disinformation, fake news, and vaccine hesitancy among pregnant patients. Clinicians around the world face daily questions and concerns regarding boosting during pregnancy. Consequently, compliance among gravidae in numerous countries and societies is low[26–28], despite their increased risk, amidst persistent patient concerns regarding the necessity and potential impact of vaccination and boosting during pregnancy[28–30]. This situation underscores the urgent need for relevant evidence regarding vaccine boosting during pregnancy.

Evidence-based answers are lacking to questions often posed by health care providers, patients and families. Currently, it is unclear whether a third boosting dose during pregnancy will boost maternal and newborn immunity, whether boosting induces immunity over and above that of the standard two-dose regimen, and whether the timing of initial vaccination (before or during pregnancy) will affect the response to boosting. Concerns have been expressed regarding the side effects of the third boosting dose and whether increased number or intensity of side effects points to a more robust immune response.

Here we aimed to provide important relevant data regarding the impact of a third, boosting dose of Pfizer BNT162b2 mRNA vaccine on maternal and neonatal protective antibody titers, and characterize the side effect profile of a third anti-COVID19 booster during pregnancy.

Materials And Methods

Study Population

This was a prospective cohort study of parturients admitted for delivery from April 2021 to January 2022 at Hadassah Mt. Scopus Medical Center. Hadassah Medical Center institutional review board approved the study (HMO-0389-20, HMO-0274-21). Parturients were approached and invited to participate in a biorepository study following their admission to the delivery room. Eligibility criteria included willingness to participate and provide informed consent, age of 18–45 years, without history of COVID-19 disease, and anti-SARS-CoV-2 vaccination before or during pregnancy. Pregnant women with positive COVID-19 reverse transcription polymerase chain reaction (PCR) at delivery were excluded from the study.

Following informed consent, participants were allocated to one of two study groups: A: vaccinated parturients that received a third boosting dose of BNT162b2 mRNA (“third dose group”); or B: vaccinated parturients who received the 2-dose regimen (“two-dose group”).

Participants had maternal and cord blood samples drawn at the time of delivery. Demographic, obstetric, and vaccine side effect profile data were collected for all patients from the electronic medical record and dedicated side-effect questionnaires.

Sample and data collection and handling.

Maternal and umbilical cord blood samples were collected from enrolled participants immediately following delivery. Blood samples were centrifuged at 1000g for 10 minutes at room temperature, and serum samples were aliquoted and stored at − 80°C until analysis. Demographic and clinical data were collected at the time of enrollment.

Antibody titers

Serum anti-SARS-CoV-2 spike receptor binding domain (RBD) specific antibodies were assessed in blinded fashion at our institution’s clinical virology laboratory using Architect SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics, Chicago, IL, USA).

Statistical analysis

Statistical analyses were performed on IBM SPSS 27 for Windows (IBM Corp, Armonk, NY), and Prism 5.01 (GraphPad Software). Comparisons between groups (antibody concentrations, clinical continuous parameters), were analyzed with Kruskal-Wallis 1-way ANOVA test, followed by Dunn's all-pairwise comparisons test; or alternatively, by Mann-Whitney U test for non-paired comparisons and Wilcoxon rank sum test for paired dyads (if only 2 groups were compared). Maternal-cord blood dyads antibody correlations were analyzed by Spearman correlation tests. Proportional data were analyzed with the Pearson χ^2 test. Bonfferoni correction for multiple comparisons was applied. All statistical tests were 2-tailed and considered significant at p-value < 0.05.

Results

Participant characteristics

The study consisted of 216 parturients presenting for delivery at Hadassah Medical Center, Mt. Scopus, as detailed in Figure 1. The demographic and medical characteristics of the study groups, as well as median time from last exposure (i.e. third boosting vaccine dose or second vaccine dose) to delivery, are shown in Table 1. Obstetric clinical parameters and neonatal outcomes did not differ among the groups except rate of diabetes. Higher rates of diabetes (pregestational and gestational) were found in the third dose group as compared to all other groups (p=0.003). Importantly, six out of eight patients received the third dose following diabetes diagnosis, as compared to one patient in the two-dose group that was also diagnosed before the second vaccine dose. Violin plots illustrate the distribution of exposure timing prior to and through the course of gestation, in both study groups (Supplemental Figure 1).

Maternal serological response to third boosting dose of mRNA BNT162b2 vaccine

Figure 2A presents anti-SARS-CoV-2 antibody levels in maternal blood, for the study groups. We observed significantly higher antibody titers upon delivery in patients who received a third boosting dose of mRNA vaccine as compared to the 2-dose group participants (4.7 fold) (Figure 2A, Supplemental Figure 2). In order to control for duration of interval from vaccination to delivery, and determine whether higher titers reflected a stronger humoral immune response, or mirrored a shorter interval from exposure to delivery, groups were stratified by trimester of exposure. Our data show that anti-SARS-CoV-2 antibody titers were significantly higher following the third booster, when compared to the second dose of vaccine, given at the same trimesters (Figure 2B). Together, our data reveal an additional significant robust increase in maternal humoral response to the third boosting dose.

We next aimed to determine whether the timing of initial vaccination affects maternal humoral response to the boosting dose. We found that vaccination that occurred before vs. during pregnancy (Supplemental Figure 3) did not alter maternal humoral response, as detected by anti-SARS-CoV-2 titers at the time of delivery.

Transplacental transmission of third dose antibody protection.

Figure 3A presents anti-SARS-CoV-2 antibody levels in the cord blood of the study groups. Cord blood titers were significantly higher following the third boosting dose compared to the two-dose vaccination regimen (Figure 3A). Maternal and cord blood anti-SARS-CoV-2 titers were measured in 79 maternal/cord blood dyads of participants that received the third boosting dose, to assess transplacental vertical transmission. Anti-SARS-CoV-2 antibody titers were found to be positively correlated ($r= 0.745$; $P< .0001$) and significantly higher ($p<0.0001$) in cord blood compared to maternal blood, as shown in Figure 3B. These findings support the notion that maternal protective immune response to the third dose is efficiently transmitted to the fetus, leading to significantly higher protective antibody titers for the newborn.

Reported vaccination side effects and maternal anti-SARS-CoV-2 antibody titers

We further characterized the side effect profile of the third boosting dose. Among the third dose group, 42.7% of patients reported no adverse related symptoms. This figure is significantly higher compared to the second dose in the two-dose group (10.6%, $p<0.001$). When comparing the duration of symptoms among groups, median time of symptoms was significantly lower among the third dose as compared to the two-dose group (1.0 vs. 2.0 days, $p=0.007$). Figure 4 illustrates the side effects reported following the two vaccination regimens. Overall, the third booster dose caused fewer side effects compared to the second dose, with lower rates of injection site pain and swelling, myalgia, and general malaise. Importantly, less than 5% of patients that received the third dose reported fever. Among our study groups, the presence and number of symptoms following vaccination were not correlated with increased maternal anti-SARS-CoV-2 titers at delivery (Figure 5). Unexpectedly, participants that reported no symptoms following the third booster had significantly higher maternal anti-SARS-CoV-2 titers (1.8 fold, $p<0.001$), as compared to participants that reported side effects.

Discussion

In the present study we aimed to characterize the impact of the third mRNA Pfizer BNT162b2 boosting dose during pregnancy on maternal and cord blood antibody levels upon delivery. We found a robust surge in maternal and cord blood levels of anti SARS-CoV-2 titers at the time of delivery, when comparing pregnancies that received a third boosting dose to two-dose vaccinated pregnancies. The observed effect of the third boosting dose remained significant when controlling for the trimester of last exposure, suggesting additive immunity extends beyond that obtained after the second dose. Within our cohort, the third boosting dose resulted in a mild side effect profile, with lower reported side effects as compared to the second dose of standard COVID-19 vaccination during pregnancy. The higher rates of diabetes among the third dose group may be related to higher compliance to receive the additional booster, as most patients received the third dose after the diagnosis of diabetes.

The CDC, ACOG, and others have recommended third boosting vaccine doses for gravidae who completed the two-dose regimen, to minimize the risks of severe disease[22,23]. However, vaccination uptake has been slow among gravidae in many societies[26–28], and may be even lower for booster shots as concerns surrounding vaccination during pregnancy persist. In Israel, where boosting has been official policy for several months, health care providers and public health regulators face recurrent questioning regarding the impact and need for vaccine boosting. In this context, our first reassuring data may serve clinicians and policymakers searching for relevant evidence to inform patients and increase vaccine boosting uptake.

In their recent paper, Yang et al.[31] demonstrated that anti-SARS-CoV-2 antibody levels fall rapidly in gravidae following vaccination, similar to the general population, which may expose gravidae to reduced protection against severe illness. We demonstrate that a third, boosting dose of BNT162b2 mRNA vaccine markedly increased anti-SARS-CoV-2 antibody titers in maternal and cord blood, likely conferring improved protection from infection in this vulnerable population. Because the newborn depends on this humoral immunity as a primary line of defense against viral disease, these enhanced antibody titers likely provide more effective and longer-lasting protection against neonatal COVID-19 disease.

As the pandemic persists, more women will commence their pregnancy already vaccinated. We show that providing a third dose in these patients results in a robust response, which is not affected by the timing of the initial vaccination, before or during pregnancy.

Caregiver recommendations regarding the third boosting dose are frequently met with questions regarding the common side effect profile of this therapy during pregnancy. Our data are the first to show that in general, the reported side effects of the third boosting dose are milder than that reported following the second dose. Specifically, there were lower rates of injection site pain and swelling, myalgia, and general malaise. We can speculate that the difference in the presence and number of reported side effects may stem from recall bias or self-selection on the part of patients attending for the third boosting dose, e.g. individuals with a lighter side-effect response following the second dose, may be more likely to present for the third, boosting dose. Importantly, less than 5% of patients that received the third dose reported fever, which may be of concern as regards neonatal outcomes[32]. Among our study groups, the presence and number of symptoms following vaccination were not associated with increased maternal anti-SARS-CoV-2 titers at delivery. These findings can provide reassurance to gravidae and their caregivers.

Strengths and limitations

The present study has several strengths. Its prospective design, recognized serological assays, blinded serum analysis, and standardized side effect questionnaire that is comparable to other studies, strengthen our findings. Although samples were collected from one center, a diverse population was recruited. Limitations include the relatively small patient numbers and lack of long term follow-up of the newborns as regards the persistence of anti-SARS-CoV-2 antibody levels. Finally, anti-SARS-CoV-2

antibody levels have been shown to correlate with protection against symptomatic breakthrough infection[33–35], however we did not assess the impact of vaccination or boosting on the prevalence of COVID-19 disease among the study group. Moreover, immunological memory encompasses memory B cells, memory CD4 + T cells, and/or memory CD8 + T cells that may support protection[36,37], but were not evaluated in the present study. Further studies are necessary to evaluate these components of the immunological response.

Conclusions

Administration of a third, boosting dose of Pfizer BNT162b2 mRNA vaccine provides a robust surge in anti-SARS-CoV-2 antibody titers in maternal and cord blood, with a mild side effect profile. These data are urgently needed by clinicians and policymakers that encounter questions and concerns regarding the benefits of a third boosting anti-SARS-CoV-2 vaccine dose during pregnancy, in order to provide evidence based guidance.

Declarations

Author contributions

OB, ACP, LTM, and SY designed the research studies. ACP, LTM, HAK, RF, MK, EOD, and SL conducted the experiments and collected the samples. ML, DGW, ACP and LTM acquired the data. OB, ACP, LTM, SY, and ML analyzed the data. OB, AW, SMC, MK, DGW, MN, OB, ACP, LTM, and SY participated in writing the manuscript

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Tables

Table 1: Maternal and neonatal characteristics and outcomes of the study groups: A: Third dose, B: Two-dose regimen (N=216)

	Third dose (N=87)	Two-dose regimen (N=129)	P-value
Obstetrics and demographics characteristics	-	-	-
Maternal age at delivery (years)	31.0 (26.0-35.0)	29.0 (25.0-33.5)	0.168
Body Mass Index (BMI)	23.9 (21.5-26.9)	24.4 (21.6-27.5)	0.816
Parity	1.0 (0.0-3.0)	2.0 (1.0-3.0)	0.221
Maternal smoking	2/79 (2.5%)	4/126 (3.2%)	1.000
Hypertensive disorders of pregnancy	5 (5.7%)	6 (4.7%)	0.759
Diabetes (pre-gestational and gestational)	8 (9.2%)**	1 (0.8%)	0.003
Multifetal pregnancy	3 (3.4%)	2 (1.6%)	0.394
Preterm delivery (<37 weeks of gestation)	9 (10.3%)	11 (8.5%)	0.642
Gestational age at delivery (weeks)	39.3 (38.2-40.2)	39.5 (39.0-40.4)	0.036
Mode of delivery			
Vaginal delivery	73 (83.9%)	117 (90.7%)	0.142
Cesarean delivery	14 (16.1%)	12 (9.3%)	
Neonatal characteristics and outcomes			-
Birthweight (grams)	3245 (2830-3565)	3320 (3030-3585)	0.169
Neonatal sex (female)*	44 (50.6%)	55 (42.6%)	0.268
Apgar at 5 minutes ≤7 *	4 (4.6%)	3 (2.3%)	0.443
NICU admissions*	4 (4.6%)	1 (0.8%)	0.161
Timing of events			
Interval from last event (third dose or second dose) to delivery in weeks	9.0 (6.0-12.0)	17.0 (12.0-21.0)	<0.001
Intervals between second to third dose (in weeks)	29.0 (27.0-32.0)	-	-
Anti-SARS-COV-2 titers			
Maternal titer at delivery	5482.5 (2981.9-11320.8)	773.7 (403.7-1580.1)	<0.001
Cord blood titer at delivery*	11445.5 (6642.6-20479.1)	1750.0 (758.1-4077.3)	<0.001

Data are presented as n (%) or median (interquartile range, IQR). Continuous parameters were analyzed by Mann-Whitney U test; Pearson χ^2 analysis was used to compare proportional data.
* In cases of twins, baby A was selected for analysis
** 6/8 patients received the third dose following diabetes diagnosis, as compared to 1 patient in the two-dose group, diagnosed before the second vaccination dose.

Figures

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Figure 1

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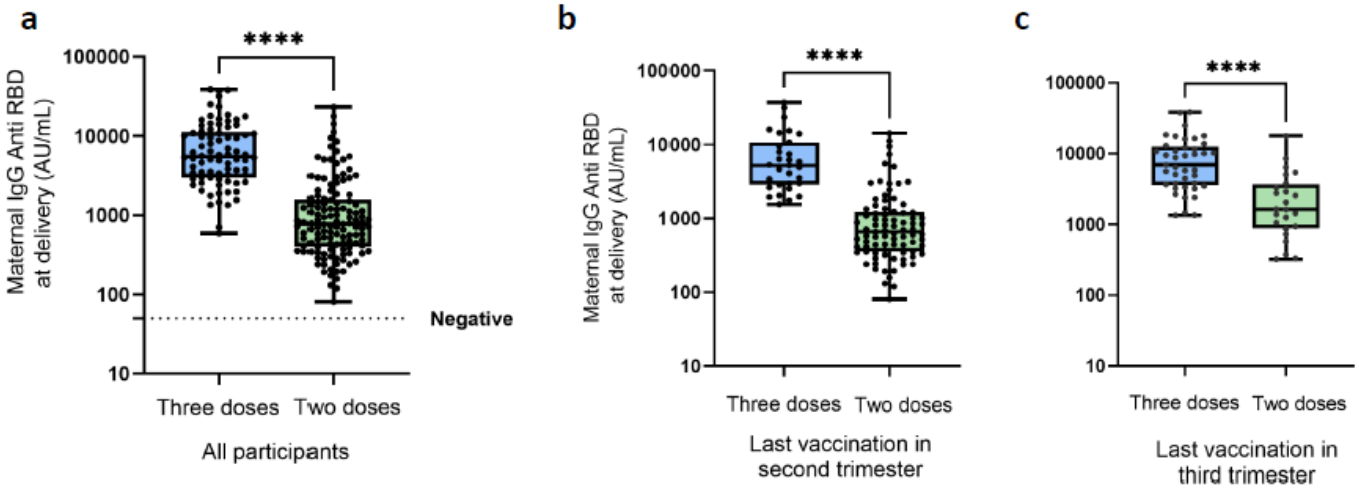

Figure 2

Third boosting dose of BNT162b2 mRNA vaccine administered during pregnancy produced a vigorous surge in anti-SARS-CoV-2 antibody titers detected at delivery. Blue: participants that received a third, booster dose during pregnancy; Green: Participants who received standard 2-dose regimen. A. Comparison of maternal anti-SARS-CoV-2 antibody titers. The horizontal dotted line indicates a titer below 50 (negative result). B-C. Comparison of maternal anti-SARS-CoV-2 antibody titers between third boosting dose group and 2-dose vaccinated group, for parturients that received their last vaccination dose in the second (B) or third (C) trimesters of pregnancy. Between group comparisons were analyzed using the Mann Whitney U test, ****p <0.0001.

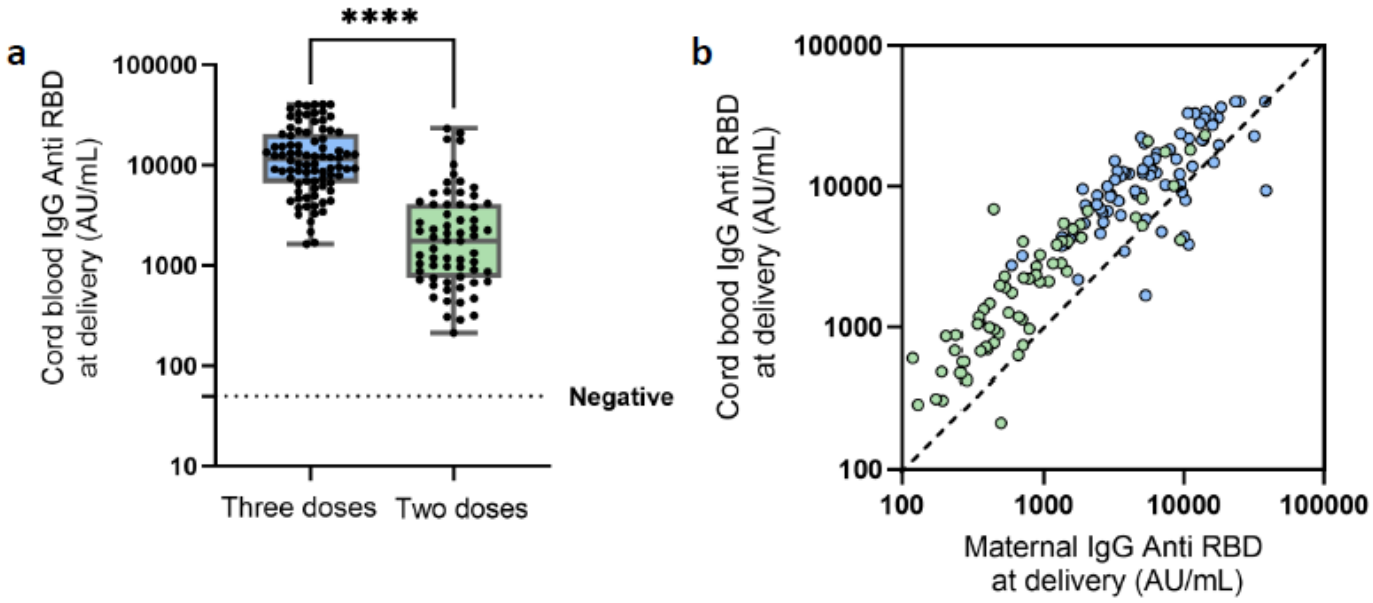

Figure 3

Third boosting dose administered during pregnancy produced a vigorous surge in anti-SARS-CoV-2 antibody titers detected in cord blood. Blue: participants that received a third, boosting vaccine dose during pregnancy; Green: 2-dose group. A. Between-groups comparison of cord blood anti-SARS-CoV-2 antibody titers. The horizontal dotted line indicates a titer below 50 (negative result). Differences between the groups were analyzed using the Mann Whitney U test, ****p <0.0001. B. Correlation between anti-SARS-CoV-2 antibody titers in maternal and cord blood dyads (third dose: n= 79, blue circles; 2-dose: n= 65, green circles) was analyzed with Spearman's correlation test. The diagonal line represents a geometric 1:1 ratio. Anti-SARS-CoV-2 antibody titers in cord blood positively correlate with maternal anti-SARS-CoV-2 concentrations (third dose: r = 0.745; P < .0001, 2-dose: r = 0.879; P < .0001).

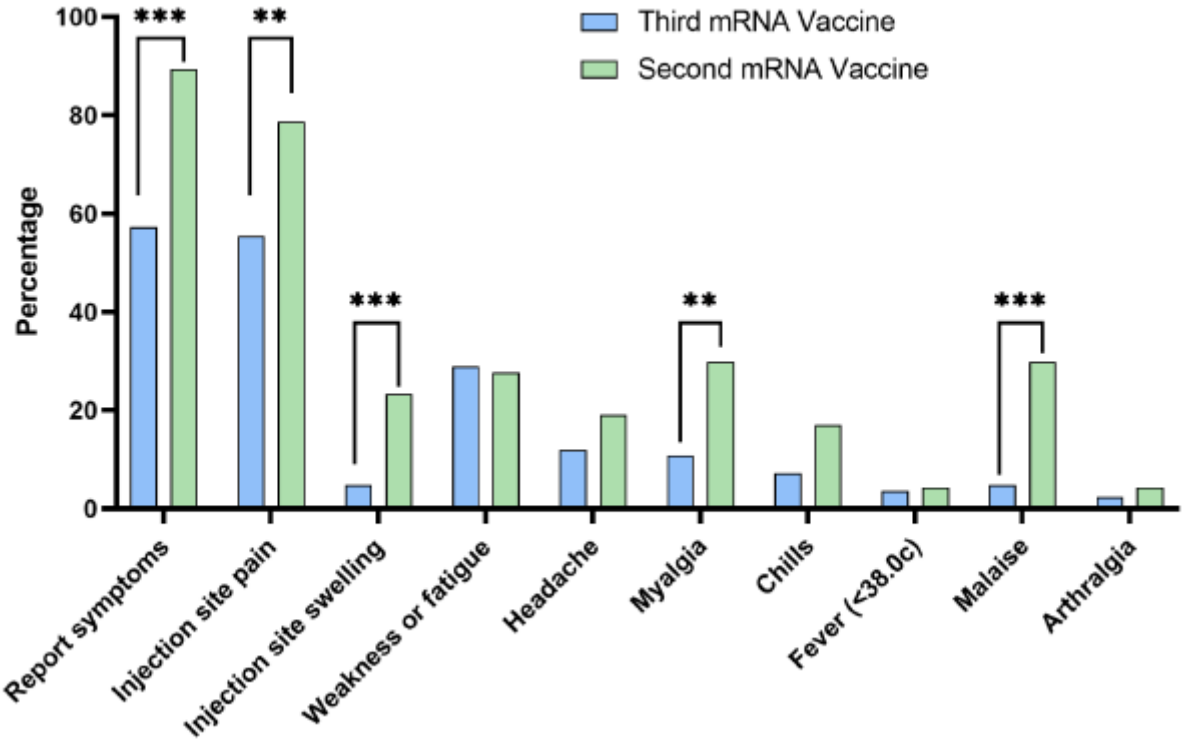

Figure 4

Comparison of the most frequent side effects reported by participants following the third, boosting vaccine dose (blue) vs. the second vaccine dose (green) parturients without history of COVID-19 disease. Data are presented as proportion of reported, frequent side effects among participants. Data were collected before or following labor using a detailed standard questionnaire. Differences between groups were analyzed by Pearson χ^2 analysis, with Bonfferoni correction for multiple comparisons (*$p < 0.05$).

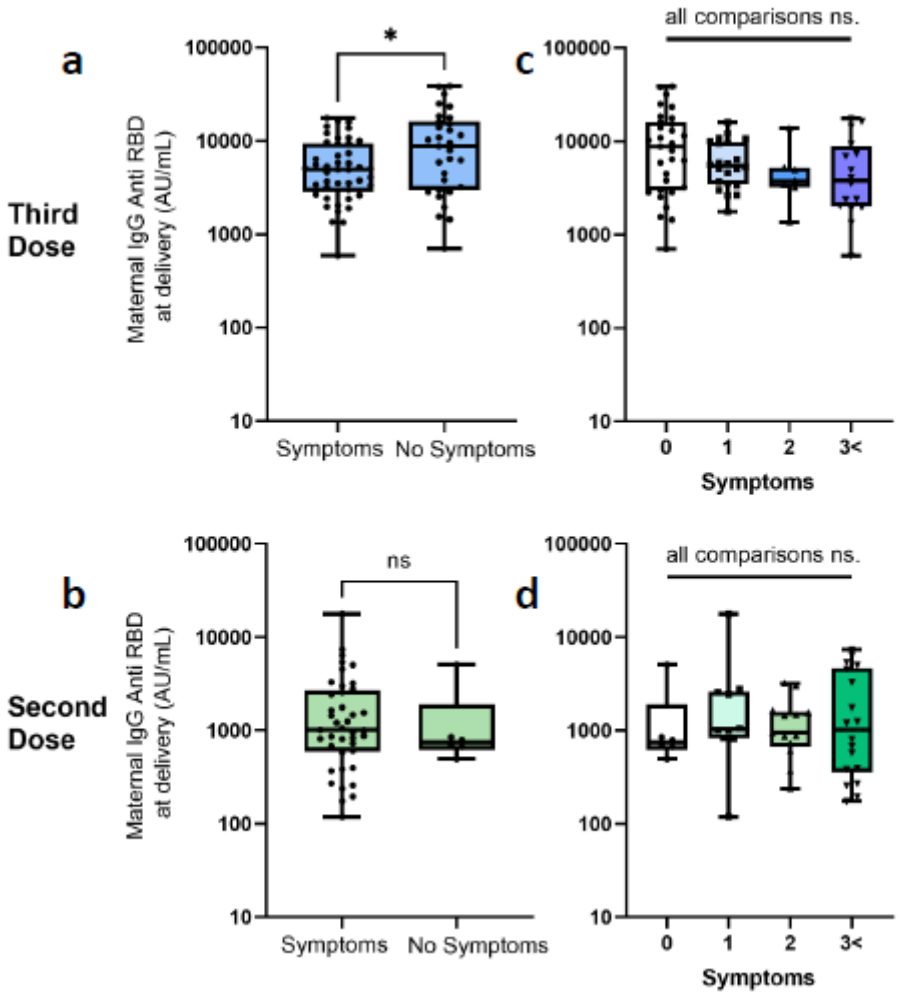

Figure 5

Maternal anti-SARS-CoV-2 antibody titers at delivery and symptoms following vaccination. Blue: participants that received a third booster dose; Green: participants that received the 2-dose regimen. A-B: Comparison of maternal anti-SARS-CoV-2 antibody titers, analyzed by presence or absence of reported symptoms, for third booster (A), and second vaccination (B). C-D: Comparison of maternal anti-SARS-CoV-2 antibody titers, analyzed by number of reported symptoms, for third booster (C), and second vaccination (D). Significant differences for comparison A were determined by Mann-Whitney U test and Kruskal-Wallis 1-way ANOVA test, followed by Dunn's correction for multiple comparisons. *p <0.05, ns = non-significant.