Effectiveness of BNT162b2 mRNA COVID-19 third vaccines during pregnancy: A national observational study in Israel

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Abstract

BACKGROUND

Current guidelines recommend a third dose of COVID-19 vaccine for pregnant women, although data regarding effectiveness during pregnancy are lacking.

METHODS

We conducted a national, population-based, historical cohort study of all pregnant women in Israel who delivered between August 1, 2021 and March 22, 2022. Data were analyzed by COVID-19 waves (Delta variant in the summer of 2021 and Omicron, BA.1, variant in the winter of 2022) and vaccination status of the women. We compared the third and second doses of vaccine effectiveness in preventing COVID-19-related hospitalizations during pregnancy. Time-dependent Cox proportional-hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for COVID-related outcomes according to vaccine dose. Vaccine effectiveness was estimated as 1-HR.

RESULTS

A total of 82,659 and 33,303 pregnant women were followed during the Delta and Omicron waves, respectively. Compared with the second dose, the third dose effectively prevents hospitalization with SARS-CoV-2 infection, with estimated effectiveness of 97% (95% CI 95–99%) during the Delta period. During the Omicron period, the third dose, but not the second dose, compared to unvaccinated, significantly effectively protects against COVID-19- related outcomes with estimated effectiveness of 43% (95% CI 31–53%), 97% (95% CI 72–100%), and 94% (95% CI 43–99%) in preventing hospitalization with SARS-CoV-2 infection, significant, and severe disease, respectively.

CONCLUSIONS

A third dose of the BNT162b2 mRNA COVID-19 vaccine during pregnancy, given at least 5 months after the second vaccine dose, significantly enhanced protection against adverse COVID-19-related outcomes.

Introduction

Millions of pregnant women have been infected with SARS-CoV-2 since the World Health Organization declared the COVID-19 a global pandemic more than two years ago. Pregnancy has been shown to significantly increase the risk for severe COVID-19 illness, mechanical ventilation, and death, as compared to age-matched non-pregnant women. Moreover, SARS-CoV-2 infection during pregnancy has also been associated with poor obstetric outcomes, including preterm birth and stillbirth[1–4].

Despite the threat posed by COVID-19, pregnant women were excluded from the initial COVID-19 vaccine trials, leading to substantial knowledge gaps on the effect of vaccines on maternal and fetal health. Nevertheless, the urgent need to protect this vulnerable population dictated the inclusion of pregnant women in vaccination campaigns, before clinical trials were completed[1,5–9]. Real-world data confirming the safety and effectiveness of COVID-19 vaccines during pregnancy are critical to support public health policy. Indeed, essential data have accumulated regarding the effectiveness and safety of the BioNTech BNT162b2 mRNA COVID-19 vaccine in pregnant women[5–8]. Two vaccine doses in pregnancy appeared to protect against infection without increase in prenatal or early neonatal morbidity[7], however early studies did not establish vaccine effectiveness against significant disease. As vaccine-induced immune protection appeared to wane, health organizations proposed booster vaccination with a third vaccine dose, including during pregnancy, without an evidence basis for the necessity and effectiveness of a third dose in this population[10,11]. Indeed, following a surge in COVID cases in the summer of 2021, Israel launched an unprecedented population-wide booster vaccination campaign using BNT162b2 mRNA vaccines, calling for all persons over the age of 16 years who had received their second dose at least 5 months prior, to present for a third dose. This campaign included pregnant women starting in August 2021.

We conducted a nationwide historical cohort study to evaluate the evidence regarding this vaccine strategy. We investigated the effectiveness of the three-dose vaccine regimen in mitigating significant disease in pregnant women during two periods of the COVID-19 pandemic: the summer outbreak, during which the Delta variant was dominant (August 1, 2021 to December 1, 2021), and the winter

outbreak, during which the Omicron BA.1 variant became dominant (December 15, 2021 to March 22, 2022) (Fig. 1)[12]. These variants (Delta and Omicron) significantly differed from one another in virulence[13] and their ability to evade vaccine-mediated immune protection[14].

Methods

Study design:

In Israel, the Ministry of Health (MOH) has collected information on all SARS-CoV-2 PCR and all institutionally conducted antigen tests since the beginning of the pandemic. The MOH database maintains information on hospitalizations, severity of cases, and outcomes of patients with confirmed COVID-19. MOH also routinely collects information on all births in Israel. The current study is based on linkage of these datasets.

The study cohort included women who had a documented delivery between August 1, 2021 (the date on which a third boosting dose of Pfizer BNT162b2 mRNA vaccines became available for the younger population, including pregnant women) to March 22, 2022.

The study included unvaccinated pregnant women and those eligible to receive a third dose (≥ 150 days from the date they received their second dose) during the study periods. Women who received one vaccine or a fourth boosting dose, were not included in this study.

The study protocol was approved by the Helsinki Committee of the Hadassah Medical Center. The committee granted exemption from informed consent, based on preserving the participants' anonymity.

Study population:

Three groups were compared for each time period: Group 1 included eligible pregnant women who received, prior to or during the given study period, a third boosting dose (third dose group); Group 2 were pregnant women who were eligible prior to or during the study period for a third boosting dose, but did not receive it (second dose group); and Group 3 included women who were unvaccinated (unvaccinated group).

Study covariates:

For each participant in the study, the following sociodemographic data were extracted: maternal age, parity (primipara- first delivery; multipara- from second to forth delivery and grandmultipara- fifth delivery or greater), number of fetuses in the index pregnancy, and gestational age at delivery. The following clinical data were extracted: delivery date, vaccination dates, RT-qPCR or institutionally administered rapid antigen test dates and results, dates of hospital admission, discharge, disease severity, or death. During the study periods, institutional tests were free and readily available via self-referral. Widely advertised calls for population testing for indications including suspected community or household exposure as well as occupational directives, were issued.

Study outcomes:

Study outcomes included cases hospitalized with a diagnosis of SARS-CoV-2 infection; hospitalization with significant illness from COVID-19; or hospitalization with severe COVID-19 disease, during pregnancy for each time period.

Any documented hospitalization in COVID-19 wards with a positive SARS-CoV-2 result, was considered as hospitalization with a diagnosis of SARS-CoV-2 infection. Significant disease was defined by documented hospitalization with moderate COVID-19-related disease as defined by the MOH, or worse, from the first day of hospitalization. Severe disease was defined by documented hospitalization with severe COVID-19-related disease (MOH) or worse, i.e., critical disease or death during the study period. MOH criteria defined moderate disease as COVID-19 related pneumonia justifying hospitalization; severe disease as a resting respiratory rate > 30 breaths per minute, oxygen saturation on room air < 94%, or ratio of PaO2 to FiO2 < 300; and critical disease as the need for mechanical ventilation and clinical severe organ failure[15].

Follow-up time:

The study was divided into two follow up periods: The Delta Period August 1, 2021 to December 1, 2021, and the Omicron period (December 15, 2021 to March 22, 2022).

Eligible women were followed from the beginning of the study periods. Women who moved from one group to another (e.g. received a third dose) contributed follow-up time according to the time they were included in each group. Women were followed until delivery or incidence of a study outcome, whichever occurred first.

A total of 82,659 pregnant women contributed to the Delta period analysis and 33,303 to the Omicron period. Individual patients could be counted in both study periods in the course of their pregnancies (n = 33,159, see Fig. 1b).

Statistical analysis

Descriptive statistics of the study population by vaccine dose at the end of follow-up is presented. Given that the independent variable (vaccine status) varied over time, univariate and multivariate survival analyses were performed with time-dependent covariates, in accordance with the study design, for each period separately. Kaplan–Meier analysis with a log-rank test was performed for univariate analysis. For each study period, time-dependent Cox proportional hazards models were constructed to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for the study outcomes in the third dose group compared to the second dose group, controlling for maternal age and parity (model 1); additional models compared the third and second dose groups to the unvaccinated group, controlling for maternal age and parity (model 2). After estimation of HR for study outcomes in each group and study period, we calculated vaccine effectiveness as a percentage, defined as 100*(1 − HR); 95% confidence intervals were calculated similarly. To allow conservative estimations of HR and effectiveness in instances where there were no cases of study outcome in a study group, we imputed a single case, if the total number of cases was equal to or greater than 5. We simulated these imputations 1000 times to achieve robust estimates of the HR. This was used to estimate HR of the third dose group, for significant and severe disease during the Omicron period, and severe disease during Delta period.

Python version 3.7.3 and lifelines 0.24.14 were used for multivariate survival analyses with time-dependent covariates. IBM-SPSS for Windows, version 24 (IBM Corp., Armonk, N.Y., USA), was used for the univariate analysis and all other statistical analyses. A p-value $\leq$ 0.05 was considered to indicate statistical significance in all analyses.

Results

During the study period from August 1, 2021 to March 22, 2022, a total of 82,803 pregnant women delivered and met the eligibility criteria (Methods) (see flow chart Fig. 2). Characteristics of the study population at delivery are presented in Table 1. The third dose group was older (23.8% between 36–45 years old) than the second dose or unvaccinated groups (18.0%, and 15.6%, respectively). The proportion of primiparous women among the third dose group was higher than that of the second dose or unvaccinated groups (29.5% vs. 26.9% and 26.8%, respectively). Higher rates of grand-multiparity were observed among the unvaccinated group than the third and second dose groups (21.4% vs 10.2% and 12.9%, unvaccinated, vs third and second dose, respectively). The unvaccinated group included 10,749 (35.1%) who had no documentation for any SARS-CoV-2 testing, compared to 3,484 (15.2%) and 2,964 (10.1%) of pregnant women in the second and third dose groups, respectively.

Table 1
Characteristics of the study cohort by vaccination status at the time of delivery

	Study period [August 1, 2021-March 22, 2022] (N = 82,809)		
	3-Dose	2-dose	Unvaccinated
n %	29,331 (35.4)	22,862 (27.6)	30,616 (37)
Maternal age in years			
< 18–26	4754 (16.3)	5991 (26.3)	11897 (39.0)
27–35	17489 (59.9)	12710 (55.7)	13864 (45.4)
36–45	6984 (23.8)	4103 (18.0)	4769 (15.6)
Multifetal delivery	590 (2.0)	402 (1.8)	552 (1.8)
Parity			
Primipara	8642 (29.5)	6149 (26.9)	8200 (26.8)
Multipara (2–4)	17710 (60.4)	13773 (60.2)	15853 (51.8)
Grandmultipara (5+)	2979 (10.2)	2940 (12.9)	6563 (21.4)
Number of SARS-CoV-2 PCR/antigen tests	3.9 (± 1.7)	3.6 (± 1.9)	2.5 (± 2.1)
0	2964 (10.1)	3484 (15.2)	10749 (35.1)
1	137 (0.5)	127 (0.6)	298 (1.0)
2	3439 (11.7)	3459 (15.1)	6314 (20.6)
3	198 (0.7)	149 (0.7)	164 (0.5)
4	3832 (13.1)	3241 (14.2)	3663 (12.0)
≥ 5	18761 (64.0)	12402 (54.2)	9428 (30.8)
* Data are n (%), and mean (± standard deviation); data are calculated according to the vaccine status of women at delivery.			

During the Delta period, 10 (0.04%) hospitalizations with COVID-19 were documented in the third dose group, 105 (0.20%) in the second dose group, and 341 (1.11%) in the unvaccinated group. During the Omicron period, 260 (1.5%), 217 (2.5%) and 207 (2.5%) were hospitalized, respectively; reflecting the greater transmissibility of the Omicron variant (Suppl. Table 1). Cumulative risk curves for hospitalizations with a diagnosis of SARS-CoV-2 infection are shown in Fig. 3. The figure shows that over time, the rate of hospitalization of women in the third dose group was consistently lowest of the three groups, and that the second dose was effective in preventing hospitalization during the Delta period but not during the Omicron period. Suppl Fig. 1 shows cumulative risk curves for hospitalization with significant disease, and with severe disease.

Table 2 presents the HR and estimated vaccine effectiveness (1-HR%) for the various study outcomes, by vaccine dose. Compared with unvaccinated women, the third dose vaccine effectiveness was estimated to be 97% (95%, CI 95–99%) and 43% (95%, CI 31–53%) for hospitalization with SARS-CoV-2 infection during the Delta and Omicron periods, respectively. The effectiveness of the third dose in preventing significant disease was 99% (95%, CI 93–100%) and 97% (95%, CI 72–100%), during the Delta and Omicron periods, respectively. Similar estimates were evident in preventing severe disease (Tables 2 and 99% (95%, CI 89–100%) and 94% (95%, CI 43–99%) for severe disease, compared to the unvaccinated group, during the Delta and Omicron periods, respectively). Being vaccinated with a second dose provided high protection ≥ 5 months following vaccination during the Delta period, with an effectiveness of 97% (95% CI 92–99%) against significant disease, and 96% (95% CI 86–99%) against severe disease, during the Delta period. During the Omicron period, the second vaccine was not effective in protecting against all study outcomes. The estimated effectiveness of the third vs. the second dose (additional protection) against hospitalization with SARS-CoV-2 infection was 92% (95% CI, 83–96%) during the Delta period, and 48% (95% CI, 37–57%) during the Omicron period. During the Delta period the contribution of the third dose, in addition to the second dose, for protection against significant disease was modest and could not be calculated, as the numbers of affected cases were small. In contrast, the third dose provided significantly enhanced protection during the Omicron period with effectiveness of 92% (95% CI 26–99%) in addition to the second dose.

Table 2
Vaccine effectiveness measures

	Delta period						Omicron period					
	Hospitalization		Significant disease		Severe disease		Hospitalization		Significant disease		Severe disease	
	HR	1-HR (95% CI)	HR	1-HR (95% CI)	HR	1-HR (95% CI)	HR	1-HR (95% CI)	HR	1-HR (95% CI)	HR	1-HR (95% CI)
3rd vs. 2nd vaccine group	0.08 (0.04–0.17)	92% (83–96)	0.15 [ab] (0.01–1.83)	0 vs. 4	0.17 [ab] (0.01–2.40)	0 vs. 3	0.52 (0.43–0.63)	48% (37–57)	0.08 (0.01–0.74)	92% (26–99)	0.41 [ab] (0.02–6.68)	0 vs. 1
2nd dose vs. unvaccinated group	0.39 (0.31–0.49)	61% (51–69)	0.03 (0.01–0.08)	97% (92–99)	0.04 (0.01–0.14)	96% (86–99)	1.12 (0.92–1.36)	[-12%] ([-36]-8)	0.49 (0.16–1.47)	51% ([-47]-84)	0.17 (0.02–1.47)	83% ([-47]-98)
3rd dose vs. unvaccinated group	0.03 (0.01–0.05)	97% (95–99)	0.01[a] (0.00-0.07)	99% (93–100) 0 vs. 108	0.02 [a] (0.00-0.11)	99% (89–100) 0 vs. 64	0.57 (0.47–0.69)	43% (31–53)	0.03 (0.00-0.28)	97% (72–100)	0.06 [a] (0.01–0.57)	94% (43–99) 0 vs. 5

HR of COVID-19 hospitalization degree for vaccinated group vs. unvaccinated group and between the vaccinated groups, in two study periods [Delta period- August 1,2021-December 1, 2021; Omicron period- December 15, 2021- March 22, 2022]. The study period populations were 82,659 and 33,303 in each of the two periods, respectively. In each study period, 28,213 and 714 individuals were first included in the 2-dose group and then re-recruited to the 3-dose group.

HR calculated using Cox proportional-hazards regression model with time-dependent covariates controlling for maternal age, parity and days of follow-up.

Outcomes definitions: Hospitalization with SARS-CoV-2 infection; Significant disease (e.g., COVID-19-related pneumonia associated with COVID-19 justifying hospitalization), and Severe disease (e.g., resting respiratory rate > 30 breaths per minute, O2 saturation on room air < 94%, etc.).

[a] A single case was imputed to allow estimations of HR. Estimation is based on the mean of 1000 simulations.

[b] Estimates (1-HR) were only calculated for cells with 5 events or more, otherwise, raw counts are reported.

Discussion

Our study showed that a third dose of the BNT162b2 mRNA COVID-19 vaccine, given at least 5 months after the second vaccine dose, provides additional protection during pregnancy against hospitalizations with a diagnosis of SARS-CoV-2 infection, and against significant and severe disease.

The mRNA vaccines currently available were designed to prevent infection and disease from the wild type SARS-CoV-2 strains. Data from non-pregnant populations demonstrate that the effectiveness of the second vaccine dose declines over time as the humoral immunity wanes and new variants emerge[16–19]. Our data concur with these reports. Previous studies reported 98% effectiveness of the second dose against hospitalization, shortly after vaccination[1,20]. We detected reduced effectiveness more than five months after the second vaccine dose (61% during the Delta period and none in the Omicron period), findings that might support waning of immunity. In this context, the third dose provided substantial additional protection during the Delta and Omicron periods (97% and 43% protection, respectively) when compared to unvaccinated patients, emphasizing the benefit of vaccine boosting.

We previously showed that a third dose of BNT162b2 mRNA vaccine significantly increased anti-SARS-CoV-2 antibody titers in maternal and cord blood[21]. In addition, a recent study found that a third booster dose was essential in building neutralizing antibody capacity against the Omicron variant among mothers and neonates[22]. These boosted antibody titers may have provided additional protection from the Delta variant and allowed protection from the Omicron variant.

When focusing on substantial COVID-19 illness, 5 months after the second dose, the second dose effectively protected against hospitalization complicated by significant disease (97%) and severe disease (96%) during the Delta period, but not during the Omicron period. The impact of the third boosting dose was significant during the Omicron period, effectively protecting against hospitalization complicated by significant disease (97%) and severe disease (94%). To the best of our knowledge, our results are the first to show data regarding significant vaccine effectiveness against severe COVID-19 disease during pregnancy. The fact that vaccines during pregnancy nearly abolish the risk for significant disease has been shown to play a role in patient decision-making regarding vaccination[23]. Hence, our study might contribute to promoting vaccination uptake among pregnant women.

In the present study, we focused on the impact of COVID-19 vaccine strategy on hospitalization with a diagnosis of SARS-CoV-2 infection, rather than population infection rates. Recorded infection rates may be significantly biased by differential rates of testing in various population subgroups, most notably among unvaccinated patients. Indeed, our data show that unvaccinated pregnant women were significantly less likely to be tested (Table 1). However, while not uniformly executed in all maternity units, routine SARS-CoV-2 testing during maternity admissions was mandatory in most hospitals in Israel. Given the unbiased approach to testing, a finding of positive SARS-CoV-2 during hospitalization represents a better sensor for infection burden, and we therefore assessed and analyzed the data accordingly.

Most previous reports analyzed pregnancy data from a single COVID-19 wave, narrowing observations. We analyzed data from two discrete periods, when two variants having different characteristics were dominant. We focused the time margins on the periods dominated by the Delta and Omicron variants, to present a more comprehensive understanding of vaccine and boosting effectiveness on different viral variants. Indeed, we found significant differences between the two time periods, which might reflect differences in virulence, ability to evade vaccine-mediated immune protection, and waning of protective titers over time.

Our findings provide insight into the impact of COVID-19 vaccines during pregnancy, providing clinicians and policymakers with essential evidence to inform consultation and decision-making.

We lack data on variant sequencing of the diagnostic tests used in this study. However, the Delta and Omicron variants were ascertained to be dominant during each of the study periods defined here, prior to and separate from our analyses. The inclusion of two distinct variants with differing transmissibility and virulence profiles, and comparison of vaccine regimens vs. no vaccine under these dynamic conditions, strengthen our findings. Our results highlight the advantage conferred by the third, boosting dose in pregnancy against serious illness, and serve to reinforce recommendations to vaccinate and boost this population.

Initial, preliminary reports of the long-term effects of maternal COVID-19 infection during pregnancy on child health, and worrying adverse neurodevelopmental sequelae[24–26] have appeared. These cases highlight the potential adverse consequences of maternal COVID-19 disease and the urgent need for data on measures to limit maternal infection.

Our study has several limitations. Since the study is based on real-world collected data, no randomization was possible. Individuals opting to decline boosting doses or to refuse vaccination or evade testing may differ in demographic or obstetric characteristics from those opting in. This is a possible source of bias. We adjusted for known confounders to overcome these potential biases, but recognize that other, unaccounted-for individual and group differences in risk factors for severe illness or the likelihood of exposure to the virus, may have impacted our results. Our findings were limited to the BNT162b2 vaccine. We cannot infer whether our observations are relevant to preventing reinfection in convalescent COVID-19 pregnant women, or populations administering other vaccines. The decision to vaccinate during pregnancy is a balance between benefit and effectiveness vs. safety. We did not evaluate COVID-19 vaccine safety, however several other large studies have done so[1,27], and demonstrated a favorable safety profile.

In conclusion, when compared to eligible non-boosted or unvaccinated pregnant women, women who received a third dose of BNT162b2 had a lower incidence of hospitalization with SARS-CoV-2 infection during the Delta period and significantly lower incidence of COVID-19 related outcomes during the Omicron period. Our data and analyses provide the necessary evidence to support current recommendations to vaccinate pregnant women with the third boosting dose of COVID-19 vaccine.

References

1. Male V. SARS-CoV-2 infection and COVID-19 vaccination in pregnancy. Nature reviews Immunology 2022;22:277–82.
2. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nature medicine 2022;28:504–12.

3. Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. American journal of obstetrics & gynecology MFM 2020;2:100107.
4. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. Bmj 2020;370:m3320.
5. Goldshtein I, Steinberg DM, Kuint J, et al. Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes. JAMA pediatrics 2022;176:470–7.
6. Goldshtein I, Nevo D, Steinberg DM, et al. Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. Jama 2021;326:728–35.
7. Blakeway H, Prasad S, Kalafat E, et al. COVID-19 vaccination during pregnancy: coverage and safety. American journal of obstetrics and gynecology 2022;226:236 e1- e14.
8. Fell DB, Dhinsa T, Alton GD, et al. Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes. Jama 2022;327:1478–87.
9. Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. The Journal of clinical investigation 2021;131.
10. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. American journal of obstetrics and gynecology 2020;223:109.e1-.e16.
11. ACOG. COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care.
12. SARS-CoV-2 variants in analyzed sequences, Israel. GISAID-Our World in Data, 2022. (Accessed June, 20, 2022, at https://ourworldindata.org/grapher/covid-variants-area?time=2021-07-26..2022-05-30&country=~ISR.)
13. Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California. Nature medicine 2022.
14. Mallapaty S. COVID-19: How Omicron overtook Delta in three charts. Nature 2022.
15. Confirmed Cases and Patients. 2022. at https://corona.health.gov.il/en/confirmed-cases-and-patients/severity/.)
16. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med 2021;385:e83.
17. Goldberg Y, Mandel M, Bar-On YM, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. N Engl J Med 2021;385:e85.
18. Keehner J, Horton LE, Binkin NJ, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med 2021;385:1330–2.
19. Levin EG, Lustig Y, Cohen C, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J Med 2021;385:e84.
20. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nature medicine 2021;27:1693–5.
21. Nevo L, Cahen-Peretz A, Vorontsov O, et al. Boosting maternal and neonatal humoral immunity following SARS-CoV-2 infection using a single mRNA vaccine dose. Am J Obstet Gynecol 2022.
22. Rottenstreich A, Vorontsov O, Alfi O, et al. Maternal and Neonatal SARS-CoV-2 Omicron Variant Neutralization after Antenatal mRNA Vaccination. Clinical Infectious Diseases 2022.
23. Skjefte M, Ngirbabul M, Akeju O, et al. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. European journal of epidemiology 2021;36:197–211.
24. Aldrete-Cortez V, Bobadilla L, Tafoya SA, et al. Infants prenatally exposed to SARS-CoV-2 show the absence of fidgety movements and are at higher risk for neurological disorders: A comparative study. PLoS One 2022;17:e0267575.
25. Ayed M, Embaireeg A, Kartam M, et al. Neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections during pregnancy: a national prospective study in Kuwait. BMC Pediatr 2022;22:319.
26. Edlow AG, Castro VM, Shook LL, Kaimal AJ, Perlis RH. Neurodevelopmental Outcomes at 1 Year in Infants of Mothers Who Tested Positive for SARS-CoV-2 During Pregnancy. JAMA Netw Open 2022;5:e2215787.
27. Prasad S, Kalafat E, Blakeway H, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. Nat Commun 2022;13:2414.

Supplemental Table 1

Supplemental Table 1: COVID-19 related infection and hospitalization according to study period and vaccine status

	Delta period [August 1, 2021-December 1,2022]			Omicron period [December 15, 2021-March 22, 2022]		
	3-Dose	2-dose	Unvaccinated	3-Dose	2-dose	Unvaccinated
N	28303	51942	30627	17123	8612	8282
SARS-CoV-2 positive result	268 (0.9)	2629 (5.1)	2090 (6.8)	3609 (21.1)	1747 (20.3)	1089 (13.1)
COVID-19 Hospitalization:	-	-	-	-	-	-
All	10 (0.04)	105 (0.20)	341 (1.11)	260 (1.5)	217 (2.5)	207 (2.5)
Significant disease (out of hospitalized cases)	0	4 (3.8)	108 (31.7)	1 (0.4)	5 (2.3)	9 (4.3)
Significant disease (out of total cohort)	0	4 (0.01)	108 (0.35)	1 (0.01)	5 (0.06)	9 (0.11)
Severe disease (out of hospitalized cases)	0	3 (2.9)	64 (18.8)	0	1 (0.5)	5 (2.4)
Severe disease (out of total cohort)	0	3 (0.01)	64 (0.21)	0	1 (0.01)	5 (0.06)
COVID-19 hospitalization duration (days):	-	-	-	-	-	-
All	2.4 (±1.4)	3.5 (±3.7)	5.2 (±7.8)	4.9 (±6.2)	4.1 (±4.6)	3.9 (±4.4)
Significant disease	-	5.8 (±3.9)	8.6 (±11.8)	-	12.2 (±17.9)	8.8 (±13.4)
Severe disease	-	5.7 (±4.7)	12.1 (±14.2)	-	-	12.8 (±17.7)
Maternal death related to COVID	0	0	1	0	0	0

Data are n (%), and mean (± standard deviation). The study period populations were 82,659 and 33,303 in each of the two periods. In each study period 28,213 and 714 individuals were first included in the 2-dose group and then re-recruited to the 3-dose group. Calculation of COVID related hospitalization is according to follow-up time in each study group until an event occurred, as described in the Methods.

Supplementary Methods – Author Access To The Data And Author Contribution

JG, ML, TK, EM and OB saw the original data, collected it and analyzed it. JG, ML, OB, RCM, AW, GS and SY conceived and designed the study. JG, ML, OB, RCM, SC, DW and SY wrote the manuscript. All authors critically reviewed the manuscript and decided to proceed with publication.

RCM, SY and OB supervised the study process.

OB vouches for the data and analysis.

TK, EM & GS combined, anonymized and QC of the MOH data.

No commercial agreements pertain to this study, specifically no agreements that relate to confidentiality

Figures

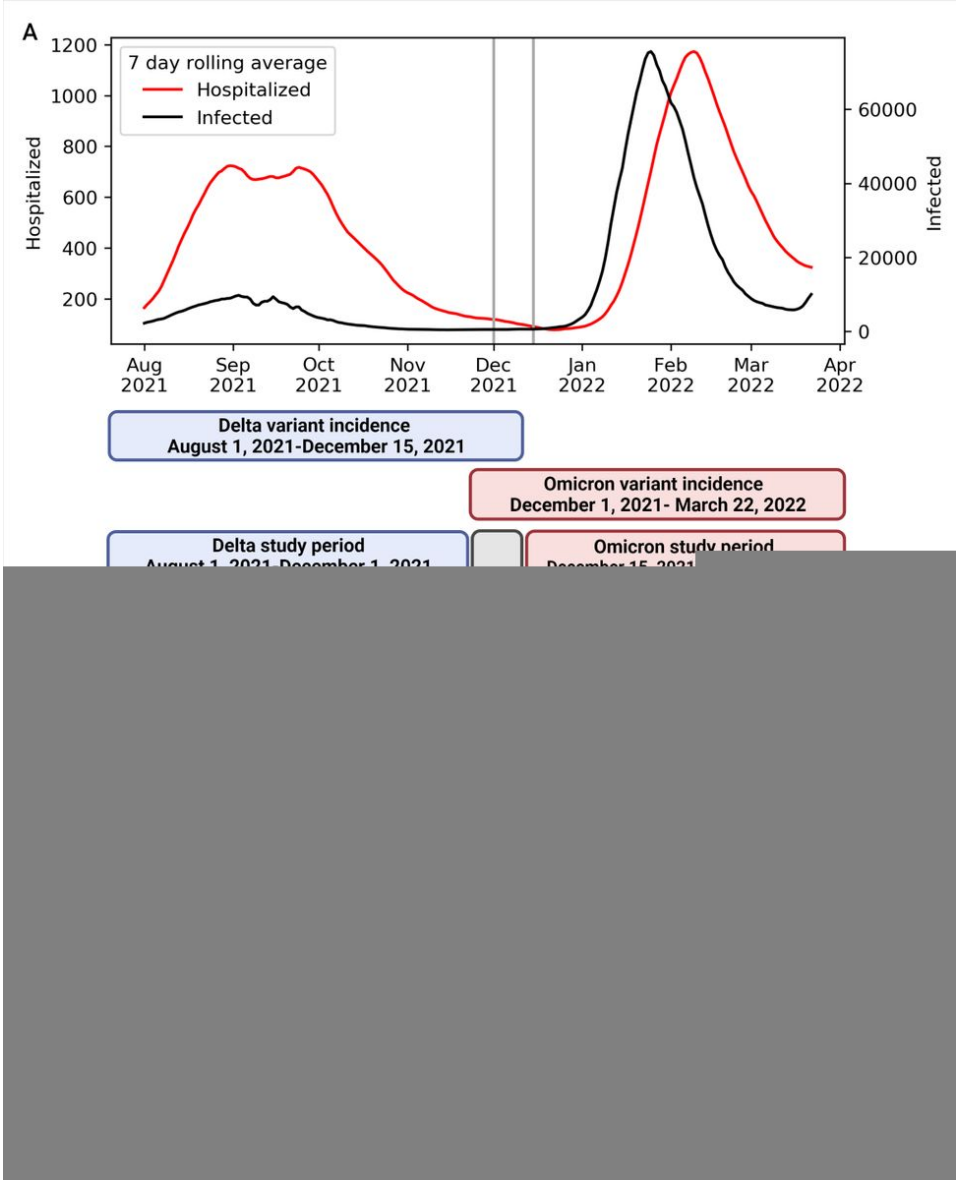

Figure 1

Israel national data of confirmed SARS-CoV-2 infections, and cases of severe COVID-19 during the study timeline, and graphic representation of participants follow-up.

A: Weekly incidence numbers, of all Israeli population, SARS-CoV-2 infection and severe COVID-19, on different scales, between August 2021 and April 2022. The study periods are demonstrated beneath the graph (Delta period in blue and Omicron in red; the grey represents the time frame excluded from the study due to overlap of the variants).

B: Sample of participant follow-up time during the two study periods. Each row represents a participant, colored by their vaccination status during follow-up. Third vaccine (green line), second vaccine (orange line), and unvaccinated (blue line). Participants change color when they move between groups.

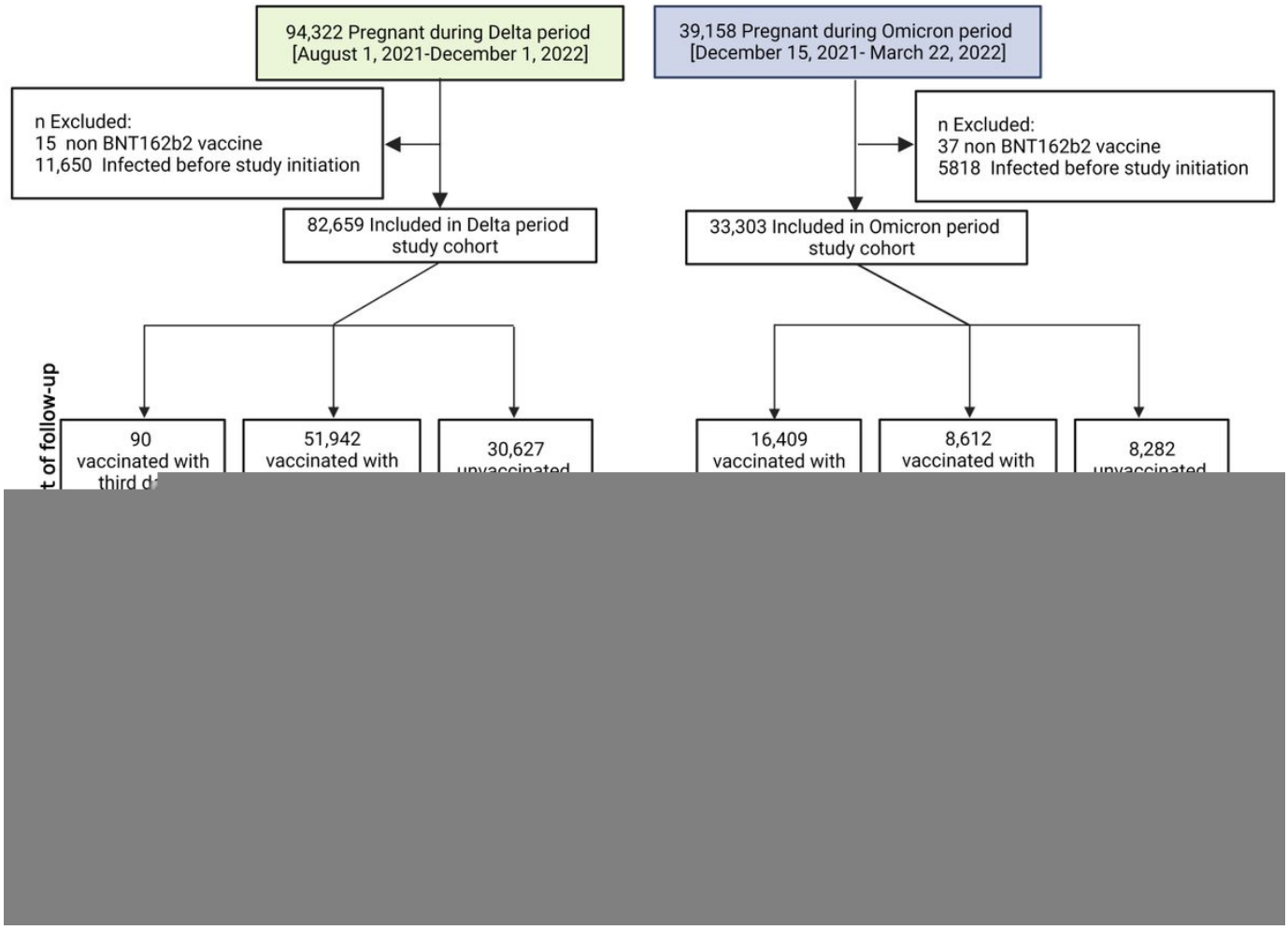

Figure 2

Study population and flow chart of cohort selection.

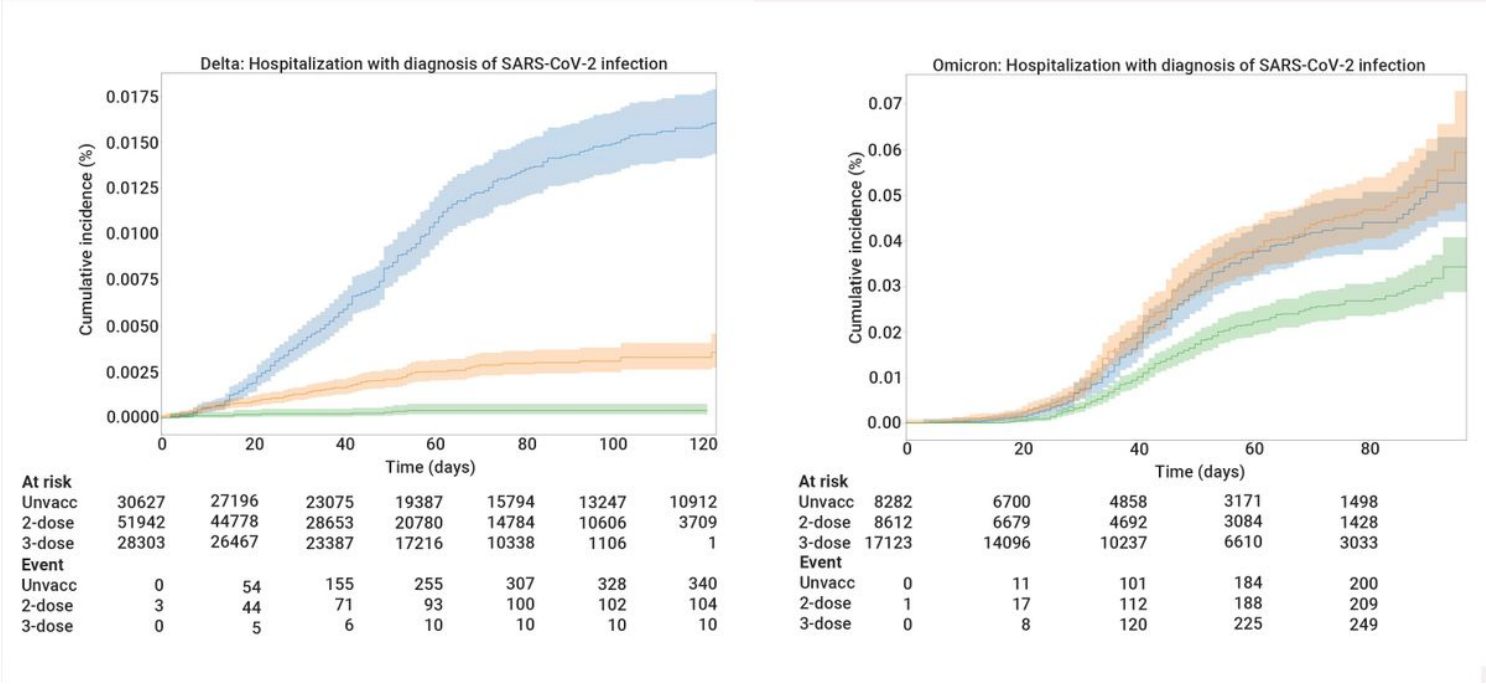

Figure 3

Cumulative incidence of study outcomes, according to COVID-19 waves and vaccination status. Cumulative incidence curves comparing the two study periods (Delta period on the left and Omicron period on the right) for hospitalizations with a diagnosis of SARS-CoV-2 infection in pregnant women, by vaccination status (Third vaccine-green line, second vaccine-orange line, and unvaccinated- blue line). Shaded areas represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each outcome.

Supplementary Files

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

- SupplFigure1cumulativeratesDeltavOmicron.jpg