Effectiveness of the BNT162b2 mRNA COVID-19 Vaccine in Pregnancy

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Brief Communication

Keywords: COVID-19, vaccination, pregnancy, vaccine effectiveness

Posted Date: July 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-665725/v1>

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Version of Record: A version of this preprint was published at Nature Medicine on September 7th, 2021.
See the published version at <https://doi.org/10.1038/s41591-021-01490-8>.

Abstract

Background: As mass vaccination campaigns against COVID-19 accelerate worldwide, there remains only limited evidence regarding vaccine effectiveness (VE) among pregnant women. Pregnant women have been shown to be at risk for severe COVID-19, resulting in adverse obstetrics outcomes, and their immune system is known to undergo alterations during pregnancy. Phase III clinical trials of the approved mRNA COVID-19 vaccines excluded pregnant women, yet current guidelines encourage offering the vaccine to pregnant women. In this study, we examine data from Israel's largest healthcare organization to evaluate the effectiveness of the BNT162b2 mRNA vaccine among pregnant women.

Methods: We conducted an observational cohort study of pregnant women 16 years or older, with no history of SARS-CoV-2, who were vaccinated between December 20, 2020 and June 3, 2021. Vaccinated subjects were matched to unvaccinated controls according to a set of demographic and clinical characteristics. Study outcomes included documented infection with SARS-CoV-2, symptomatic COVID-19, COVID-19-related hospitalization, severe illness and death. For each outcome, VE was estimated at several periods following vaccination as one minus the risk ratio using the Kaplan–Meier estimator.

Results: 10,861 vaccinated women were matched to an identical number of unvaccinated controls. Estimated VE from 7 through 28 days after the second dose was 97% (95% CI 91%-100%) for any documented infection, 96% (86-100%) for infections with documented symptoms, and 85% (32%-100%) for COVID-19-related hospitalization. Only one event of severe illness was observed in the unvaccinated group, and no deaths were observed in either group – insufficient incidence for estimating VE for these outcomes.

Discussion: The BNT162b2 mRNA vaccine was found to have high VE among pregnant women. Since high VE has been reported as one of the strongest predictors of COVID-19 vaccine acceptance among pregnant women, the high VE estimates found in this study have the potential to increase vaccine acceptance in this group. In addition, the present VE estimates are similar to those reported in the general population for the same variants, suggesting that it may be possible to infer the VE for pregnant women from studies in the general population for both current and future variants.

Introduction

Hundreds of millions of people worldwide have been infected by the SARS-CoV-2 virus, and millions have died from COVID-19 and related complications. COVID-19 vaccines are currently the leading approach for combating the pandemic's advance. Phase III clinical trials conducted to evaluate the safety and efficacy of mRNA COVID-19 vaccines did not include pregnant women, even though they are at risk for severe COVID-19(1) and potentially for adverse pregnancy outcomes(2). Ongoing trials are limited to late pregnancy vaccination and surrogate efficacy outcomes (i.e., immunogenicity). Despite the current lack of evidence regarding the safety and efficacy of the vaccines for this population(3, 4), current guidelines state that pregnant women should be offered the vaccines(5).

As the number of vaccinated individuals increases worldwide, there is an opportunity to evaluate the real-world effectiveness and safety of the mRNA COVID-19 vaccines using observational data. Initial reports regarding vaccine safety indicate no obvious safety signals among pregnant women(6). However, information regarding vaccine effectiveness (VE) among pregnant women is still limited(5).

The immune system is known to undergo alterations during pregnancy. For example, there is evidence that levels of CD4 + and CD8 + lymphocytes decrease during pregnancy, as do the levels of some inflammatory cytokines(7). Since mRNA-based vaccines are a novel technology that has not been widely tested among pregnant women, it is plausible that the immune response triggered by these vaccines in pregnant women may be altered compared to the general population, increasing the need to evaluate VE specifically for this sub-population. In a previous report, confidence in VE among pregnant women was mentioned as one of the strongest predictors of COVID-19 vaccine acceptance in this group(8). The objective of this study is thus to provide real-world VE measures in a large cohort of vaccinated pregnant women.

Methods

Data Source

Clalit Health Services (CHS) is an integrated healthcare payer-provider organization that serves 52% of the Israeli population. The present study is based on CHS data covering patients vaccinated from the start of the vaccination campaign in Israel on December 20, 2020 through June 3, 2021. CHS data systems contain medical and claims data covering all facets of patient care, including primary care, specialist care, imaging, labs, and hospitalizations, with over 20 years of historical depth for most individuals. CHS community care includes dedicated systems for prenatal care, with specific data fields for “date of last menstrual period” and “projected birth date.” These data are integrated daily with data collected centrally by the Israeli Ministry of Health regarding COVID-19 vaccines, SARS-CoV-2 tests, as well as COVID-19 related hospitalizations, disease severity and death.

Study Design and Study Population

We conducted an observational cohort study that emulates a target trial to estimate the effectiveness of the BNT162b2 mRNA COVID-19 vaccine among pregnant women. We used a similar methodology to previous studies on VE using the same database(9). Eligibility criteria considered at the start of follow-up were being pregnant (as recorded in the CHS data systems), age 16 or older, continuous membership in the CHS health organization for a complete year, no prior positive SARS-CoV-2 PCR test, no prior SARS-CoV-2 vaccination, not residing in long-term care facilities, no home confinement due to medical reasons, not being a healthcare worker, and no interaction with the healthcare system (physician appointment, laboratory test or hospitalization) in the previous 2 days (as this may signal a pre-existing SARS-CoV-2 infection). Individuals with missing data (only relevant for the BMI and living area variables) were excluded, as these are rare in the CHS data.

Each day during the study period, eligible women vaccinated on that day were individually matched to eligible women who had not yet been vaccinated and who were not previously matched as controls. Matching factors included age (in 3 year bins), trimester of pregnancy, geostatistical living area (corresponding to a small town or a single neighborhood within a large city, or city/town of residence when the smaller geostatistical living area was not available), population sector (General Jewish, Arab or Ultraorthodox Jewish), count of influenza vaccinations in the last 5 years (in 2 bins), and existence of a CDC risk factor for severe COVID-19(10). Definitions for all variables used in the study are included in Table S1.

The outcomes studied were: Documented SARS-CoV-2 infection - defined as a positive SARS-CoV-2 PCR test; Symptomatic SARS-CoV-2 infection (COVID-19) - defined by an infection accompanied by the documentation of COVID-19 symptoms in dedicated fields in the outpatient health record (or an infection that warranted an hospitalization); COVID-19 related hospitalization; Severe COVID-19 - as defined by the Israeli ministry of health using international criteria(11); and COVID-19 related death. The outcome date was set to the date of the first positive test for the first two outcomes and the date of first occurrence for the latter outcomes.

Statistical Analysis

Following matching, we used the Kaplan-Meier estimator to construct cumulative incidence curves. We estimated VE at different periods following vaccination: days 14–20 after the first dose, days 21–27 after the first dose and days 7–56 after the second dose. In each period, we restricted the analysis to matched pairs where both members were not censored and had not developed the outcome prior to the beginning of that period. We then calculated the risk ratio and risk difference during that period, with VE defined as one minus the risk ratio. To estimate the analog of a per-protocol effect, we censored both members of the matching pair when either member received a vaccination. Confidence intervals were estimated using the nonparametric percentile bootstrap method with 1,000 repetitions. Analysis was performed using the R programming language, version 4.0.4.

Ethics

This study was approved by the CHS institutional review board.

Results

Of 38,836 women in CHS vaccinated during pregnancy, 28,227 met the eligibility requirements, and 10,861 were successfully matched to unvaccinated controls (Figure S1). The full population was similar to the eligible population (Table S2). Matched individuals were also similar to the eligible population, albeit with a lower proportion of existing conditions for some of the risk factors for severe COVID-19 (Table S2).

The baseline characteristics of the matched individuals were very similar in the vaccinated and unvaccinated groups (Table S3). The median age was 30 years, with 26%, 48%, and 26% in the first, second and third trimesters, respectively. Of the matched individuals, 18% had at least one risk factor for severe COVID-19 (the most common being obesity).

During a median follow-up of 77 days, 131 infections were documented in the vaccination group and 235 infections in the control group. Event counts in each of the analysis periods are included in Table S4. Cumulative incidence curves from the time of the first vaccine dose are shown in Fig. 1. The curves in the vaccinated and unvaccinated groups are similar until day 14 following the first vaccine dose, when incidence in the vaccinated group begins to decline sharply.

The estimated VE for documented infections was 67% (95% CI: 40%-84%) in days 14–20 following the first dose, 71% (33%-94%) in days 21 – 17 following the first dose, and 96% (89%-100%), in days 7–56 following the second dose. The estimated VE for symptomatic infection was 66% (95% CI: 32%-86%) in days 14–20 following the first dose, 76% (30%-100%) in days 21 – 17 following the first dose, and 97% (91%-100%), in days 7–56 following the second dose. VE for COVID-19 related hospitalization was 89% (43%-100%) in days 7–56 following the second dose (Table 1). The VE could not be estimated for the other outcomes and periods due to the small number of events.

Table 1

Risk ratios and risk differences (per 100,000) of COVID-19 outcomes for vaccination vs. no vaccination at several periods following vaccination, in pregnant women who are members of Clalit Health Services, December 20, 2020 through June 3, 2021. The study population numbered 10,861 individuals in each arm. 1,529 individuals were first included as unvaccinated and then re-recruited as vaccinated.

Period	Documented Infection		Symptomatic Infection		Hospitalization		Severe Disease	
	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)
Days 14–20 after 1st dose	67% (40%-84%)	309.22 (145.43-485.69)	66% (32%-86%)	223.59 (82.44-361.63)	3 vs. 0*		2 vs. 0*	
Days 21–27 after 1st dose	71% (33%-94%)	157.30 (41.42-285.23)	76% (30%-100%)	116.52 (26.92-217.92)	5 vs. 0*		0 vs. 0*	
Days 7–56 after 2nd dose	96% (89%-100%)	933.40 (685.60-1192.33)	97% (91%-100%)	621.70 (433.68-847.26)	89% (43%-100%)	132.28 (31.67-241.03)	1 vs. 0*	
*Estimates were only calculated for cells with more than 5 events, otherwise raw counts were reported.								

Discussion

In this study we estimated that the BNT162b2 mRNA COVID-19 vaccine is as effective for pregnant women as previously reported for the general population for the same variant composition: 96% effectiveness against documented infection and 97% effectiveness against symptomatic infection 7–56 days following receipt of the second vaccine dose. Effectiveness against COVID-19-related hospitalization was high, but a paucity of cases prevented precise estimation. These results reflect the VE mainly against the original SARS-CoV-2 reference strain and the B.1.1.7 (Alpha) variant, which were the dominant strains circulating in Israel during the study period.

As the original phase III trials did not include pregnant women, data regarding the effectiveness of the novel mRNA COVID-19 vaccines in this population is still scarce in the medical literature. One study confirmed the immunogenicity of these vaccines in pregnant women by confirming cellular and humoral immune responses against SARS-CoV-2(12). To the best of the authors' knowledge, the present study is the first to directly evaluate VE against infection and symptomatic disease among women vaccinated during pregnancy.

The VE of the BNT162b2 mRNA COVID-19 vaccine against documented and symptomatic infections was previously reported for a general population using the data repositories of the same healthcare organization and covering the same variant distribution – after the second vaccine dose, VE was found to be 92% (88%-95%) and 94% (87%-98%), respectively(9). In an updated analysis of the same data over a longer period of time, the confidence intervals were narrower, with estimates of 93% (91%-94%) for documented infection and 96%(94%-97%) for symptomatic infection(13). The VE estimated in the present study suggests that pregnant women have similar VE as the general population, or maybe even slightly higher VE than the general adult population, which is older on average and has a higher burden of comorbidities (some of which were demonstrated to reduce VE). That pregnancy was not found to reduce VE suggests that it may be reasonable to infer VE for pregnant women based on studies in the general population, for both current and future variants.

Vaccination of pregnant women may also provide protection for their newborns. A recent study found binding and neutralizing antibodies in the cord blood of infants born to mothers who were vaccinated with mRNA vaccines, and in the mothers' breast milk(12). Another study found that vaccination of breastfeeding women resulted in a rapid increase of anti-SARS-CoV-2-specific antibodies in their breast milk(14). The duration of the potential protection is still unclear. However, it is plausible that the antibody secretion in breast milk will provide protection to newborns, especially among those women vaccinated during the later stages of pregnancy.

The high VE among pregnant women estimated in this study may also contribute to increased vaccination acceptance rates among this group. It was previously reported that high VE is an important factor for encouragement of pregnant women to receive COVID-19 vaccines: If VE of above 90% was achieved, 52%

of the pregnant women reported that they would be willing to receive the vaccine. Furthermore, pregnant women indicated higher likelihood of vaccination with higher VE(8).

This study has several limitations. First, despite the careful matching between cohorts, there is the lingering possibility of residual confounding. This is particularly true because information regarding pre-natal complications was not available. However, the very similar incidence of documented and symptomatic infections between the study groups during the early period following the first vaccine dose suggests that residual confounding, if present, is minor. Second, due to the low incidence of the more severe outcomes, this study was not able to provide precise VE estimates for them. Third, the strict matching process required to achieve exchangeability between the study groups resulted in a relatively large fraction of the eligible population not being included in the study. As a result, the proportion of women with some chronic conditions was somewhat lower in the final study population. VE for women with chronic conditions may be somewhat lower than the average VE reported in this study, as previously reported for the general population (13).

In conclusion, the results of this study indicate that the BNT162b2 mRNA COVID-19 vaccine is highly effective among pregnant women for the original SARS-CoV-2 strain and the B.1.1.7 (Alpha) variant. The similarity between the VE estimates among pregnant women and those reported for the same variants in the general population suggests that it may be possible to infer VE for pregnant women from studies in the general population for both current and future variants. Further studies are needed to better characterize the dynamics of VE throughout pregnancy, as well as the relationship between vaccination timing and infant protection after birth.

Declarations

Author Contributions

ND, NB, TBS, CK, SHD, BR and RDB conceived and designed the study. ND, NB and MMA participated in data extraction and analysis. ND, NB, ZK, MAH, ML, SHD, BR and RDB wrote the manuscript. TBS and SHD provided clinical guidance. All authors critically reviewed the manuscript and decided to proceed with publication. BR and RDB supervised the study process and vouch for the data and analysis.

Funding

This research was supported by the Ivan and Francesca Berkowitz Family Precision Medicine Clinic at Clalit Research Institute and the Ivan and Francesca Berkowitz Family Living Laboratory at Harvard Medical School. ML was supported by the Morris-Singer Fund.

Competing interests

ND, NB, MMA and RDB report institutional grants to Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. ML reports grants from Pfizer, personal fees from Merck, personal fees from Bristol-Meyers Squibb, personal fees from

Sanofi Pasteur, personal fees from Janssen, grants from NIH (US), grants from National Institute for Health Research (UK), grants from CDC (US), grants from Open Philanthropy Project, grants from Wellcome Trust, grants from Pfizer outside the submitted work; he has provided unpaid advice on COVID vaccines or vaccine studies to One Day Sooner (nonprofit), Pfizer, Astra-Zeneca, Janssen, and COVAXX (United Biosciences). MAH reports grants from NIH, grants from VA, personal fees from Cytel, personal fees from ProPublica, outside the submitted work; he has provided unpaid advice on COVID vaccine studies to Pfizer. SHD reports consulting fees from Roche and UCB outside the submitted work. BYR reports grants from NIH outside the submitted work.

Data availability

Due to data privacy regulations, the raw data of this study cannot be shared.

Code availability

The modeling code used in this study is part of standard R libraries that are freely available.

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Figures

Figure 1

Cumulative incidence of outcomes. Cumulative incidence curves of COVID-19 outcomes in pregnant women, Clalit Health Services, December 20, 2020 through June 3, 2021. Shaded areas are 95% confidence intervals. The vertical lines at days 28 and 77 demarcate the period in which an individual is considered “fully vaccinated” in the manuscript (7 through 58 days after receipt of the second dose). The tables below each curve present the number at risk at each time point, along with the cumulative number of events. Each individual was included only once in each study group, but individuals could move from the unvaccinated group to the vaccinated group after receipt of the vaccine.

Supplementary Files

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