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BRIEF COMMUNICATION

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Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy

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To evaluate the effectiveness of the BNT162b2 messenger RNA vaccine in pregnant women, we conducted an observational cohort study of pregnant women aged 16 years or older, with no history of SARS-CoV-2, who were vaccinated between 20 December 2020 and 3 June 2021. A total of 10,861 vaccinated pregnant women were matched to 10,861 unvaccinated pregnant controls using demographic and clinical characteristics. Study outcomes included documented infection with SARS-CoV-2, symptomatic COVID-19, COVID-19-related hospitalization, severe illness and death. Estimated vaccine effectiveness from 7 through to 56 d after the second dose was 96% (95% confidence interval 89–100%) for any documented infection, 97% (91–100%) for infections with documented symptoms and 89% (43–100%) 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. In summary, the BNT162b2 mRNA vaccine was estimated to have high vaccine effectiveness in pregnant women, which is similar to the effectiveness estimated in the general population.

Hundreds of millions of individuals worldwide have been infected by the SARS-CoV-2 virus and millions have died from COVID-19 and related complications. Vaccines are currently the leading approach for combating the pandemic's advance. Phase 3 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[3] are limited to late pregnancy vaccination and surrogate efficacy outcomes (that is, immunogenicity). Given the current lack of evidence regarding the safety and efficacy of the vaccines for this population[4,5], vaccination guidelines[6–8] for pregnant women have been inconsistent, ranging from contraindicated to permitted to recommended in pregnancy.

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[9]. However, information regarding vaccine effectiveness among pregnant women is still limited[10].

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[11]. Because mRNA-based vaccines are a new technology that has not been widely tested in 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 vaccine effectiveness specifically for this subpopulation. In a previous report, confidence in vaccine effectiveness among pregnant women was mentioned as one of the strongest predictors of COVID-19 vaccine acceptance in this group[12].

The objective of this study was to estimate real-world vaccine effectiveness in a large observational cohort of pregnant women, aged 16 years or older, with no previous SARS-CoV-2 infection and recruited between 20 December 2020 and 3 June 2021. Vaccinated women were exactly matched to unvaccinated controls on a set of demographic and clinical characteristics and followed for a median of 77 d. Vaccine effectiveness was estimated in several follow-up periods for documented infection with SARS-CoV-2, symptomatic COVID-19, COVID-19-related hospitalization, severe COVID-19 and COVID-19-related death.

Results

Of 38,836 women members of Clalit Health Services (CHS) vaccinated during pregnancy, 28,227 met the eligibility criteria (Methods); 10,861 of these vaccinated women were successfully matched to unvaccinated pregnant controls (Extended Data Fig. 1). The full population was similar to the eligible population (Supplementary Table 1). Matched individuals were also similar to the eligible population, albeit with a lower prevalence of some risk factors for severe COVID-19 (Supplementary Table 1).

The baseline characteristics of the matched individuals were very similar in the vaccinated and unvaccinated groups (Supplementary Table 2). The median age was 30 years, with 26%, 48% and 26% of pregnancies in the first, second and third trimesters, respectively.

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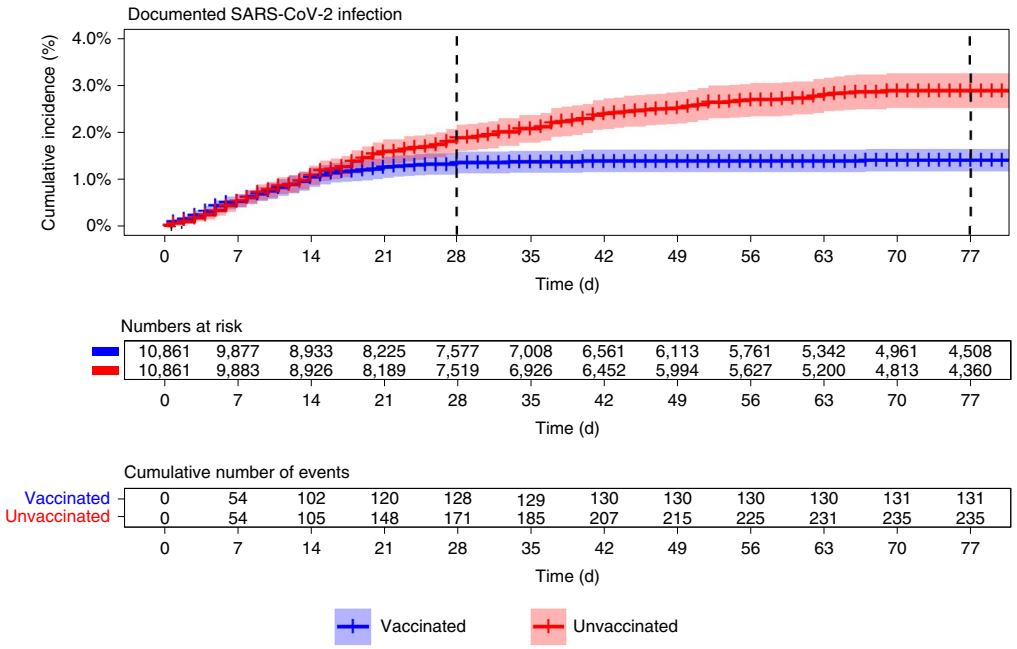

Fig. 1 | Cumulative incidence of SARS-CoV-2 documented infection in vaccinated pregnant women and matched controls. Cumulative incidence curves of the documented infection outcome in pregnant women, CHS, 20 December 2020 through to 3 June 2021. The main line is the point estimate of the cumulative incidence and the shaded areas are the 95% CIs. The vertical lines at days 28 and 77 demarcate the period when an individual was considered 'fully vaccinated' in the manuscript (7 through to 56 d after receipt of the second dose). The curve represents the numbers 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 to the vaccinated group after receipt of the vaccine.

Table 1 | Vaccine effectiveness measures

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 first dose	67% (40–84%)	309.22 (145.43–485.69)	66% (32–86%)	223.59 (82.44–361.63)	3 versus 0[a]		2 versus 0[a]	
Days 21–27 after first dose	71% (33–94%)	157.30 (41.42–285.23)	76% (30–100%)	116.52 (26.92–217.92)	5 versus 0[a]		0 versus 0[a]	
Days 7–56 after second 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 versus 0[a]	

RRs and RDs (per 100,000 persons) of COVID-19 outcomes for vaccination versus no vaccination at several time points after vaccination in pregnant women who are members of the CHS, 20 December 2020 through to 3 June 2021. The study population numbered 10,861 individuals in each arm and 1,529 individuals were first included as unvaccinated and then re-recruited as vaccinated.
[a]Estimates were only calculated for cells with more than five events; otherwise, raw counts are reported.

Of the matched individuals, 18% had at least 1 risk factor for severe COVID-19, the most common being obesity.

During a median follow-up of 77 d, 131 infections were documented in the vaccination group and 235 infections in the control group (Fig. 1). Event counts in each of the analysis periods (for individuals who were eligible to be included in the analysis for that period) are included in Supplementary Table 3. Cumulative incidence curves from baseline (first vaccine dose for the vaccinated group) are shown in Fig. 1 for the documented infection outcome and in Extended Data Figs. 2–4 for the additional outcomes. The curves in the vaccinated and unvaccinated groups are similar until day 14, when incidence in the vaccinated group begins to decline sharply.

The estimated vaccine effectiveness for documented infections was 67% (95% confidence interval (CI) = 40–84%) in days 14–20 after the first dose, 71% (33–94%) in days 21–27 after the first dose and 96% (89–100%) in days 7–56 after the second dose (Table 1). The estimated vaccine effectiveness for symptomatic infection was 66% (95% CI = 32–86%) in days 14–20 after the first dose, 76% (30–100%) in days 21–27 after the first dose and 97% (91–100%) in days 7–56 after the second dose. Vaccine effectiveness for COVID-19-related hospitalization was 89% (43–100%) in days 7–56 after the second dose. Vaccine effectiveness could not be meaningfully estimated for the other outcomes and time periods due to the small number of events.

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 during the same time period: 96% effectiveness against documented infection and 97% effectiveness against symptomatic infection 7–56 d after receipt of the second vaccine

dose. The estimated vaccine effectiveness for COVID-19-related hospitalization was high but a paucity of cases prevented precise estimation. These results reflect the effectiveness 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.

Since the original phase 3 trials did not include pregnant women, data regarding the effectiveness of the new 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 (ref. [13]).

We previously estimated the vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine for a general population using the data repositories of the same healthcare organization and covering the same variant distribution. After the second vaccine dose, vaccine effectiveness was estimated to be 92% (88–95%) for documented infections and 94% (87–98%) for symptomatic infections[14]. In an updated analysis of the same data over a longer period, the 95% CIs were narrower, with estimates of 93% (91–94%) for documented infection and 96% (94–97%) for symptomatic infection[15]. Our study suggests that the vaccine effectiveness estimate for pregnant women is not lower than that for the general population. This is consistent with the lower prevalence of comorbidities (some of which were associated with lower vaccine effectiveness[15]) in pregnant women compared with the general population. Our findings make it plausible that the vaccine effectiveness estimated in the general population for future variants may be used to infer the effectiveness in pregnant women for the same variants, particularly for mRNA-based vaccines.

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[13]. Another study found that vaccination of breastfeeding women resulted in a rapid increase of anti-SARS-CoV-2-specific antibodies in their breast milk[16]. The magnitude and duration of this potential protection is still unclear.

The high vaccine effectiveness in pregnant women estimated in this study might also contribute to increased vaccination acceptance rates among this population. It was previously reported that high vaccine effectiveness is an important factor for the encouragement of pregnant women to receive COVID-19 vaccines. If vaccine effectiveness >90% was achieved, 52% of pregnant women reported that they would be willing to receive the vaccine. Furthermore, pregnant women indicated higher likelihood of vaccination with higher vaccine effectiveness[12].

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 prenatal complications was not available. However, the very similar incidence of documented and symptomatic infections between the two study groups during the early period after the first vaccine dose suggests that residual confounding, if present, was minor. Second, owing to the low incidence of the more severe outcomes, this study could not provide precise vaccine effectiveness 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. Thus, the proportion of women with some chronic conditions was somewhat lower in the final study population. Vaccine effectiveness for women with chronic conditions may be somewhat lower than the average vaccine effectiveness estimated in this study, as previously reported for the general population[15].

In conclusion, the results of this study indicate that the BNT162b2 mRNA COVID-19 vaccine is highly effective in pregnant women for the variants circulating in Israel at the time of the study, with vaccine effectiveness that was comparable to that estimated in the general population[14]. Further studies are needed to better characterize the dynamics of vaccine effectiveness throughout pregnancy, the relationship between vaccination timing and infant protection after birth and pregnancy- and non-pregnancy-related safety outcomes.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01490-8.

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Methods

Ethics. This study was approved by the CHS community institutional review board.

Data source. CHS is an integrated healthcare payer-provider organization that serves 52% of the Israeli population. Medical insurance in Israel is mandatory for all residents, and covers a wide range of services, including prenatal care. The CHS population is fairly representative of the general Israeli population[17]. The present study was based on CHS data covering patients vaccinated from the start of the vaccination campaign in Israel on 20 December 2020 through to 3 June 2021. CHS data systems contain medical and claims data covering all facets of patient care, including primary care, specialist care, imaging, laboratory diagnostics 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'. Pregnancies are recorded in these dedicated systems from the moment a woman begins prenatal care, which is freely and universally available in Israel. These data are integrated daily with data collected centrally by the Israeli Ministry of Health regarding COVID-19 vaccines, SARS-CoV-2 tests and 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 in pregnant women. We used a similar methodology to previous studies on vaccine effectiveness using the same database[14]. Eligibility criteria considered at the start of follow-up were pregnancy (as recorded in the CHS data systems), age of 16 years or older, continuous membership in CHS for 1 complete year, no previous positive SARS-CoV-2 PCR test, no previous 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 d (since this may signal a preexisting SARS-CoV-2 infection). Individuals with missing data (only relevant for the body mass index 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 at least 1 Centers for Disease Control and Prevention risk factor for severe COVID-19 (ref. [18]). Definitions for all variables used in the study are included in Supplementary Table 4.

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 as an infection accompanied by the documentation of COVID-19 symptoms in dedicated fields in the outpatient health record (or an infection that warranted hospitalization); COVID-19-related hospitalization; severe COVID-19, as defined by the Israeli Ministry of Health using international criteria[19]; 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. After matching, we used the Kaplan–Meier estimator to construct cumulative incidence curves. We estimated vaccine effectiveness at different periods after 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 before the beginning of that period. We then calculated the risk ratio (RR) and risk difference (RD) during that period, with vaccine effectiveness defined as $1-\mathrm{RR}$. To estimate the analog of a per-protocol effect, we censored both members of the matched pair when the control received a vaccination but then allowed the control to be re-recruited as a vaccinated individual if a matched control was found. 95% CIs were estimated using the nonparametric percentile bootstrap method with 1,000 repetitions. Analysis was performed using R v.4.0.4.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Due to national and organizational data privacy regulations, individual-level data such as those used for this study cannot be shared openly.

Code availability

The modeling in this paper used R v.4.0.4 and the tidyverse v.1.3.0, survival v.3.2-7, survminer v.0.4.7 and boot v.1.3-27 R packages, all of which are freely available.

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Author contributions

S.H.D., B.Y.R. and R.D.B. contributed equally as senior authors to this study. N.D., N.B., T.B.S., C.K., S.H.D., B.Y.R. and R.D.B. conceived and designed the study. N.D., N.B. and M.M.A. participated in data extraction and analysis. N.D., N.B., I.S.K., M.A.H., M.L., S.H.D., B.Y.R. and R.D.B. wrote the manuscript. T.B.S. and S.H.D. provided clinical guidance. All authors critically reviewed the manuscript and decided to proceed with publication. B.Y.R. and R.D.B. supervised the study. R.D.B. vouches for the data and analysis.

Competing interests

N.D., N.B., M.M.A. and R.D.B. report institutional grants to the Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. M.L. reports grants from Pfizer, personal fees from Merck, Bristol Meyers Squibb, Sanofi Pasteur and Janssen, grants from the National Institutes of Health (NIH), the National Institute for Health Research, Centers for Disease Control and Prevention, Open Philanthropy Project, Wellcome Trust and Pfizer outside the submitted work; he has provided unpaid advice on COVID vaccines or vaccine studies to 1Day Sooner (nonprofit), Pfizer, AstraZeneca, Janssen and COVAXX (United Biosciences). M.A.H. reports grants from the NIH and Veterans Affairs, and personal fees from Cytel and ProPublica. S.H.D. reports consulting fees from Roche and UCB outside the submitted work. B.Y.R. reports grants from the NIH outside the submitted work. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-021-01490-8.

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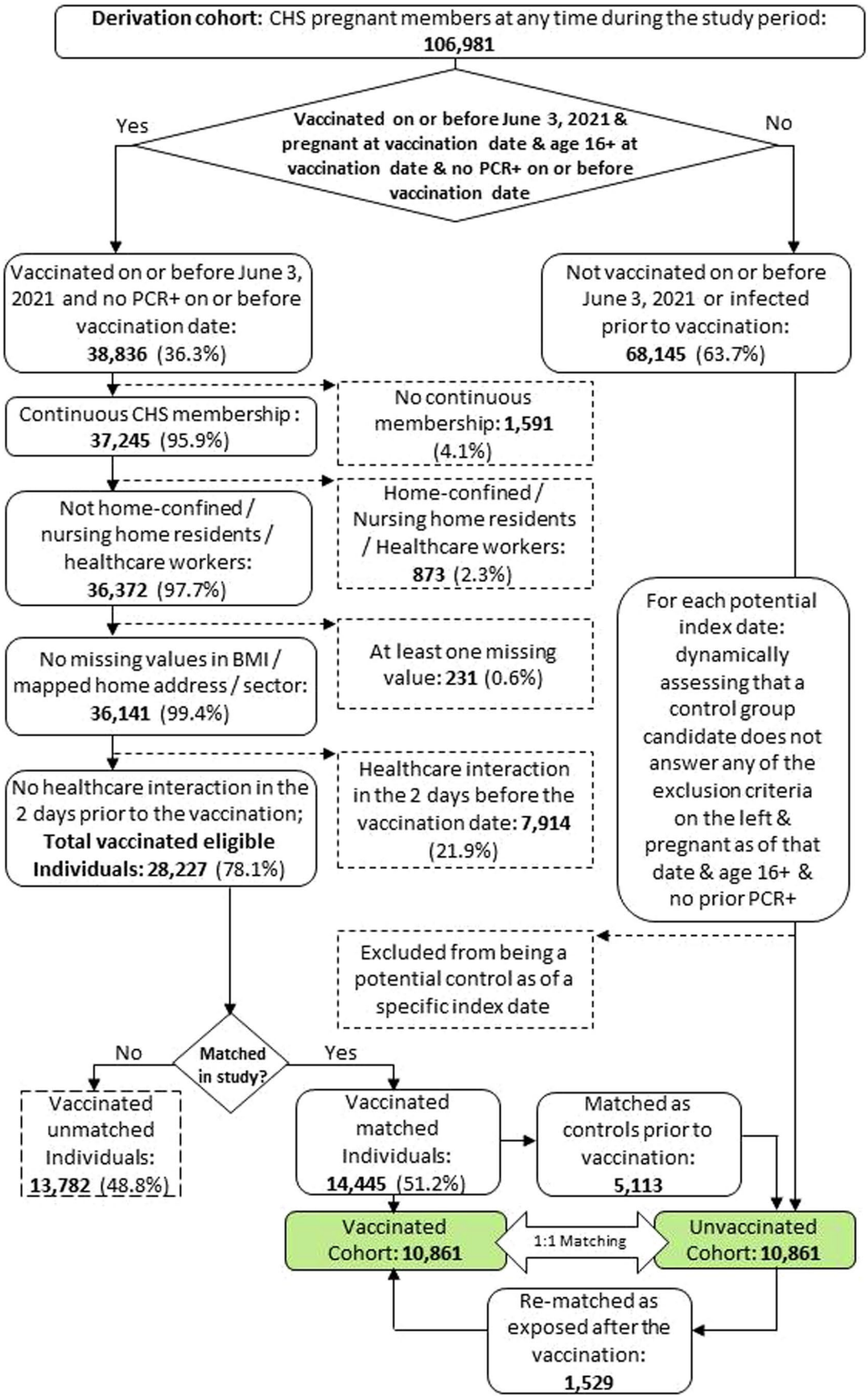
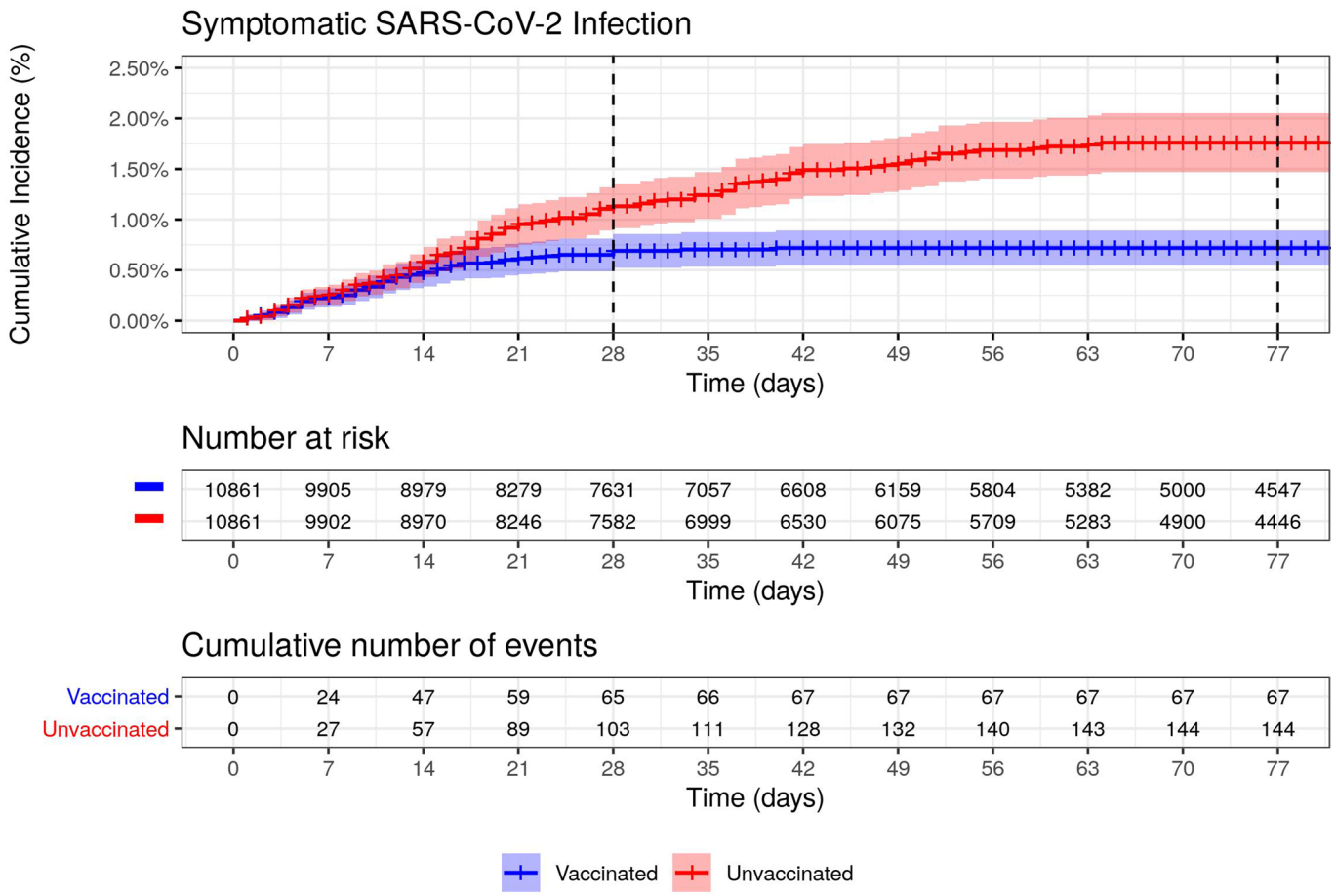
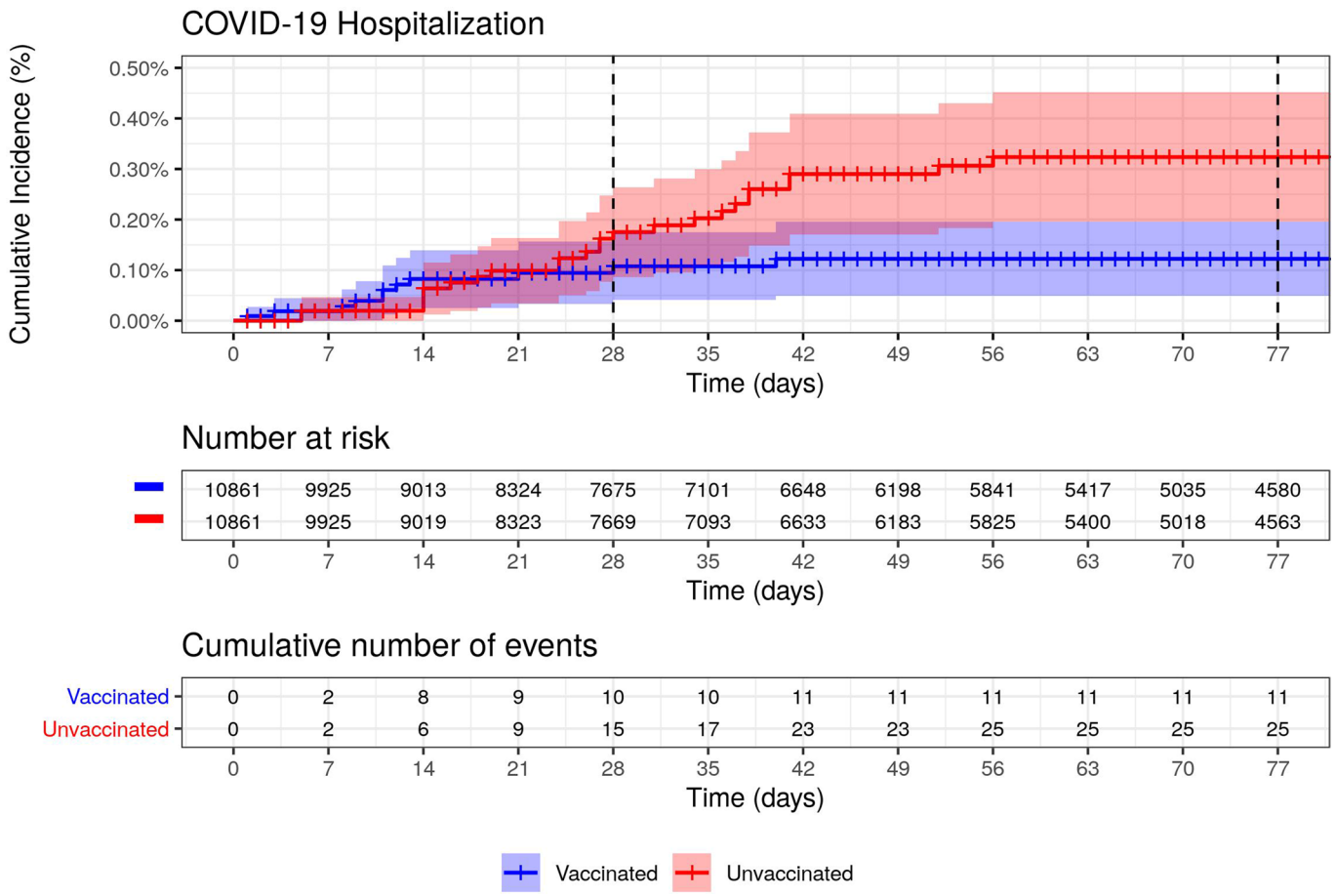


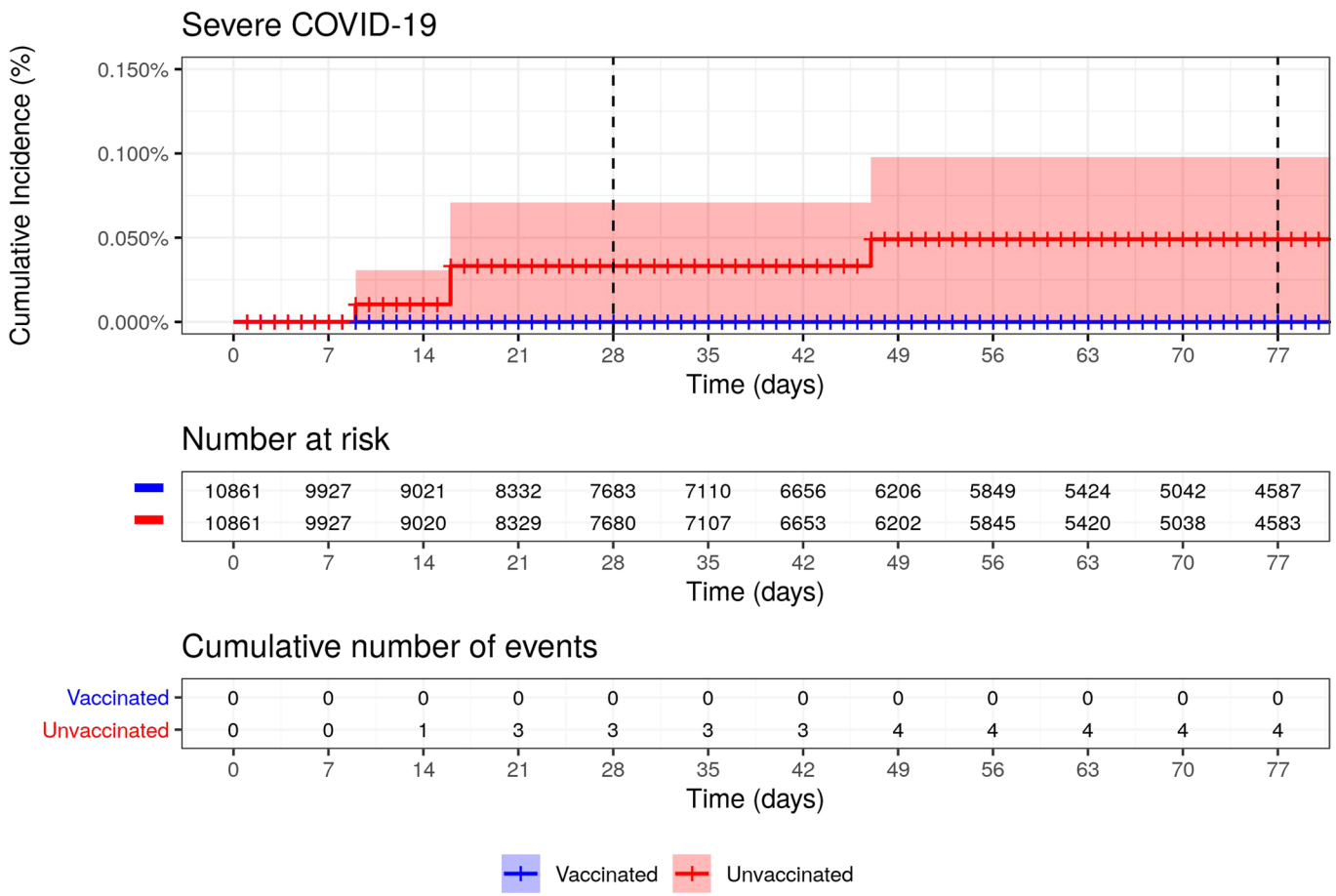
Extended Data Fig. 1 | Population flow chart. Size and percentage change of study population resulting from each inclusion and exclusion criteria. The figure focuses on the vaccinated population.



Extended Data Fig. 2 | Cumulative incidence of SARS-CoV-2 symptomatic infection in vaccinated pregnant women and matched controls. Cumulative incidence curves of the SARS-CoV-2 symptomatic infection outcome in pregnant women, Clalit Health Services, December 20, 2020 through June 3, 2021. The main line is the point estimate of the cumulative incidence and the 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 56 days after receipt of the second dose). The table below the curve presents 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.



Extended Data Fig. 3 | Cumulative incidence of COVID-19 hospitalization in vaccinated pregnant women and matched controls. Cumulative incidence curves of the COVID-19 hospitalization outcome in pregnant women, Clalit Health Services, December 20, 2020 through June 3, 2021. The main line is the point estimate of the cumulative incidence and the 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 56 days after receipt of the second dose). The table below the curve presents 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.



Extended Data Fig. 4 | Cumulative incidence of severe COVID-19 in vaccinated pregnant women and matched controls. Cumulative incidence curves of the severe COVID-19 outcome in pregnant women, Clalit Health Services, December 20, 2020 through June 3, 2021. The main line is the point estimate of the cumulative incidence and the 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 56 days after receipt of the second dose). The table below the curve presents 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.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

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- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Due to national and organizational data privacy regulations, individual-level data such as those used for this study cannot be openly shared.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is a retrospective cohort analysis, based on existing medical records. Methods are strictly quantitative.
Research sample	The population of this study is the patient population of a large integrated healthcare provider operating in Israel. Women who were pregnant during the study period (December 20, 2020 through June 3, 2021) were included. The age median (IQR) was 30 (26-33). This is the full population of the health organization, and is considered representative of the Israeli population as a whole.
Sampling strategy	Due to the retrospective nature of this study all qualified members were included and no sample-size calculation was done.
Data collection	All data used in this study is based on existing electronic medical records. No dedicated data collection was performed. Access to the data was performed through Microsoft SQL Server. The researcher was not blinded to the experimental hypothesis.
Timing	Individuals who were pregnant from December 20, 2020 until June 3, 2021 were eligible. Background variables were extracted from the period prior to inclusion in the study.
Data exclusions	As detailed in Figure S1, individuals were excluded if they were not continuous members, if they were home-confined due to medical reasons, if they were nursing home residents, if they were healthcare workers, if they had missing data for BMI, population sector or home address, if they had a healthcare interaction in the 2 days prior to start of follow-up. Of eligible individuals, only those that successfully matched were included in the final study cohort. Eligibility criteria were pre-established.
Non-participation	As detailed in Figure S1, the original cohort (pregnant, age 16+, no prior SARS-CoV-2 diagnosis) numbered 38,836. Of these, 28,227 were eligible. Of these, 14,445 matched into the study cohort.
Randomization	This is an observational study, no randomization was performed.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	See above
Recruitment	Participants were not recruited but rather selected from a retrospective Clalit medical database. All eligible participants were considered.
Ethics oversight	This study was approved by the Clalit research ethics committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.