

Target trial emulation of effectiveness of COVID-19 mRNA vaccination during pregnancy in four European countries

Received: 13 October 2025

Accepted: 19 September 2026

Published online: 16 October 2026

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Evidence on real-world effectiveness of COVID-19 vaccination during pregnancy remains limited. Using health data from the UK, Sweden, Spain, and Norway, we emulated two target trials to estimate vaccine effectiveness (VE) of mRNA COVID-19 vaccines administered during pregnancy against COVID-19 infection, hospitalisation, and admission to an Intensive Care Unit (ICU). The first trial compares initiation of a primary (two-dose) vaccination with unvaccinated, and the second compares the receipt of a first booster (third dose) with unboosted after primary vaccination. Pregnant women receiving a first or booster vaccination were matched weekly to comparable unexposed pregnant women. A total of 62,061 and 41,096 pregnant women were included in the first and second trial, respectively. Meta-analysis across the four databases showed a VE for primary vaccination of 26.2% (95% CI 16.2–35.1) against infection and 55.6% (95% CI 44.1–64.8) against hospitalisation. For boosters, the VE was 33.6% (95% CI 1.6 to 56.6) against infection and 34.1% (95% CI 0.6–56.4) against hospitalisation. ICU admission outcomes were too rare to analyse. In this work, we show that primary and first-booster mRNA vaccination during pregnancy is associated to a lower risk of COVID-19-related hospitalisation, while protection against infection is more modest and heterogeneous across databases.

Pregnancy is associated with an increased risk of severe complications from coronavirus disease 2019 (COVID-19). Pregnant women with COVID-19 are at increased risk of admission to intensive care units (ICU), receiving invasive ventilation, and experiencing severe pregnancy complications, including preeclampsia, preterm birth, and stillbirth^{1,2}. In light of these risks, pregnant women were included in

vaccination campaigns before clinical trials on this population were completed. The lack of pregnancy-specific evidence when the COVID-19 vaccination campaigns started led to variation in recommendations on vaccination during pregnancy over time and across countries. During this period, vaccine uptake among pregnant women was low³.

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Current evidence suggests that COVID-19 vaccines administered during pregnancy are safe^{4–9} and have similar effectiveness to that observed in the general population^{7,10}. However, existing observational studies on COVID-19 vaccine effectiveness (VE) during pregnancy have primarily focused on BNT162b2 (Pfizer-BioNTech)^{11,12}, and have largely been single-database studies with short follow-up and limited representativeness. More research on VE during pregnancy is needed to help inform public health policy, particularly in light of divergent recommendations. At the time of writing, the World Health Organisation (WHO) continues to recommend a single-dose vaccination during pregnancy regardless of previous vaccination status¹³, while some countries, including the United Kingdom (UK), have discontinued booster dose recommendations for this population as it was considered unlikely to be cost-effective¹⁴.

In this study, we leveraged data from four European countries to estimate the effectiveness of the BNT162b2 and mRNA-1273 (Moderna) vaccines as primary (two-dose) and first booster (third dose) vaccination during pregnancy in preventing COVID-19 infection, COVID-19-related hospitalisation, and COVID-19-related ICU admission.

Results

Individuals were identified from four databases: the Norwegian Linked Health Registries (NLHR; Norway), the Information System for Research in Primary Care database (SIDAP; Spain), the Swedish Covid-19 Investigation for Future Insights—a Population Epidemiology Approach using Register Linkage (SCIFI-PEARL; Sweden), and Clinical Practice Research Datalink (CPRD) GOLD (UK). We identified 305,415 pregnant women who met the eligibility criteria for the first trial

(primary [two-dose] vaccination compared to unvaccinated) and 198,269 for the second trial (first booster [third dose] compared to primary [two-dose] vaccination). For the first trial, 62,061 vaccinated pregnant women (CPRD GOLD: 2741; SCIFI-PEARL: 36,398; SIDAP: 7479; NLHR: 15,443) were matched 1:1 to unexposed pregnant women (Fig. 1 and Supplementary Figs. 2–4). For the second trial, 41,096 pregnant women vaccinated with a third dose (CPRD GOLD: 1892; SCIFI-PEARL: 26,195; SIDAP: 2218; NLHR: 10,791) were matched 1:1 to unexposed pregnant women eligible to receive a third dose at the time of matching (Fig. 1 and Supplementary Figs. 2–4). Across analyses, 7–18% of enrolled controls were later re-enrolled as exposed (Supplementary Table 2).

Standardised Mean Differences (SMDs) were suggestive of covariate balance between exposed and unexposed participants for both trials. The median age of participants was 31–34 years old, with most women vaccinated during the first and second trimester (Tables 1 and 2). Over 80% of women received a first dose of BNT162b2 across all databases, except for NLHR (66%). BNT162b2 was administered for 80% of women receiving a first booster (third dose), except for CPRD GOLD (64.7%) and SIDAP (30.3%). Extended tables characterising populations at baseline can be found in Supplementary Tables 3–10. SMDs can be explored in the interactive web App (<https://dpa-pde-oxford.shinyapps.io/COVID19VaccineEffectivenessDuringPregnancy/>).

Median follow-up across databases ranged from 42 [25–75th percentiles: 33–81] to 55 [39–120] days for the first trial and from 73 [18–172] to 116 [58–178] days for the second trial. The most common reason for censoring in the first trial was receiving a second dose more

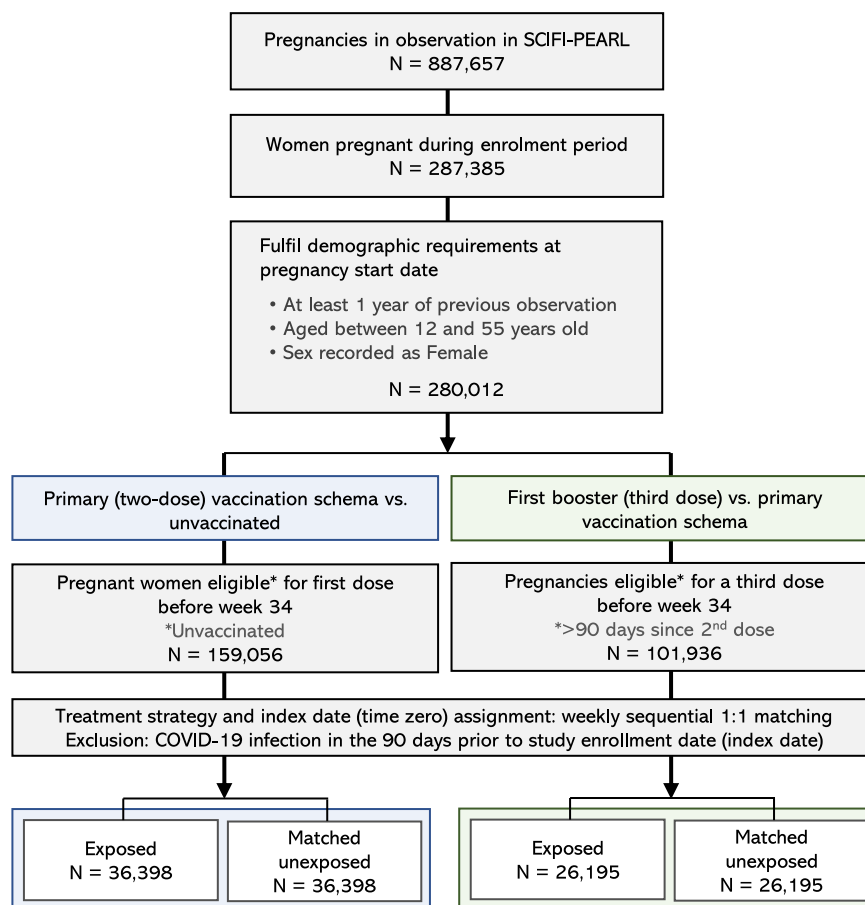


Fig. 1 | Study population and flow chart for SCIFI-PEARL. Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden (SCIFI-PEARL) is the Swedish database. Flow chart

diagrams for the other databases in the study can be found in the Supplementary Information.

Table 1 | Baseline characteristics of matched pregnant women included for the analysis of vaccine effectiveness of primary (two-dose) vaccination vs. no vaccination

Variable name	CPRD GOLD		SCIFI-PEARL		SIDIAP		NLHR	
	Exposed	Matched unexposed	Exposed	Matched unexposed	Exposed	Matched unexposed	Exposed	Matched unexposed
Pregnancies, N	2741	2741	36,398	36,398	7479	7479	15,443	15,443
Age, median [Q25 - Q75]	32 [28–35]	32 [28–35]	31 [28–35]	31 [28–35]	32 [28–36]	32 [28–36]	31 [28–34]	31 [28–34]
Health visits*, median [Q25 - Q75]	24 [14–42]	20 [11–38]	8 [2–22]	4 [1–14]	32 [16–52]	20 [10–36]	30 [16–48]	20 [11–34]
First-dose vaccine brand, N (%)								
BNT162b2 (Pfizer)	2461 (89.8%)	—	29,050 (79.8%)	—	5983 (80.0%)	—	10,195 (66.0%)	—
mRNA-1273 (Moderna)	280 (10.2%)	—	7348 (20.2%)	—	1496 (20.0%)	—	5248 (34.0%)	—
Trimester at index date, N (%)								
Trimester 1	1107 (40.4%)	1107 (40.4%)	9441 (25.9%)	9441 (25.9%)	2183 (29.2%)	2183 (29.2%)	5201 (33.7%)	5201 (33.7%)
Trimester 2	954 (34.8%)	954 (34.8%)	18,782 (51.6%)	18,782 (51.6%)	3351 (44.8%)	3351 (44.8%)	6421 (41.6%)	6421 (41.6%)
Trimester 3	680 (24.8%)	680 (24.8%)	8175 (22.5%)	8175 (22.5%)	1945 (26.0%)	1945 (26.0%)	3821 (24.7%)	3821 (24.7%)
Conditions**, N (%)								
Asthma	212 (7.7%)	173 (6.3%)	1778 (4.9%)	1502 (4.1%)	455 (6.1%)	370 (4.9%)	2207 (14.3%)	2004 (13.0%)
Chronic hypertension	30 (1.1%)	28 (1.0%)	1267 (3.5%)	995 (2.7%)	178 (2.4%)	155 (2.1%)	1122 (7.3%)	1049 (6.8%)
COPD	0 (0.0%)	0 (0.0%)	13 (0.0%)	6 (0.0%)	8 (0.1%)	6 (0.1%)	75 (0.5%)	74 (0.5%)
Diabetes	110 (4.0%)	94 (3.4%)	1017 (2.8%)	983 (2.7%)	445 (5.9%)	405 (5.4%)	823 (5.3%)	826 (5.3%)
Obesity	287 (10.5%)	254 (9.3%)	2691 (7.4%)	2671 (7.3%)	1279 (17.1%)	1166 (15.6%)	1085 (7.0%)	1008 (6.5%)
Solid cancer	5 (0.2%)	<5 (<5%)	209 (0.6%)	161 (0.4%)	30 (0.4%)	17 (0.2%)	134 (0.9%)	109 (0.7%)
Blood cancer	0 (0.0%)	0 (0.0%)	44 (0.1%)	27 (0.1%)	<5 (<5%)	<5 (<5%)	10 (0.1%)	10 (0.1%)
Immunodeficiency	0 (0.0%)	<5 (<5%)	26 (0.1%)	27 (0.1%)	15 (0.2%)	8 (0.1%)	60 (0.4%)	45 (0.3%)
Prior vaccinations*, N (%)								
Tdap	1562 (57.0%)	1439 (52.5%)	—	—	3329 (44.5%)	3366 (45.0%)	90 (0.6%)	97 (0.6%)
Influenza	964 (35.2%)	830 (30.3%)	—	—	2107 (28.2%)	1752 (23.4%)	4307 (27.9%)	3154 (20.4%)

COPD Chronic Obstructive Lung Disease; CPRD Clinical Practice Research Datalink, UK SCIFI-PEARL: Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden; SIDIAP Information System for Research in Primary Care, Spain; Tdap Tetanus, Diphtheria and Pertussis; NLHR Norwegian Linked Health Registries, Norway.

* “Exposed” refers to pregnant women who have received the first dose, while “unexposed” refers to unvaccinated pregnant women. Weekly sequential matching identified 1:1 matched pairs. The index date for each matched pair was defined as the date of the first-dose vaccination.

* Assessed in the year prior. Data on Tdap and influenza vaccines were not available in SCIFI-PEARL.

** Assessed any time before the index date, except for solid and blood cancers, which were assessed in the 5 years before the index date.

than 6 weeks after the first dose (deviating from the treatment strategy assigned at baseline) in CPRD GOLD (70%) and SCIFI-PEARL (35%). Vaccination of the unexposed person during follow-up was also a common reason for censoring, affecting 30–36% of pregnancies in SCIFI-PEARL, SIDIAP, and NLHR. The main reasons for censoring in the second trial across databases were pregnancy end (54–78%) and the unexposed person receiving a booster during follow-up (20–45%). Supplementary Tables 11–18 give more details on censoring.

Supplementary Fig. 5 shows the number of matches over calendar time. A peak in first-dose uptake was observed between May and September 2021, just before the Delta variant became dominant (August to early December 2021). First booster (third dose) uptake peaked between December 2021 and February 2022 across all databases, coinciding with the Omicron variant. Overall, uptake in the UK was approximately one month earlier than in the other contributing countries.

For the first trial, the VE of primary (two-dose) vaccination against infection (i.e., defined as a positive test result or clinical diagnosis) compared to no vaccination was estimated at 68.5% (95% confidence interval [CI] 42.3–82.7) in CPRD GOLD, 25.0% (18.5–30.9) in SCIFI-

PEARL, 17.4% (7.8–25.9) in SIDIAP, and 27.7% (19.3–35.2) in NLHR. VE against hospitalisation (i.e., defined as a hospital admission with a COVID-19 record within –21 to +3 days of admission) was estimated at 53.6% (35.7–66.5) in SCIFI-PEARL, 57.5% (27.2–75.1) in SIDIAP, and 57.7% (35.8–72.1) in NLHR. Meta-analysis showed that VE for primary vaccination was 26.2% (16.2–35.1; $P=0.7$) against COVID-19 infection and 55.6% (44.1–64.8; $P=0$) against COVID-19-related hospitalisation (Fig. 2).

For the second trial, VE of a first booster (third dose) compared to primary (two-dose) vaccination against COVID-19 was estimated at 32.9% (11.2–49.2) in CPRD GOLD, 21.1% (8.6–31.8) in SIDIAP, 13.3% (4.8–21.1) in SCIFI-PEARL, and 57.5% (54.2–60.6) in NLHR. VE against hospitalisation was 52.4% (27.4–68.7) in SCIFI-PEARL and 32.8% (3.7–53.1) in NLHR. VE against hospitalisation in SIDIAP had a wide CI (–18.0% [–155.2–45.4]), as only 12 unexposed and 14 exposed events were captured. Meta-analysis showed that VE for a first booster was 33.6% (–1.6–56.6; $P=1$) against COVID-19 infection and 34.1% (0.6–56.4; $P=0.5$) against COVID-19-related hospitalisation (Fig. 3).

We could not evaluate VE against ICU admission in either of the trials, due to insufficient events. No significant differences in VE against

Table 2 | Baseline characteristics of matched pregnant women included for the analysis of vaccine effectiveness of booster (third dose) vs. primary (two-dose) vaccination

Variable name	CPRD GOLD		SCIFI-PEARL		SIDIAF		NLHR	
	Exposed	Matched unexposed	Exposed	Matched unexposed	Exposed	Matched unexposed	Exposed	Matched unexposed
Pregnancies, N	1892	1892	26,195	26,195	2218	2218	10,791	10,791
Age, median [Q25 - Q75]	32 [29–35]	32 [29–35]	31 [29–34]	31 [29–34]	34 [31–37]	34 [31–37]	31 [28–34]	31 [28–34]
Health visits*, median [Q25 - Q75]	30 [18–46]	28 [16–44]	6 [0 - 20]	4 [0–15]	30 [16–52]	26 [14–46]	26 [16–44]	24 [12–40]
Vaccine brand, N (%)								
BNT162b2 (Pfizer)	1224 (64.7%)	—	21,187 (80.9%)	—	673 (30.3%)	—	8771 (81.3%)	—
mRNA-1273 (Moderna)	668 (35.3%)	—	5008 (19.1%)	—	1545 (69.7%)	—	2020 (18.7%)	—
Trimester at index date, N (%)								
Trimester 1	894 (47.3%)	894 (47.3%)	5558 (21.2%)	5558 (21.2%)	719 (32.4%)	719 (32.4%)	3372 (31.2%)	3372 (31.2%)
Trimester 2	712 (37.6%)	712 (37.6%)	15,411 (58.8%)	15,411 (58.8%)	1018 (45.9%)	1018 (45.9%)	6200 (57.5%)	6200 (57.5%)
Trimester 3	286 (15.1%)	286 (15.1%)	5226 (20.0%)	5226 (20.0%)	481 (21.7%)	481 (21.7%)	1219 (11.3%)	1219 (11.3%)
Conditions**, N (%)								
Asthma	145 (7.7%)	131 (6.9%)	1310 (5.0%)	1081 (4.1%)	145 (6.5%)	133 (6.0%)	1700 (15.8%)	1589 (14.7%)
Chronic hypertension	25 (1.3%)	30 (1.6%)	870 (3.3%)	895 (3.4%)	53 (2.4%)	35 (1.6%)	816 (7.6%)	806 (7.5%)
COPD	0 (0.0%)	0 (0.0%)	9 (0.0%)	6 (0.0%)	<5 (<5%)	<5 (<5%)	76 (0.7%)	67 (0.6%)
Diabetes	70 (3.7%)	61 (3.2%)	627 (2.4%)	596 (2.3%)	111 (5.0%)	91 (4.1%)	519 (4.8%)	536 (5.0%)
Obesity	236 (12.5%)	228 (12.1%)	1598 (6.1%)	1541 (5.9%)	345 (15.6%)	289 (13.0%)	861 (8.0%)	836 (7.7%)
Solid cancer	<5 (<5%)	<5 (<5%)	182 (0.7%)	105 (0.4%)	10 (0.5%)	<5 (<5%)	106 (1.0%)	80 (0.7%)
Blood cancer	0 (0.0%)	0 (0.0%)	15 (0.1%)	6 (0.0%)	0 (0.0%)	0 (0.0%)	19 (0.2%)	7 (0.1%)
Immunodeficiency	0 (0.0%)	<5 (<5%)	24 (0.1%)	16 (0.1%)	<5 (<5%)	<5 (<5%)	44 (0.4%)	25 (0.2%)
Prior vaccinations*, N (%)								
Tdap	995 (52.6%)	1000 (52.9%)	—	—	887 (40.0%)	934 (42.1%)	6534 (60.6%)	84 (0.8%)
Influenza	665 (35.1%)	655 (34.6%)	—	—	1228 (55.4%)	1063 (47.9%)	69 (0.6%)	5481 (50.8%)

COPD Chronic Obstructive Lung Disease; CPRD Clinical Practice Research Datalink, UK SCIFI-PEARL: Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden; SIDIAF Information System for Research in Primary Care, Spain; Tdap Tetanus, Diphtheria and Pertussis; NLHR Norwegian Linked Health Registries, Norway.

*Exposed refers to pregnant women who have received a first booster (third dose). “Unexposed” refers to pregnant women who had received the second dose at least 3 months prior. Weekly sequential matching identified 1:1 matched pairs. The index date for the matched pair was defined as the date of the third-dose vaccination.

* Assessed in the year prior. Data on Tdap and influenza vaccines were not available in SCIFI-PEARL.

** Assessed any time before the index date, except for solid and blood cancers, which were assessed in the 5 years before the index date.

COVID-19 infection or hospitalisation were observed across trimesters except for CPRD GOLD (Fig. 4). Results stratified by vaccine brand showed similar estimates (Supplementary Fig. 6). Kaplan-Meier curves and log-log survival curves suggested waning effectiveness over time (Supplementary Figs. 7–10). Supplementary Fig. 11 shows Hazard Ratios (HRs) in different time windows.

Negative control outcomes (NCOs) with sufficient counts for assessment ranged between 27 and 39 NCOs across databases, except for CPRD GOLD (16–17 NCOs). Among those with sufficient counts, <15% of NCOs were associated with vaccination (Supplementary Figs. 12–15). Findings from secondary analyses extending follow-up to the end of data availability, rather than to the end of pregnancy, were consistent with the main analysis (Supplementary Figs. 16–19).

In sensitivity analyses, VE against COVID-19-related hospitalisation was reduced when including hospital admissions related to delivery, decreasing from 55.6% (44.1–64.8; $P = 0.6$) to 28.2% (20.9–34.8; $P = 0.1$) for the first trial, and 34.1% (0.6–56.4; $P = 0.3$) to 19.5% (4.2–32.4; $P = 0.3$) for the second trial (Supplementary Fig. 20). When restricting the definition of infection to only positive test results, VE against COVID-19 was similar to that obtained in the main analysis. However,

some estimates for VE for the first booster were altered, especially in NLHR, where the VE estimate against infection increased from 57.5% (54.2–60.1) to 78.3% (75.8–80.5) (Supplementary Figs. 21 and 22).

Discussion

The findings of this multinational study of over 124,122 pregnancies suggest that primary (two-dose) vaccination against COVID-19 during pregnancy lowers the risk of infection during pregnancy with a VE of 26%, and a VE against COVID-19-related hospitalisation of 55%. A first booster (third dose) vaccination during pregnancy provided 33–34% greater protection against COVID-19 infection and COVID-19-related hospitalisation than an unboosted primary (two-dose) vaccination. We could not evaluate VE against ICU admission due to the rarity of this outcome in the study.

We found lower VE levels against both infection and hospitalisation than previously published literature. These discrepancies may be attributable to different study periods, length of follow-up, settings, and design choices. Prior pregnancy-specific literature was mostly based on Israeli health data, reporting short-term estimates for the BNT162b2 vaccines. Dagan et al. estimated a VE for BNT162b2 of 96%

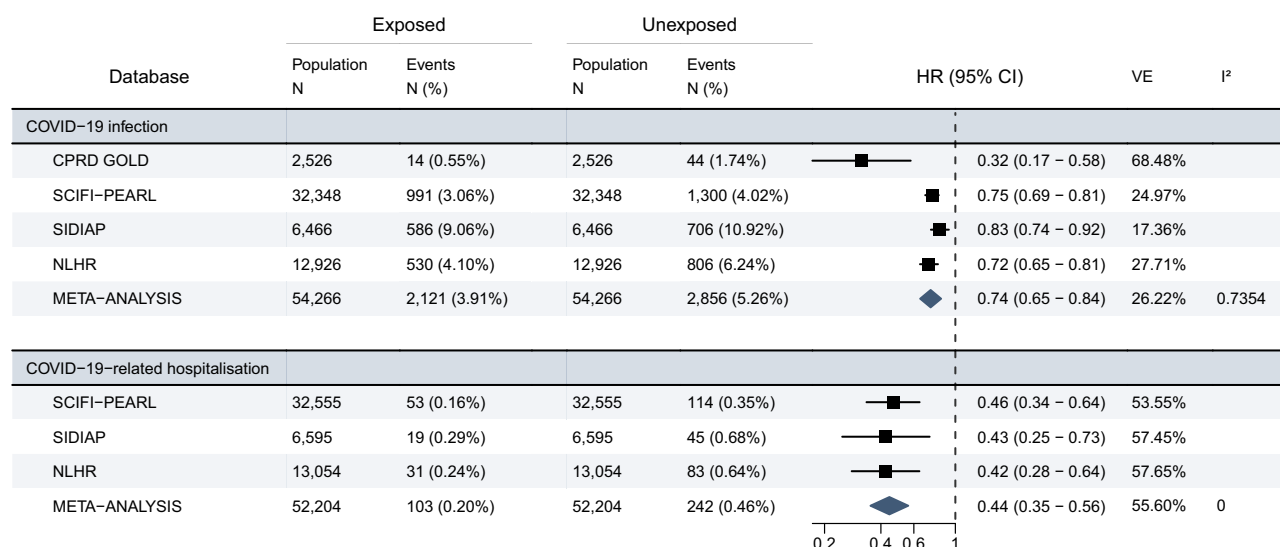


Fig. 2 | Vaccine effectiveness estimates: primary (two-dose) vaccination vs. unvaccinated. Vaccine effectiveness (VE) was assessed from 15 days after vaccination (first dose); individuals censored before day 15 were not included. Database-specific estimates are presented as hazard ratios (HRs), with black squares representing the HR point estimate and horizontal lines representing the corresponding 95% confidence interval (CI). Overall estimates were derived using random-effects meta-analysis; blue diamonds represent the pooled HR point estimate and corresponding 95% CI. I^2 quantifies the proportion of variability in effect estimates

attributable to heterogeneity across databases rather than sampling variability. Source data are provided as a Source Data file. CI Confidence Interval; CPRD Clinical Practice Research Datalink, UK; HR Hazard Ratio; SCIFI-PEARL Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden; SIDIAP Information System for Research in Primary Care, Spain; NLHR the Norwegian Linked Health Registries, Norway; VE Vaccine Effectiveness.

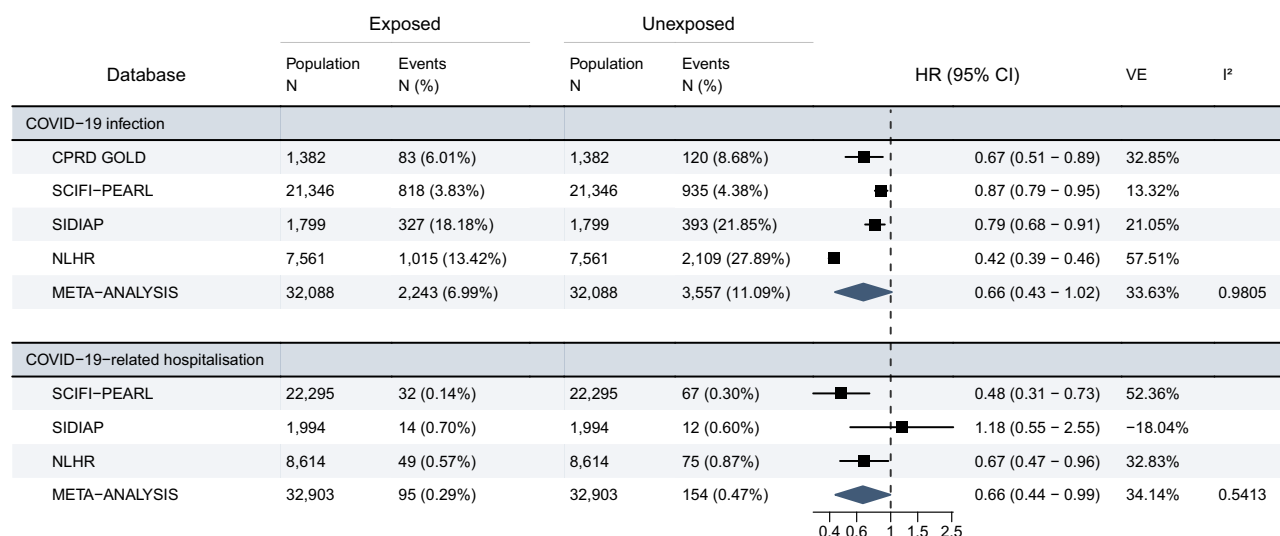


Fig. 3 | Vaccine effectiveness estimates: first booster (third dose) vs. primary (two-dose) vaccination. Vaccine effectiveness (VE) was assessed from 15 days after vaccination (third dose); individuals censored before day 15 were not included. Database-specific estimates are presented as hazard ratios (HRs), with black squares representing the HR point estimate and horizontal lines representing the corresponding 95% confidence interval (CI). Overall estimates were derived using random-effects meta-analysis; blue diamonds represent the pooled HR point estimate and corresponding 95% CI. I^2 quantifies the proportion of variability in effect

estimates attributable to heterogeneity across databases rather than sampling variability. Source data are provided as a Source Data file. CI Confidence Interval; CPRD Clinical Practice Research Datalink, UK; HR Hazard Ratio; SCIFI-PEARL Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden; SIDIAP Information System for Research in Primary Care, Spain; NLHR the Norwegian Linked Health Registries, Norway; VE Vaccine Effectiveness.

(95%CI: 89–100%) against infection and 89% (43–100%) against COVID-19-related hospitalisation in days 7–56 after second-dose vaccination during the original SARS-CoV-2 reference strain and the B.1.1.7 (Alpha) variant¹¹. The main circulating variants during our study were Delta and Omicron, with the latter known to more efficiently evade vaccine-induced immunity against infection^{10,12,15}. Guedalia et al. estimated the

effectiveness of a third BNT162b2 vaccine given during pregnancy at least 5 months after the second dose, compared to non-booster pregnant women. They reported a VE against hospitalisation of 92% (83–96%) during the Delta-dominated period, declining to 48% (37–57%) during Omicron circulation¹², which is still higher than our meta-analytic estimate of 34.1% ([0.6–56.4]; $I^2 = 0.5$). Zidan et al.¹⁶.

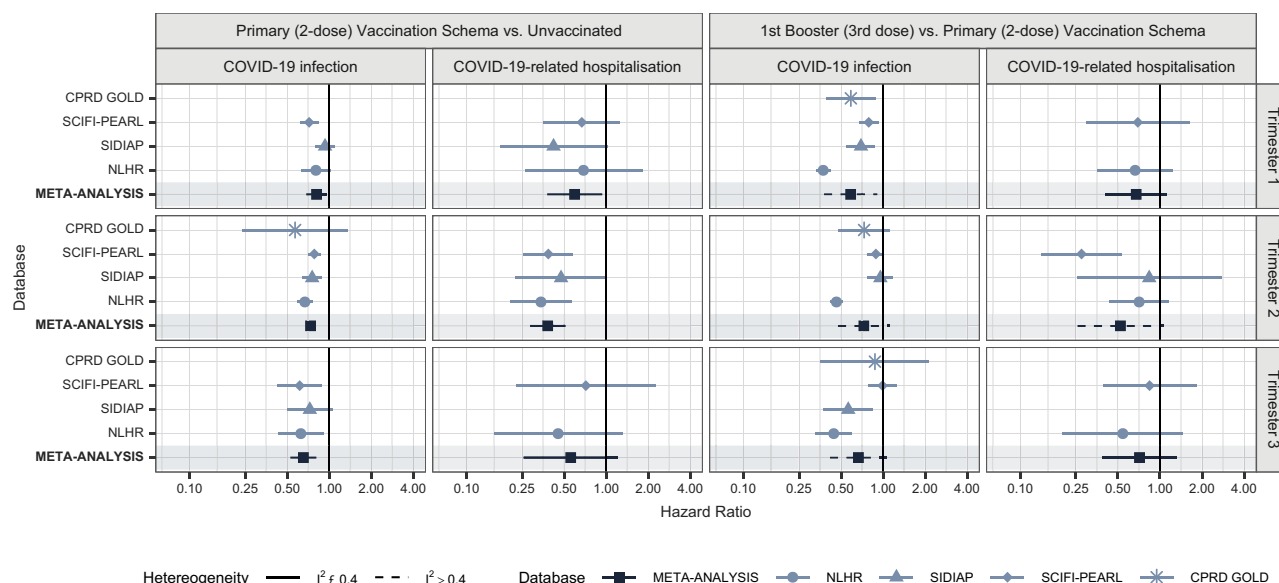


Fig. 4 | Hazard ratios for COVID-19 infection and hospitalisation stratified by pregnancy trimester at time of vaccination: primary (two-dose) vaccination schema vs. unvaccinated, and booster (third dose) vs. primary (two-dose) vaccination schema. Hazard ratios (HRs) are presented for primary (two-dose) vaccination versus no vaccination and first booster (third dose) versus primary (two-dose) vaccination, stratified by pregnancy trimester at the time of vaccination. For primary vaccination versus no vaccination, the numbers of exposed pregnant women were 8150 in SCIFI-PEARL, 4270 in NLHR, 1909 in SIDIAP, and 994 in CPRD GOLD, in the first trimester; 16,777 in SCIFI-PEARL, 5424 in NLHR, 2898 in SIDIAP, and 899 in CPRD GOLD in the second trimester; and 7421 in SCIFI-PEARL, 3232 in NLHR, 1659 in SIDIAP, and 633 in CPRD GOLD in the third trimester, respectively. For first booster versus primary vaccination, the numbers of exposed were 4673 in SCIFI-PEARL, 2413 in NLHR, 588 in SIDIAP, and 641 in CPRD GOLD in the first trimester; 12,487 in SCIFI-PEARL, 4235 in NLHR, 823 in SIDIAP, and 536 in CPRD GOLD in the second trimester; and 4186 in SCIFI-PEARL, 913 in NLHR, 388 in SIDIAP,

and 205 in CPRD GOLD in the third trimester, respectively. HRs were assessed from 15 days after vaccination; individuals censored before day 15 were not included. Points represent HR point estimates, and horizontal lines represent the corresponding 95% confidence intervals (CIs). Overall estimates were derived using random-effects meta-analysis. Blue symbols represent database-specific estimates (diamond, SCIFI-PEARL; asterisk, CPRD GOLD; triangle, SIDIAP; circle, NLHR), while dark blue squares represent the pooled meta-analytic estimates. Meta-analytic estimates are shown with a solid line when $I^2 < 0.4$ and a dashed line when $I^2 \geq 0.4$. I^2 quantifies the proportion of variability in effect estimates attributable to heterogeneity across databases rather than sampling variability. Event counts below five were masked to preserve privacy. Source data are provided as a Source data file. CPRD Clinical Practice Research Datalink, UK; HR Hazard Ratio; SCIFI-PEARL Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage, Sweden; SIDIAP Information System for Research in Primary Care, Spain; NLHR the Norwegian Linked Health Registries, Norway.

recently emulated the BNT162b2 trial (NCT04754594) using Norwegian data, comparing pregnancies vaccinated with a first dose during gestational weeks 24–34 with unvaccinated pregnancies. In their intention-to-treat analysis, follow-up started at the first dose (without requiring a second dose) and continued until one month postpartum. Their VE estimate during an Omicron-dominated period was 20%, which is close to our meta-analytic estimate of 26%.

The strategies used to account for confounding differed across studies. Dagan et al. used exact matching on a subset of demographic and clinical variables, Guedalia et al. only controlled for maternal age and parity, and Zidan et al. used a target trial emulation approach with gestational week sequential matching based on propensity scores. We used a similar design to the latter, matching on calendar week with exact matching on gestational age and maternal age, in addition to propensity score matching, including a large covariate set. We also assessed covariate balance using SMDs and used NCOs to explore residual confounding. Prior studies excluded individuals with previous documented COVID-19 infection^{11,12,16,17}, whereas we included these individuals after a 90-day washout, while accounting for differences in testing. Our approach likely reflects the current context, where a large majority of individuals have been exposed to COVID-19 through natural infection.

To ensure temporal alignment of eligibility, treatment assignment, and follow-up, individuals were followed from the date of first and third dose administration in the first and second trials, respectively. Median follow-up among matched participants ranged from 42–55 days in the first trial and 73–116 days in the second. This strategy

differs from that used by Dagan et al. for primary vaccination, where VE was assessed after the receipt of the second dose¹¹. This discrepancy likely contributed to the lower effectiveness observed in our study, as we captured a period where immunity was gradually building. A prior study conducted by Dagan et al. estimated VE against infection at 46% (40–51%) and 60% (53–66%) 14 to 20 and 21 to 27 days after the first dose, compared to 92% (88–95%) 7 days after the second dose¹⁸. The short follow-up observed in our study can partially be attributed to the rapid pace of vaccination campaigns, which led to many unexposed women being vaccinated shortly after the index date. In our first trial, many exposed individuals were censored as they did not receive the second dose within the recommended 6 weeks after the first dose (deviating from the treatment strategy). Our estimates for primary (two-dose) vaccination thus partially reflect the VE of a first dose, rather than the full two-dose regimen, particularly in CPRD GOLD and SCIFI-PEARL, as the UK and Sweden exhibited longer intervals between the first and second doses. We also observed a time-related decline in VE, consistent with waning immunity described in prior studies^{11,15,17}.

Our random-effects meta-analysis results should be interpreted cautiously as we observed heterogeneity, sometimes substantial ($I^2 \geq 0.5$) across databases. This heterogeneity is likely attributable to geographical differences in the timing and magnitude of pandemic waves, herd immunity levels, and differences in national COVID-19 vaccination policies, such as dosage intervals and booster dose timing. For example, the UK recommended a longer gap between the two primary doses of 12 weeks, whereas other countries recommended 3 weeks¹⁹. While this heterogeneity limits direct comparability, it

reflects real-world variation in pandemic dynamics and vaccination strategies.

Several study limitations should be considered. As the assignment to treatment strategies was not randomised, we cannot completely rule out residual confounding. Our study did not employ a test-negative design, as negative SARS-CoV-2 test results were not available across all contributing data sources. While such designs may reduce bias related to healthcare-seeking behaviour, we aimed to address confounding through extensive matching and adjustment, and by using NCOs to detect potential unmeasured bias. However, some NCOs were rare and had few or no events, resulting in wide CIs. Although immunity builds gradually and should take weeks to show an effect, we found a protective effect during the first 14 days after first-dose vaccination^{20,21}. Other observational studies assessing COVID-19 VE have found the same protective effect, which might stem from changes in personal behaviour immediately before and after vaccination^{16,22}. We adjusted only for baseline covariates, assuming no time-varying confounding given the relatively short follow-up. However, when an individual was censored, follow-up was also stopped for the matched pair to account for differences in censoring. We defined primary vaccination as two doses administered within a maximum of 42 or 49 days after first-dose vaccination with BNT162b2 or mRNA-1273, respectively. This led to the censoring of many individuals, particularly in CPRD GOLD and SCIFI-PEARL. Further analysis with less restrictive intervals might yield different estimates in these settings. We did not study the effect of heterogeneous vaccine regimens or schedules between vaccine doses, which were beyond the scope of this study and require further investigation.

By drawing on data from four European countries, this study increased the representativeness and geographical diversity of available evidence and provided vaccine brand-specific VE estimates, addressing an important evidence gap for mRNA-1273, for which pregnancy-specific real-world effectiveness data remain scarce.

Methods

This project was approved by the CPRD's Research Data Governance Process (Protocol No 21_000557), the Clinical Research Ethics Committee of the IDIAPIJGol (project code: 23/023-EOm), the Swedish Ethical Review Authority (EPM 2020-01800 with subsequent amendments), and the Regional Committee for Research Ethics (approval number: 155294 /REK Nord), the Data Protection Officer at the University of Oslo (approval number: 523275). All informed patient consent was waived or deemed not applicable due to the retrospective, de-identified nature of the data.

Design: target trial specifications

We specified two target trials to assess the effectiveness of BNT162b2 and mRNA-1273 vaccination during pregnancy against COVID-19 infection, hospitalisation, and ICU admission (Supplementary Table 1). The first trial evaluated primary (two-dose) vaccination, with second doses given 17–42 days after BNT162b2 and 24–49 days after mRNA-1273. Dosage intervals between first and second doses were based on reasonable variation around the 6 weeks following recommendations of clinical studies when first approved^{23,24}. The second trial assessed the effectiveness of a first booster (third dose) during pregnancy in women who had received their second dose at least 3 months earlier, regardless of whether it was during or before pregnancy.

Data sources

The two target trials were conducted using four routinely collected healthcare databases with complete vaccination coverage from Norway, Spain, Sweden, and the UK. Data from Norway and Sweden were obtained from nationwide registries: NLHR and SCIFI-PEARL. Data from Spain and the UK were obtained from primary care electronic health records. Spanish data were obtained from the SIDIAP database,

which captures more than 75% of the population living in Catalonia, Spain and is linked to hospital discharge data²⁵. Data from the UK were obtained from CPRD GOLD, a primary care database covering mostly the regions of Scotland, Wales and Northern Ireland²⁶. A detailed description of these data sources is provided in Supplementary Note 1.

Pregnancy data were provided directly by the data sources, through linkage, or inferred. For NLHR and SCIFI-PEARL, pregnancy data came from the Medical Birth Registry of Norway and the Swedish Birth Registry, which had information on pregnancies lasting longer than 12 and 22 weeks, respectively. In NLHR, an algorithm²⁷ was used to identify pregnancies ending before gestational week 12 to complement those notified to the Medical Birth Registry of Norway. SIDIAP provided detailed pregnancy information from reproductive health clinics. Pregnancy episodes in CPRD GOLD were inferred from primary care data using an algorithm²⁸. All databases were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. Pregnancy episodes were mapped to the perinatal expansion table, which facilitates the identification of pregnancy episodes in OMOP-formatted data²⁹.

Study population

Study enrolment ran from the start of the vaccination roll-out in each country (December 2020) until 90 days before the end of data availability (Supplementary Note 1). Both trials included pregnant women aged 12–55 years with a gestational age of less than 34 weeks during the enrolment period. The study population was restricted to pregnancies among individuals with sex recorded as female in the contributing healthcare databases. Sex was obtained from routinely collected healthcare records and was not collected specifically for this study; information on whether sex was self-reported or assigned was not consistently available across databases. We excluded participants who had COVID-19 in the 90 days before enrolment or who did not have data visibility for at least 365 days before the start of pregnancy.

Outcomes

Outcomes were COVID-19 infection, COVID-19-related hospitalisation, and ICU admission. COVID-19 infection was identified by a positive test result or clinical diagnosis, as recorded by health professionals as part of routine care. COVID-19-related hospitalisation was defined as an admission with a COVID-19 record between 21 days before and 3 days after admission. The same criteria were used to identify ICU admissions with COVID-19²⁵. We restricted hospitalisations to those unrelated to delivery by excluding hospitalisations occurring within 3 days of delivery. Hospital information was not available in CPRD GOLD. ICU admissions were only available in SCIFI-PEARL (up to 20/11/2022) and SIDIAP.

Follow-up and covariate assessment

We used sequential matching by calendar week to form exposed and unexposed cohorts. Each week, pregnant women receiving the vaccine dose of interest were matched 1:1 to unvaccinated (unexposed) pregnant women. Missing vaccination data were interpreted as not vaccinated that day. Exact matching was done on age at pregnancy start (2-year band) and gestational age (4-week band). Propensity scores with a 0.2 caliper width were used. Inclusion and exclusion criteria, matching variables, and baseline covariates were measured at the start of each week. Supplementary Fig. 1 details all matching covariates.

In the first trial, the exposure of interest was primary vaccination (two-dose), starting treatment with the first vaccine dose; eligible unvaccinated pregnant women formed the unexposed arm. In the second trial, the dose of interest was a first booster (third dose) and eligible pregnant women with 90 days or more since their second dose formed the unexposed arm. Time since second dose (1-month bands) was also an exact matching variable for the second trial. Unexposed pregnant women who became exposed during follow-up were allowed

to re-enter the study as exposed from that time point if a suitable match was found.

Time zero (index date) was defined as the vaccination date (first [start of primary vaccination] and third-dose date for the first and second trial, respectively). Follow-up ended at the earliest of: 1) end of pregnancy, 2) end of patient data or death, 3) occurrence of the outcome of interest, or 4) deviation from treatment strategy. Both individuals in a matched pair were censored if either deviated from the treatment strategy assigned at baseline. Deviations were defined as: unexposed individuals getting vaccinated (initiating primary vaccination schema [first dose date] or third dose), exposed individuals receiving additional boosters (third or fourth dose), or, in the first trial, not receiving the second dose within the defined window.

Statistical analysis

SMDs assessed observed confounding, with an absolute SMD ≤ 0.1 indicating covariate balance. SMDs were estimated for all recorded conditions and medications prescribed in 3 separate time windows: 1–30, 31–180, and 181–365 days before the index date.

We used 70 NCOs to detect unobserved confounding: 43 pre-specified²² and 27 identified by a clinical epidemiologist. Outcome risk was estimated with HRs from Cox proportional hazard models, and cumulative incidence curves from Kaplan-Meier estimators. The Huber (sandwich) estimator was used to obtain 95% CI, accounting for re-enrolment of unexposed women. Analyses were stratified by vaccine brand and pregnancy trimester. VE (%) was estimated as $100 \times (1 - \text{HR})$ and was assessed from 15 days after vaccination until the end of follow-up. VE was also assessed in different follow-up periods: 0–14, 15–28, 29–90, 91–180, and 181–365 days.

As a secondary analysis, follow-up was not censored at pregnancy end. We conducted two sensitivity analysis: one where COVID-19 infection was restricted to positive test results, and another where all COVID-19 hospitalisation were included (regardless of whether delivery occurred within 3 days of admission).

Random-effects meta-analysis was conducted when estimates were available from at least three databases. Event counts with fewer than five occurrences were clouded to preserve privacy.

All analyses were conducted using R (version 4.2.3). All analytical code scripts, package versions, code lists for variables (outcomes, COVID-19 tests, diagnoses, etc.), and NCOs are publicly available through GitHub and permanently archived in Zenodo³⁰. The analyses reported in this study were conducted using release version 1.0.0 of the GitHub repository.

Reporting summary

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

Data availability

Patient-level data cannot be shared without approval from the data custodians owing to local information governance and data protection regulations. The CPRD GOLD data used in this study is maintained by the Clinical Practice Research Datalink (CPRD). Currently, to access CPRD data, researchers must first gain CPRD Client approval: information can be found at <http://www.cprd.com/Data-access>. To approved clients, CPRD offers different licence options: a single-study dataset licence or a 1-year multi-study licence. After a CPRD licence is issued, for each study, researchers need to submit a Research Application, known as a protocol, to be reviewed via CPRD's Research Data Governance (RDG) process (<http://www.cprd.com/research-applications>). After protocol approval, researchers can start working with the data. More details about data access can be found at <https://www.cprd.com/how-access-cprd-data>. The latest CPRD GOLD data specification, its glossary-term dictionary, and the data source profile can be found at <https://www.cprd.com/primary-care-data-public-health-research>.

CPRD GOLD releases are provided monthly and, for each of them, release notes, metrics, and a DOI are available at <https://www.cprd.com/digital-object-identifiers-dois-datasets>. Enquiries can be submitted to CPRD via enquiries@cpdr.com. Data from the SIDIAP database used in this study are not publicly available due to legal restrictions under European and national law. Data access is limited to the study investigators; however, SIDIAP permits data requests from researchers at public institutions who satisfy its eligibility criteria. Interested parties should consult the SIDIAP application portal or contact sidiap@idiapigol.org for further information. The Swedish data used in this research project are pseudonymised and sourced from Swedish healthcare registers based on relevant ethics approvals for the current research and cannot be shared by the researchers. Interested researchers may seek ethical approval in Sweden and seek access to equivalent data from the appropriate Swedish public data holders according to the relevant legislation. The Norwegian individual-level data used in this study are available under restricted access due to Norwegian privacy legislation and registry regulations. Access can be obtained by submitting an application to the relevant Norwegian registry holders and obtaining the necessary ethical, legal and institutional approvals. The authors are not permitted to make the data publicly available or share individual-level data. Source data for the manuscript figures are provided as a Source Data file. The publicly available Shiny App (<https://dpa-pde-oxford.shinyapps.io/COVID19VaccineEffectivenessDuringPregnancy/>) contains all aggregated study results underlying the Supplementary Figs. and Tables, allowing these display items to be reproduced. To preserve privacy, event counts below five, together with their corresponding estimates, are masked. Source data are provided with this paper.

Code availability

The analytic code used in this study is publicly available through GitHub (<https://github.com/rwepi-idiapigol/COVIDVaccineEffectivenessDuringPregnancy>) and permanently archived in Zenodo (<https://zenodo.org/records/21887096>)³⁰.

References

- Allotey, J. et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* **370**, m3320 (2020).
- Villar, J. et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection. *JAMA Pediatrics* **175**, 817 (2021).
- Stock, S. J. et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat. Med.* **28**, 504–512 (2022).
- Goldshtein, I. et al. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes. *JAMA Pediatrics* **176**, 470 (2022).
- Fell, D. B. et al. Association of COVID-19 vaccination in pregnancy with adverse peripartum outcomes. *JAMA* **327**, 1478 (2022).
- Raffetti, E. et al. COVID-19 diagnosis, vaccination during pregnancy, and adverse pregnancy outcomes of 865,654 women in England and Wales: a population-based cohort study. *Lancet Reg. Health - Eur.* **45**, 101037 (2024).
- Prasad, S. et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat. Commun.* **13**, 2414 (2022).
- Magnus, M. C. et al. Covid-19 infection and vaccination during the first trimester and risk of congenital anomalies: Nordic registry-based study. *BMJ* **386**, e079364 (2024).
- Fernández-García, S. et al. Effectiveness and safety of COVID-19 vaccines on maternal and perinatal outcomes: a systematic review and meta-analysis. *BMJ Glob. Health* **9**, e014247 (2024).

10. Ciapponi, A. et al. Safety and effectiveness of COVID-19 vaccines during pregnancy: a living systematic review and meta-analysis. *Drug Saf.* **47**, 991–1010 (2024).
11. Dagan, N. et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. *Nat. Med.* **27**, 1693–1695 (2021).
12. Guedalia, J. et al. Effectiveness of a third BNT162b2 mRNA COVID-19 vaccination during pregnancy: a national observational study in Israel. *Nat. Commun.* **13**, 6961 (2022).
13. WHO roadmap on uses of COVID-19 vaccines in the context of Omicron and high population immunity. World Health Organization (2023).
14. JCVI statement on COVID-19 vaccination in 2025 and spring 2026: Government of the United Kingdom. *Department of Health & Social Care* <https://www.gov.uk/government/publications/covid-19-vaccination-in-2025-and-spring-2026-jcvi-advice/jcvi-statement-on-covid-19-vaccination-in-2025-and-spring-2026> (2025).
15. Wu, N. et al. Long-term effectiveness of COVID-19 vaccines against infections, hospitalisations, and mortality in adults: findings from a rapid living systematic evidence synthesis and meta-analysis up to December, 2022. *Lancet Respir. Med.* **11**, 439–452 (2023).
16. Zidan, M. et al. BNT162b2 mRNA COVID-19 vaccine effectiveness in pregnancy: Emulating trial NCT04754594 using observational data from Norwegian health registries. *Vaccine* **S0264-410X**, 012058, <https://doi.org/10.1016/j.vaccine.2025.127908> (2025).
17. Barda, N. et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* **398**, 2093–2100 (2021).
18. Dagan, N. et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. *N. Engl. J. Med.* **384**, 1412–1423 (2021).
19. Changing the UK COVID-19 vaccine dosing schedule: UK Parliament. <https://post.parliament.uk/changing-the-uk-covid-19-vaccine-dosing-schedule/> (2021).
20. Polack, F. P. et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N. Engl. J. Med.* **383**, 2603–2615 (2020).
21. Baden, L. R. et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* **384**, 403–416 (2021).
22. Català, M. et al. Observational methods for COVID-19 vaccine effectiveness research: an empirical evaluation and target trial emulation. *Int. J. Epidemiol.* **53**, dyad138 (2024).
23. Spikevax: Summary of product characteristics (annex I): European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/spikevax-epar-product-information_en.pdf (2021).
24. Comirnaty: Summary of product characteristics (annex I): European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf. (2021).
25. Raventós, B. et al. Transforming the information system for research in primary care (SIDIAP) in Catalonia to the OMOP common data model and its use for COVID-19 research. *Clin. Epidemiol.* 969–986 (2023).
26. Sanchez-Santos, M. T., Axson, E. L., Dedman, D. & Delmestri, A. Data resource profile update: CPRD GOLD. *Int. J. Epidemiol.* **54**, dyaf077 (2025).
27. Nordeng, H., Lupattelli, A. & Hilde, M. Detecting and dating early non-live pregnancy outcomes: generation of a novel pregnancy algorithm from Norwegian linked health registries. *Pharmacoepidemiol. Drug Saf.* **33**, e70002 (2024).
28. Matcho, A. et al. Inferring pregnancy episodes and outcomes within a network of observational databases. *PLOS ONE* **13**, e0192033 (2018).
29. Abellan, A. et al. Expanding the OMOP common data model to support perinatal research in network studies. *Pharmacoepidemiol. Drug Saf.* **34**, e70106 (2025).
30. Núria Mercadé-Besora. rwepi-idiapjgol/COVID vaccine effectiveness during pregnancy: v1.0.0. *Zenodo* <https://doi.org/10.5281/zenodo.21887096> (2026).

Acknowledgements

We acknowledge the significant scientific contributions of Professor Angela Lupattelli, who passed away during this study. Prof Lupattelli played an important role in the study's design and contributed substantially to the handling of Norwegian data. Her dedication, insight, and expertise are highly appreciated. The authors thank Dr. Carlen Reyes, who contributed to the identification of NCOs; Dr. Alicia Abellan and colleagues, who developed and implemented the OMOP pregnancy extension table, which was instrumental in the development of this study; and Dr. Marissa Erin Leblanc for her valuable suggestions. We acknowledge English language editing by Dr. Jennifer de Beyer, Centre for Statistics in Medicine, NDORMS, University of Oxford. The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author contributions

N.M.-B. and BR are joint first authors. N.M.-B., B.R., T.D.-S. and H.M.E.N. conceived the study. N.T., H.L., T.B., D.M., E.B., M.C. and F.N. contributed to the study design. N.M.-B. developed the analytical code for the study, with input from M.C. and E.B. H.M.E.N., N.T., S.H., F.I., H.L., T.D.-S., A.G., T.B., D.P.-A. and N.M.-B. contributed to the study execution (data holders). N.M.B. and B.R. wrote the first manuscript draft, with valuable input from D.P.-A. All coauthors interpreted the results and contributed to the revision of the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

BR and TD-S work for a research group that receives/received unconditional research grants from UCB, Johnson and Johnson, Innovative Medicines Initiative, and the European Medicines Agency, none of which relate to the content of this manuscript. DPA's research group from the University of Oxford has received research grants from the European Medicines Agency, the Innovative Medicines Initiative, Gilead Science, and UCB Biopharma, none of which are related to this manuscript. FN has funding for this research from SciLifeLab / the Knut and Alice Wallenberg Foundation (KAW 2021-0010/VC2021.0018 and KAW 2020.0299/VC 2022.0008) and the Swedish Research Council (2021-05045 and 2021-05450). The overarching SCIFI-PEARL study (contributing Swedish data to the current analysis) through P.I. FN also has core funding from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (Avtal om Läkarutbildning och Forskning/Medical Training and Research Agreement), grants ALFGBG-938453, ALFGBG-971130, ALFGBG-978954, ALFGBG-1006729, a grant from FORTE (Research Council for Health, Working Life, and Welfare), grant 2024-01711, and previously from a joint grant from FORTE and FORMAS (Research Council for Environment, Agricultural Sciences and Spatial Planning), grant 2020-02828. Acquisition of the Norwegian data in this study was funded by Professor Nordeng's EU-COVID-19 project, funded by the Norwegian Research Council's COVID-19 Emergency Call (project no. 31270).

Competing interests

All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. FN reports research project support (paid to his institution, no personal fees) by Bayer, with no relation to the work reported here. FN

owns some AstraZeneca shares. TB reports consultancy for Institut Biochimique SA, with no relation to the work reported here.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-026-78469-x>.

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Peer review information *Nature Communications* thanks Michele Jons-son-Funk, Kirsten Maertens and the other anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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