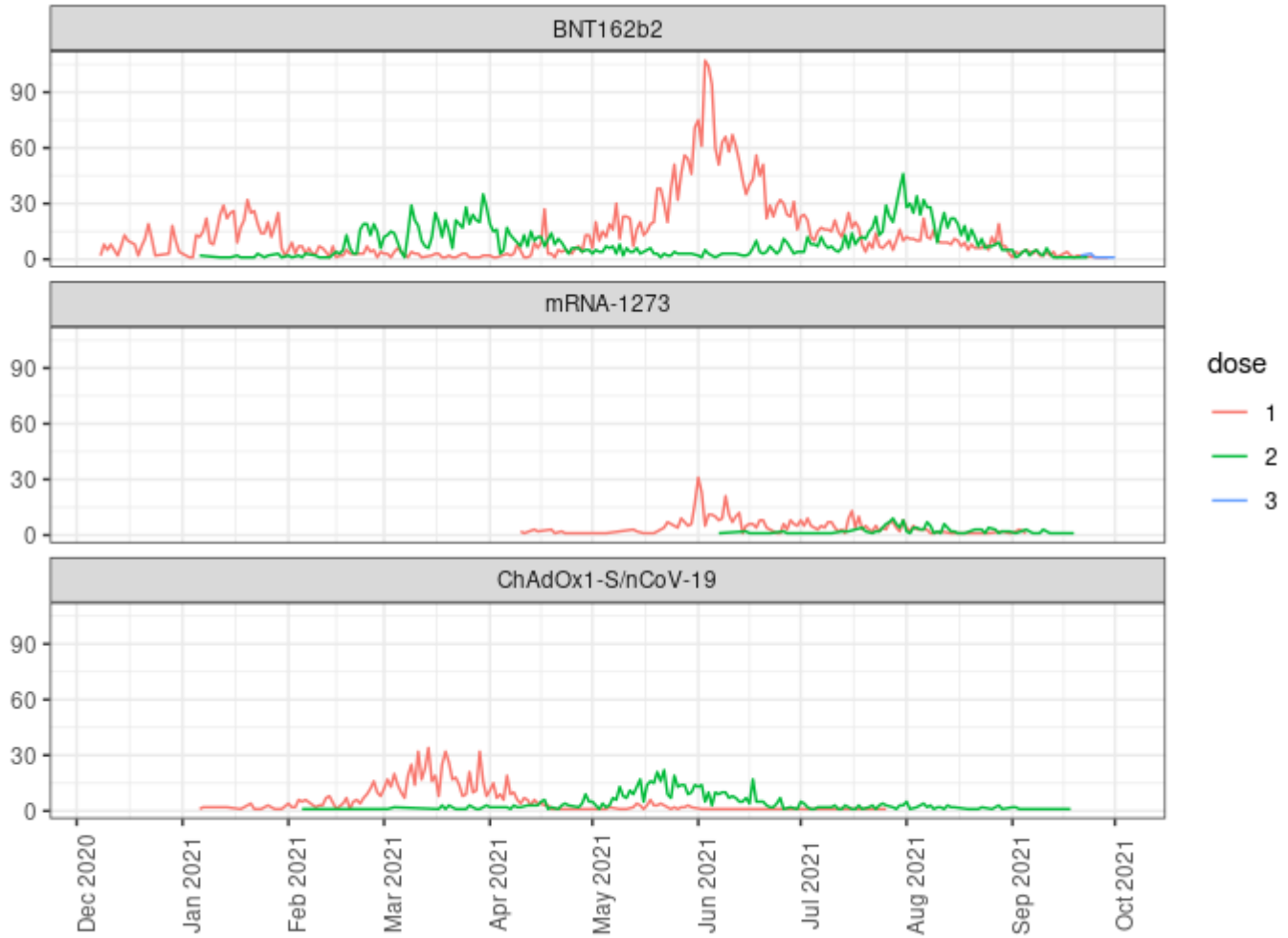
Supplementary Information

Supplementary Figures

Supplementary Figure 1: Number of babies exposed to COVID-19 vaccination between six weeks preconception and up to 19 weeks and six days gestation by the calendar time, dose number and type of vaccine



Supplementary Tables

Supplementary Table 1: Sensitivity analyses for association between vaccination and major congenital anomalies, calculated using conditional logistic regression models

	N pregnancies	N total babies	N babies with any major congenital anomaly	Total prevalence (/1,000 total babies)	OR (95% CI)*	p value*	Adjusted OR (95% CI)**	p value**
Sensitivity analysis 1: including babies from pregnancies of any duration								
Any major congenital anomaly								
Unvaccinated	25318	25545	466	18.2	1		1	
Vaccinated	8407	8515	153	18.0	0.98 (0.82-1.18)	0.87	1.01 (0.84-1.22)	0.90
Any major non-genetic congenital anomaly								
Unvaccinated	25318	25545	368	14.4	1		1	
Vaccinated	8407	8515	120	14.1	0.98 (0.79-1.20)	0.83	0.99 (0.80-1.23)	0.93
Sensitivity analysis 2: exposure period restricted to conception to 9+6 weeks gestation								
Any major congenital anomaly								
Unvaccinated	6549	6573	147	22.4	1		1	
Vaccinated	2154	2191	39	17.8	0.79 (0.55-1.13)	0.20	0.76 (0.52-1.10)	0.15
Any major non-genetic congenital anomaly								
Unvaccinated	6549	6573	123	18.7	1		1	
Vaccinated	2154	2191	29	13.2	0.70 (0.47-1.06)	0.09	0.66 (0.43-1.02)	0.06

OR=Odds Ratio; CI=Confidence Interval

*Accounting for matching factors: maternal age at conception and gestational week at matching

**In sensitivity analysis 1, additionally adjusted for: maternal deprivation, maternal ethnicity, maternal urban rural status, maternal clinical vulnerability, maternal diabetes, maternal body mass index, and whether the baby was from a singleton or multiple pregnancy. (Maternal smoking status could not be included due to high levels of missing data for pregnancies ending at <12 weeks gestation.)

In sensitivity analysis 2, additionally adjusted as above and for maternal smoking status

Supplementary Table 2: Key characteristics of vaccinated and control groups included in the subgroup analyses

	mRNA vaccines (BNT162b2/mRNA-1273) subgroup analysis		Viral vector vaccines (ChAdOx1-S/nCoV-19) subgroup analysis	
	Vaccinated cohort	**Unvaccinated controls**	**Vaccinated cohort**	**Unvaccinated controls**
Key characteristics				
Number of pregnancies reaching ≥12 weeks gestation	5411	16352	1202	3660
Total babies resulting from these pregnancies	5498	16494	1222	3666
Total live births resulting from these pregnancies	5290	15843	1144	3492
Median maternal age (min-max) [standard deviation]	32 (16-46) [5.0]	32 (16-46) [4.8]	31 (18-46) [5.4]	31 (17-47) [5.2]
Maternal deprivation (SIMD quintile)				
1 (most deprived)	806 (14.7%)	3513 (21.3%)	309 (25.3%)	822 (22.4%)
2	918 (16.7%)	3192 (19.4%)	263 (21.5%)	699 (19.1%)
3	1041 (18.9%)	2987 (18.1%)	224 (18.3%)	671 (18.3%)
4	1366 (24.8%)	3655 (22.2%)	214 (17.5%)	803 (21.9%)
5 (least deprived)	1367 (24.9%)	3133 (19%)	212 (17.3%)	668 (18.2%)
Unknown	0	14 (0.1%)	0	3 (0.1%)
Maternal ethnicity				
White	4893 (89%)	13827 (83.8%)	1119 (91.6%)	3095 (84.4%)
South Asian	205 (3.7%)	610 (3.7%)	38 (3.1%)	125 (3.4%)
Black/Caribbean /African	65 (1.2%)	370 (2.2%)	20 (1.6%)	64 (1.7%)
Other/mixed ethnicity	205 (3.7%)	672 (4.1%)	24 (2%)	172 (4.7%)
Unknown	130 (2.4%)	1015 (6.2%)	21 (1.7%)	210 (5.7%)
Maternal urban/rural status				
Large urban areas	2051 (37.3%)	6101 (37%)	421 (34.5%)	1387 (37.8%)
Other urban areas	1795 (32.6%)	5850 (35.5%)	440 (36.0%)	1221 (33.3%)
Accessible small towns	449 (8.2%)	1258 (7.6%)	112 (9.2%)	289 (7.9%)
Remote small towns	175 (3.2%)	482 (2.9%)	51 (4.2%)	103 (2.8%)
Accessible rural areas	675 (12.3%)	1915 (11.6%)	142 (11.6%)	428 (11.7%)

Remote rural areas	295 (5.4%)	725 (4.4%)	47 (3.8%)	190 (5.2%)
Unknown	58 (1.1%)	163 (1%)	9 (0.7%)	48 (1.3%)
Maternal clinical vulnerability				
Not vulnerable	4113 (74.8%)	12187 (73.9%)	683 (55.9%)	2664 (72.7%)
Vulnerable	1341 (24.4%)	4173 (25.3%)	477 (39.0%)	970 (26.5%)
Extremely vulnerable	44 (0.8%)	134 (0.8%)	62 (5.1%)	32 (0.9%)
Maternal diabetes				
No - assumed & confirmed	5089 (92.6%)	15136 (91.8%)	1035 (84.7%)	3368 (91.9%)
Pre-existing diabetes	40 (0.7%)	124 (0.8%)	74 (6.1%)	31 (0.8%)
Gestational Diabetes/onset unknown	369 (6.7%)	1234 (7.5%)	113 (9.2%)	267 (7.3%)
Maternal smoking status				
Non-smoker	4088 (74.4%)	11301 (68.5%)	791 (64.7%)	2532 (69.1%)
Ex-smoker	1030 (18.7%)	3322 (20.1%)	259 (21.2%)	705 (19.2%)
Smoker	359 (6.5%)	1811 (11.0%)	162 (13.3%)	413 (11.3%)
Unknown	21 (0.4%)	60 (0.4%)	10 (0.8%)	16 (0.4%)
Maternal body mass index				
Underweight	85 (1.5%)	322 (2.0%)	12 (1.0%)	84 (2.3%)
Healthy weight	2013 (36.6%)	5924 (35.9%)	337 (27.6%)	1340 (36.6%)
Overweight	1649 (30.0%)	5094 (30.9%)	328 (26.8%)	1101 (30.0%)
Obese/severely obese	1553 (28.2%)	4597 (27.9%)	497 (40.7%)	1002 (27.3%)
Unknown	198 (3.6%)	557 (3.4%)	48 (3.9%)	139 (3.8%)
Baby from singleton or multiple pregnancy				
Singleton	5324 (96.8%)	15984 (96.9%)	1184 (96.9%)	3563 (97.2%)
Multiple	174 (3.2%)	510 (3.1%)	38 (3.1%)	103 (2.8%)
Exposure (vaccination)				
Gestation at first vaccination within exposure period*				
Up to six weeks preconception	1370 (24.9%)	-	668 (54.7%)	-
2+0-9+6 weeks	1489 (27.1%)	-	432 (35.4%)	-
10+0-13+6 weeks	851 (15.5%)	-	42 (3.4%)	-

14+0-19+6 weeks	1788 (32.5%)	-	80 (6.5%)	-
Number of vaccinations within exposure period				
1	4044 (73.6%)	-	827 (67.7%)	-
2+	1454 (26.4%)	-	395 (32.3%)	-
Dose number at first vaccination within exposure period				
Dose 1	4607 (83.8%)	-	898 (73.5%)	-
Dose 2	880 (16.0%)	-	324 (26.5%)	-
Dose 3	11 (0.2%)	-	0	-
Outcome (major congenital anomaly)				
Total N babies with any anomaly	110	376	41	91
Total N live births with any anomaly	78	270	30	65
Total live birth prevalence of any anomaly (/1,000 live births)	15	17	26	19
Total N babies with any non-genetic anomaly	84	309	34	66
Total N live births with any non-genetic anomaly	65	242	27	53
Total live birth prevalence of any non-genetic anomaly (/1,000 live births)	12	15	24	15
N (%) babies with the following types of anomaly [N with non-genetic anomaly]				
Nervous system	11 (10%) [10]	35 (9.3%) [35]	3 (7.3%) [3]	8 (8.8%) [6]
Eye	2 (1.8%) [2]	1 (0.3%) [0]	0	0
Ear, face and neck	2 (1.8%) [2]	2 (0.5%) [2]	0	0
Congenital heart defects	30 (27.3%) [26]	79 (21%) [65]	11 (26.8%) [9]	26 (28.6%) [19]
Respiratory	1 (0.9%) [1]	4 (1.1%) [4]	0	1 (1.1%) [1]
Oro-facial clefts	4 (3.6%) [1]	15 (4%) [12]	3 (7.3%) [2]	1 (1.1%) [1]
Digestive system	9 (8.2%) [9]	35 (9.3%) [31]	4 (9.8%) [3]	10 (11%) [7]
Abdominal wall defects	2 (1.8%) [2]	4 (1.1%) [4]	1 (2.4%) [1]	2 (2.2%) [2]
Urinary	6 (5.5%) [5]	26 (6.9%) [26]	5 (12.2%) [2]	5 (5.5%) [4]
Genital	10 (9.1%) [9]	31 (8.2%) [31]	5 (12.2%) [5]	12 (13.2%) [10]

Limb defect	16 (14.5%) [15]	60 (16%) [59]	5 (12.2%) [5]	15 (16.5%) [14]
Other anomalies/syndromes**	13 (11.8%) [6]	22 (5.9%) [14]	5 (12.2%) [3]	8 (8.8%) [4]
Chromosomal	14 (11.8%) [0]	59 (15.7%) [0]	5 (12.2%) [0]	21 (23.1%) [0]

SIMD=Scottish Index of Multiple Deprivation

*Between 6 weeks preconception and up to the earliest of: (1) end of pregnancy or (2) 19 weeks 6 days gestation.

**The "Other anomalies/syndromes group" includes a disparate range of conditions including genetic syndromes and microdeletions, skeletal dysplasias, and recognised teratogenic syndromes and associations. No unusual pattern in the distribution of these other anomalies was seen in either of the vaccinated groups.

Supplementary Table 3: Subgroup analysis of association between vaccination and major congenital anomalies by vaccine group, calculated using conditional logistic regression models

	N pregnancies	N total babies	N babies with any major congenital anomaly	Total prevalence (/1,000 total babies)	OR (95% CI)*	p value*	Adjusted OR (95% CI)**	p value**
mRNA vaccines (BNT162b2/mRNA-1273) subgroup analysis								
Any major congenital anomaly								
Unvaccinated	16352	16494	376	22.8	1		1	
Vaccinated	5411	5498	110	20.0	0.87 (0.70-1.08)	0.22	0.92 (0.73-1.14)	0.44
Any major non-genetic congenital anomaly								
Unvaccinated	16352	16494	309	18.7	1		1	
Vaccinated	5411	5498	84	15.3	0.81 (0.64-1.04)	0.09	0.85 (0.66-1.10)	0.22
Viral vector vaccines (ChAdOx1-S/nCoV-19) subgroup analysis								
Any major congenital anomaly								
Unvaccinated	3660	3666	91	24.8	1		1	
Vaccinated	1202	1222	41	33.6	1.35 (0.94-1.96)	0.11	1.35 (0.90-2.03)	0.15
Any major non-genetic congenital anomaly								
Unvaccinated	3660	3666	66	18.0	1		1	
Vaccinated	1202	1222	34	27.8	1.55 (1.02-2.35)	0.04	1.56 (0.97-2.51)	0.06

OR=Odds Ratio; CI=Confidence Interval

*Accounting for matching factors: maternal age at conception and gestational week at matching

**Additional adjusted for: maternal deprivation, maternal ethnicity, maternal urban rural status, maternal clinical vulnerability, maternal diabetes, maternal body mass index, maternal smoking status, and whether the baby was from a singleton or multiple pregnancy

Supplementary Table 4: Sensitivity analyses for association between SARS-CoV-2 infection and major congenital anomalies, calculated using conditional logistic regression models

	N pregnancies	N total babies	N babies with any major congenital anomaly	Total prevalence (/1,000 total babies)	OR (95% CI)*	p value*	Adjusted OR (95% CI)**	p value**
Sensitivity analysis 1: including babies from pregnancies of any duration								
Any major congenital anomaly								
Uninfected	5472	5478	90	16.4	1		1	
Infected	1803	1826	32	17.5	1.07 (0.71-1.60)	0.75	0.93 (0.60-1.45)	0.74
Any major non-genetic congenital anomaly								
Uninfected	5472	5478	77	14.1	1		1	
Infected	1803	1826	26	14.2	1.01 (0.65-1.59)	0.95	0.93 (0.58-1.52)	0.79
Sensitivity analysis 2: exposure period restricted to conception to 9+6 weeks gestation								
Any major congenital anomaly								
Uninfected	1548	1548	30	19.4	1		1	
Infected	508	516	12	23.3	1.20 (0.61-2.37)	0.59	1.14 (0.57-2.29)	0.72
Any major non-genetic congenital anomaly								
Uninfected	1548	1548	24	15.5	1		1	
Infected	508	516	10	19.4	1.26 (0.60-2.65)	0.55	1.05 (0.47-2.34)	0.91

OR=Odds Ratio; CI=Confidence Interval

*Accounting for matching factors: maternal age at conception, season of conception and gestational week at matching

**In sensitivity analysis 1, additionally adjusted for: maternal deprivation, maternal ethnicity, maternal urban rural status, maternal clinical vulnerability, maternal diabetes, maternal body mass index, and whether the baby was from a singleton or multiple pregnancy. (Maternal smoking status could not be included due to high levels of missing data for pregnancies ending at <12 weeks gestation.)

In sensitivity analysis 2, additionally adjusted for: maternal urban rural status, maternal clinical vulnerability, maternal diabetes, and maternal BMI. (Restricted range of covariates used due to the small numbers involved.)