Supplementary Appendix

Supplement to: Halasa NB, Olson SM, Staat MA, et al. Maternal vaccination and risk of hospitalization for Covid-19 among infants. N Engl J Med. DOI: 10.1056/NEJMoa2204399

This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Halasa N.B., Olson S.M., Staat M.A., Newhams M.M., et al. Maternal vaccination and risk of Covid-19 hospitalization among infants

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SUPPLEMENTARY METHODS & RESULTS

Enrollment of case-infants and control-infants

In the Overcoming Covid-19 Network, investigators at each site screened for potentially eligible case-patients with Covid-19 through a review of hospital admission logs and electronic medical records. Due to concerns about potential biases related to the selection of controls,[1,2] the original study protocol aimed to enroll two groups of hospitalized patients as controls at the study onset: those who had negative results for SARS-CoV-2 on RT-PCR assay or antigen testing (test-negative) but who had Covid-19–like symptoms; and those without Covid-19–like symptoms who may or may not have undergone SARS-CoV-2 testing (syndrome-negative). At each site, investigators targeted a case-to-control ratio of approximately 1:1 for each of the two control groups. Eligible controls were selected from among infants <6 months of age with a date of hospital admission within 3 weeks after the case patient's hospitalization date. If a control-infant was not identified, sites were instructed to enroll a control hospitalized within 4 weeks. Infants included in this study were identified beginning July 1, 2021. Surveillance experience in July and early August indicated that sites had difficulties in identifying syndrome-negative control-infants. Thus, enrollment of 1 control per case was allowed. This change to the surveillance implementation was conducted prior to first assessment of the data or initial data analysis on maternal vaccine effectiveness on January 6, 2022. Furthermore, the Overcoming Covid-19 Network was also simultaneously evaluating vaccine effectiveness against Covid-19 requiring hospitalization in adolescents 12-18 years of age, the first group eligible for vaccination. We continued enrollment of two groups of controls in adolescents and did not identify substantive differences in vaccine effectiveness by control groups.[3] Primary reasons for admission or the admission diagnosis for case-infants and control-infants are presented in Tables S1 and S2, respectively.

Logistic regression models

Vaccine effectiveness was calculated by estimating the odds of maternal Covid-19 vaccination among case-infants vs control-infants using multivariable logistic regression, where Covid-19 among infants was the outcome and vaccination status among mothers was the exposure variable, with vaccine effectiveness = (1 – adjusted odds ratio) × 100%. Analyses of maternal vaccine effectiveness during pregnancy against infant hospitalization using data from the Overcoming COVID-19 network were published in *Morbidity and Mortality Weekly Report* on February 15, 2022 using data exported on February 7, 2022.[4] For the Halasa, et al *New England Journal of Medicine* publication, data were exported on March 10, 2022 to begin cleaning and assessing for sufficient sample size for additional analyses, and the final dataset for this analysis was exported on March 29, 2022.

In the primary analysis, we stratified by delta (admitted from July 1, 2021 – December 18, 2021) vs omicron period (admitted from December 19, 2021 – March 8, 2022) and by those receiving the second dose of vaccine 0-20 weeks of pregnancy vs those receiving the second dose >20 weeks of pregnancy. We estimated vaccine effectiveness within each stratum as:

$$logit\ (covid = 1) = \beta_0 + \beta_1(vacc) \ldots + \beta_Z Z$$

where

covid = 1 if laboratory confirmed Covid-19 case-infant (0 otherwise)

vacc = 1 if maternal completion of a 2-dose primary Covid-19 mRNA series during pregnancy and ≥14 days prior to delivery; (0 otherwise)

Z = vector of adjustment variables including U.S. Census region as an indicator variable (4 regions), calendar time of admission as an indicator variable (bi-week periods), continuous age, sex (female vs male), race/ethnicity as an indicator variable (non-Hispanic White, non-Hispanic Black, non-Hispanic other race, Hispanic of any race, unknown), *with vaccine effectiveness (VE) defined as*

$$\widehat{VE} = [1 - \exp(\beta_1)] * 100\%$$

Potential confounding variables (Z) listed above were selected *a priori* based on past vaccine effectiveness studies. Other potential confounding factors in the analytic dataset were considered. These included presence of underlying health conditions (≥1 vs 0), specific underlying conditions (respiratory, cardiovascular, neurologic/ neuromuscular, immunosuppression or autoimmune, or other chronic conditions), prematurity (born <37 weeks gestation), and continuous score on the Centers for Disease Control and Prevention's Social Vulnerability Index. Using a change-in-estimate approach, we assessed confounding from these additional available factors. Additional case-infant and control-infant characteristics not considered in final models due to high frequency of missingness (breastfeeding history and daycare attendance) are included in Table S3. To derive a parsimonious fully adjusted model, we sequentially added these variables individually to the model to assess if they changed the relative odds ratio for vaccination by >5%. If a variable changed the odds ratio by >5%, we added that variable to the model, and reassessed if adding an additional variable changed our revised estimate by >5%. If another variable was added to the model and reverted the model to the same point estimate as the *a priori*, the *a priori* model was chosen as the final model. Each model, including the primary models and the subgroups (i.e. Delta and Omicron) were adjusted separately. All fully adjusted models thus only included *a priori* variables because additional factors did not change the odds ratio for vaccination by more than 5% (Table S4). Goodness of fit between alternative models was compared with the Akaike information criterion; measures of model fit are presented in Table S5; regression coefficients and standard errors are shown in Table S6; residuals are shown in Figure S1. Number of case-infants and control-infants varied by hospital (Table S7). We accounted for clustering of patients by hospital through generalized linear mixed models (proc glimmix function in SAS with hospital specified as a cluster variable, modeling with G-side effects [i.e, conditional models])to calculate odds ratios conditional on

the hospital-specific random effect.[5] We also accounted for marginal effects (proc glimmix function in SAS modeling with R-side effects [i.e, marginal models]) that integrate over the random effects to provide a population-average inference. Both approaches yielded similar point estimates and confidence intervals (Table S9). The estimate for the between-hospital variance was low (<0.0001). Further, the COVTEST ZeroG was used to test the significance of random effect of hospitals included in the conditional models and showed lack of statistical significance, inferring that the clustering effect was minimal.[6]

TABLE S1. Primary reason for admission among 537 case-infants with SARS-CoV-2 positive test

Case-infants with Covid-19 (N=537)		
Primary reason(s) for admission	**n**	**(%)**
Acute respiratory illness	249	(46%)
Acute respiratory & GI illness	117	(22%)
Febrile illness	84	(16%)
Febrile & GI illness	35	(7%)
Covid-19 (symptoms unknown)	23	(4%)
Acute GI illness	16	(3%)
Acute respiratory illness (SARS-CoV-2 & RSV)	3	(1%)
Acute respiratory & GI illness (+ meningitis)	1	(0.2%)
Acute respiratory & GI illness (+ seizure)	1	(0.2%)
Acute respiratory illness (+pancytopenia)	1	(0.2%)
Acute respiratory illness (+spasms)	1	(0.2%)
Acute respiratory illness (SARS-CoV-2 & HSV)	1	(0.2%)
Acute respiratory illness, GI illness & UTI	1	(0.2%)
Acute respiratory illness, GI illness, UTI, & sepsis	1	(0.2%)
Acute respiratory infection & UTI	1	(0.2%)
Cardiac arrest	1	(0.2%)
Febrile & GI illness (+ seizure)	1	(0.2%)

*GI denotes gastrointestinal; UTI denotes urinary tract infection; RSV denotes respiratory syncytial virus; HSV denotes herpes simplex virus.

TABLE S2. Primary admission diagnosis among 512 hospitalized control-infants with SARS-CoV-2 negative test

Control-infants without Covid-19 (N=512)		
Primary reason for admission	**n**	**(%)**
Acute respiratory illness	305	(60%)
Gastrointestinal illness	46	(9%)
Febrile Illness	46	(9%)
Other*	20	(4%)
Hepatobiliary disorder	15	(3%)
Cardiac	13	(3%)
Urinary tract infection	10	(2%)
Acute neurologic illness	10	(2%)
Sepsis	7	(1%)
Insufficient nutritional intake	7	(1%)
Seizure	6	(1%)
Brief resolved unexplained event	5	(1%)
Bacteremia	5	(1%)
Rule out sepsis	4	(1%)
Trauma	3	(1%)
Post-surgical	3	(1%)
Dermatologic infection	3	(1%)
Oncology	2	(0%)
Dehydration	2	(0%)

*Other denotes isolated individual diagnoses

Table S3. Additional Characteristics of Case-infants with Covid-19 and Control-infants from 30 Pediatric Hospitals in 22 States, July 2021-March 2022.

Characteristic	**Case status**		**Maternal Vaccination Status**	
	Case-infants (N=537)	**Control-infants (N=512)**	**Fully vaccinated (N=234)**	**Unvaccinated (N=815)**
Month of admission – no. (%)				
July	30 (6)	20 (4)	5 (2)	45 (6)
August	41 (8)	53 (10)	13 (6)	81 (10)
September	40 (7)	46 (9)	10 (4)	76 (9)
October	20 (4)	27 (5)	11 (5)	36 (4)
November	33 (6)	37 (7)	22 (9)	48 (6)
December	107 (20)	96 (19)	48 (21)	155 (19)
January	237 (44)	182 (36)	107 (46)	312 (38)
February	27 (5)	44 (9)	16 (7)	55 (7)
March	2 (<1)	7 (1)	2 (1)	7 (1)
Maternal Vaccine Type – no./total no. (%)				
BNT162b2	64/86 (74)	92/145 (63)	156/231 (68)	--
mRNA-1273	22/86 (26)	53/145 (37)	75/231 (32)	--
Breastfeeding* – no./total no. (%) (190/537 [35%] cases and 206/512 [40%] controls missing)	178/347 (51)	186/306 (61)	124/178 (70)	240/475 (51)
Daycare attendance* – no./total no. (%) (213/537 [51%] cases and 224/512 [44%] controls missing)	16/324 (5)	20/288 (7)	17/169 (10)	19/443 (4)

* Breastfeeding and in-person daycare attendance were based on information reported by parent or guardian. Breastfeeding included any breastfeeding (including exclusive or partial).

TABLE S4. Model selection using change in estimate approach to evaluate for potential confounding.

Model Selection - Overall	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.48	52
Plus Social Vulnerability Index	0.50	50
Plus underlying conditions	0.49	51
Plus prematurity	0.48	52
Plus respiratory	0.49	51
Plus cardiovascular	0.49	52
Plus neurologic/neuromuscular	0.49	51
Plus immunosuppression or autoimmune	0.49	51
Plus other chronic conditions	0.49	51
Model Selection - Delta	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.20	80
Plus Social Vulnerability Index	0.21	79
Plus underlying conditions	0.19	81
Plus prematurity	0.19	81
Plus respiratory	0.20	80
Plus cardiovascular	0.20	80
Plus neurologic/neuromuscular	0.20	80
Plus immunosuppression or autoimmune	0.20	80
Plus other chronic conditions	0.20	81
A priori - sex, age, race, region, calendar time + social vulnerability index	**0.21**	79
Plus underlying conditions	0.21	79
Plus prematurity	0.20	80
Plus respiratory	0.21	79
Plus cardiovascular	0.21	79
Plus neurologic/neuromuscular	0.21	79
Plus immunosuppression or autoimmune	0.21	79
Plus other chronic conditions	0.21	79
Model Selection - Omicron	**OR**	**VE**
A priori - sex, age, race, region, calendar time	0.62	38
Plus Social Vulnerability Index	0.63	37
Plus underlying conditions	0.63	37
Plus prematurity	0.63	37
Plus respiratory	0.63	37
Plus cardiovascular	0.63	37
Plus neurologic/neuromuscular	0.63	37
Plus immunosuppression or autoimmune	0.63	37
Plus other chronic conditions	0.63	37

VE denotes vaccine effectiveness; OR denotes odds ratio

TABLE S5. Measure of fit for the logistic regression models

Model Fit Statistics	Overall	Delta	Omicron	Vaccinated after 20 weeks of pregnancy	Vaccinated 0 to 20 weeks of pregnancy
AIC: Intercept Only	1455.627	549.269	900.335	1282.842	1276.387
AIC: Intercept and covariates	1426.752	542.808	876.806	1256.683	1275.111
SC: Intercept Only	1460.583	553.253	904.815	1287.672	1281.214
SC: Intercept and covariates	1570.464	634.439	952.967	1396.747	1415.112
-2 Log L: Intercept Only	1453.627	547.269	898.335	1280.842	1274.387
-2 Log L: Intercept and covariates	1368.752	496.808	842.806	1198.683	1217.111
Hosmer and Lemeshow Goodness-of-fit test P-value	0.3632	0.8431	0.3248	0.4215	0.4723
Deviance Goodness-of-Fit P-value	<.0001	<.0001	<.0001	<.0001	<.0001
Pearson Goodness-of-Fit P-value	0.2322	0.1555	0.2892	0.2364	0.2172

Table S6. Estimated regression coefficients and standard errors for overall vaccine effectiveness model

Parameter	Response	Regression Coefficient Estimate	Standard Error
Intercept		-0.3803	0.3971
Vaccinated	**Yes**	-0.7258	0.1665
Continuous Age		-0.1464	0.5133
US Census Region	**Midwest**	0.0758	0.2431
US Census Region	**South**	0.1461	0.2242
US Census Region	**West**	0.0868	0.2334
Female		0.0374	0.1312
Biweekly Admission Intervals	**5**	-0.1584	0.6760
Biweekly Admission Intervals	**6**	0.6140	0.5249
Biweekly Admission Intervals	**7**	0.6854	0.5033
Biweekly Admission Intervals	**8**	-0.1565	0.4309
Biweekly Admission Intervals	**9**	0.0299	0.4584
Biweekly Admission Intervals	**10**	0.5283	0.4687
Biweekly Admission Intervals	**11**	-0.8388	0.4769
Biweekly Admission Intervals	**12**	0.2770	0.5223
Biweekly Admission Intervals	**13**	-0.1088	0.5688
Biweekly Admission Intervals	**14**	-0.00257	0.4878
Biweekly Admission Intervals	**15**	0.0627	0.5178
Biweekly Admission Intervals	**17**	-0.0199	0.4154

Parameter	Response	Regression Coefficient Estimate	Standard Error
Biweekly Admission Intervals	**18**	0.7886	0.3401
Biweekly Admission Intervals	**19**	0.5278	0.3437
Biweekly Admission Intervals	**20**	0.0650	0.3838
Biweekly Admission Intervals	**21**	-0.3425	0.4545
Biweekly Admission Intervals	**22**	-0.5633	0.6382
Biweekly Admission Intervals	**23**	-13.3705	425.1
Race/ethnicity	**Black, Non-Hispanic**	0.4684	0.1922
Race/ethnicity	**Hispanic, any race**	0.2717	0.1690
Race/ethnicity	**Other, Non-Hispanic**	0.0760	0.2784
Race/ethnicity	**Unknown**	0.5605	0.2613

Table S7. Number of case-infants and control-infants enrolled at each hospital prior to analytic exclusion criteria (N=1327)

Hospital Site	Case-infants	Control-infants
1	79	101
2	66	67
3	59	61
4	58	63
5	49	45
6	47	57
7	43	57
8	42	28
9	28	24
10	27	24
11	19	13
12	19	23
13	15	14
14	13	17
15	12	11
16	11	13
17	11	20
18	9	12
19	6	5
20	5	3
21	5	5
22	4	4
23	4	4
24	3	1
25	3	1
26	2	4
27	1	1
28	1	1
29	1	2
30	1	3

Table S8. Representativeness of study participants

Disease, problem, or condition under investigation	Infants <6 months of age hospitalized with Covid-19 among those with and without maternal vaccination during pregnancy
Special considerations related to	
Sex	Male case-infants were slightly overrepresented in this study though the distribution is aligned with national studies of Covid-19 among hospitalized infants.[7]
Age	In this study of infants <6 months, the median age was 2 months for case-infants. Nearly three-quarters of all children were 0-2 months. The focus of this study was on infants <6 months because antibodies derived through maternal vaccination or infection are suspected to provide protection through this young age period when infants are at high risk for complications from infectious diseases such as Covid-19, influenza, and pertussis.[8-10] Prevalence of young hospitalized Covid-19 has increased in the omicron era, with infant rates 6x higher compared with pre-omicron era.[7] Infants <6 months of age also account for ~44% of all Covid-19 hospitalizations among children <5 years of age.
Race/Ethnicity	Case-infants were of diverse race ethnicity: 20% Black, non-Hispanic; 30% Hispanic, any race; and 34% White, non-Hispanic. This distribution of race/ethnicity is similar to that reported from another national study of Covid-19 hospitalizations across 14 U.S. States, and reflects the disproportionate impact of Covid-19 among Black and Hispanic children and infants.[7,11]
Geography	In this study, the highest proportion of infants were from the South (37%) reflecting the study hospital location and the higher disease burden in that region during the study period compared with other regions.[12] Also, the distribution of maternal vaccination during pregnancy for infants differed by U.S. Census region, with the South also having the highest percentage of infants without maternal vaccination (39%) similar to national differences in vaccination by region in the general population.[13]

Overall representativeness of this study	Case-infants with Covid-19 and Control-infants were from 30 Pediatric Hospitals in 22 states, which is not representative from all 50 states.
Prior SARS-CoV-2 infection or breastfeeding	The study was not able to ascertain prior SARS-CoV-2 infection in pregnant persons which can also induce maternal immunity and potentially protect the infant. Similarly, breastfeeding history was not ascertained in detail and was missing on 38% of the infants thus the study could not assess the possible effect of breastfeeding on the study results.

TABLE S9. Maternal vaccine effectiveness against infant Covid-19 hospitalization using conditional and marginal models† with clustering by hospital

Model Type	VE	95% LL	95% UL	OR	95% LL	95% UL
Conditional Model	52	37	64	0.48	0.36	0.63
Marginal Model ‡	52	33	66	0.48	0.34	0.67

VE denotes vaccine effectiveness; LL denotes lower confidence limits; UL denotes upper confidence limits; OR denotes odds ratio

† Models included infant age (continuous), sex, race and ethnic group, and calendar date of admission (biweekly intervals). The between-cluster variance was low (<0.0001).

Table S10. Sensitivity analyses of maternal vaccine effectiveness during pregnancy against SARS-CoV-2 hospitalization in infants

Overall VE	No. of vaccinated mothers/ total (%)		Maternal Vaccine Effectiveness (95% CI)
	Case-infants	Control-infants	
Final Analysis (Plausible self-report and verified vaccination)	87/537 (16%)	147/512 (29%)	52% (95% CI: 33%-65%)
Excluding those without verified vaccination*	77/525 (15%)	141/504 (28%)	56% (95% CI: 38%-68%)
Reclassifying vaccination status for those without verified vaccination†	79/537 (15%)	143/512 (28%)	54% (95% CI: 36%-67%)
Including infants born to mothers vaccinated before pregnancy‡	99/549 (18%)	160/525 (30%)	49% (95% CI: 31%-63%)
Including infants born to mothers vaccinated before pregnancy and receiving the second dose 7-14 days before delivery§	100/550 (18%)	163/528 (31%)	50% (95% CI: 32%-64%)

Abbreviations: VE – vaccine effectiveness, CI – confidence intervals

*Vaccinated mothers were verified by SARS-CoV-2 vaccination card, electronic medical record, state surveillance registry, or other verification source. A total of 20 infants (12 case-infants and 8 control-infants) were born to mothers with unverified vaccination statuses and were excluded from this analysis.

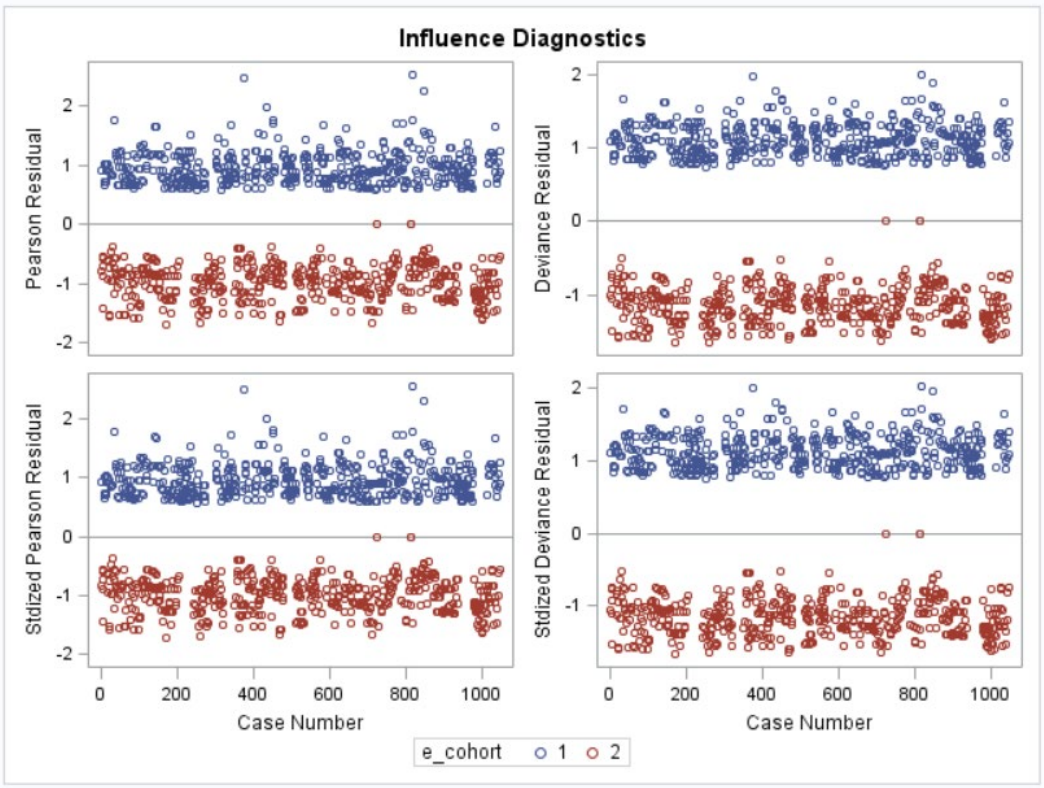
†To control for potential misclassification of the 20 infants born to mothers with unverified vaccination, vaccination status was reclassified. For example, if the mother plausibly self-reported vaccination status without verification, the vaccination status was reclassified as unvaccinated, or if the mother reported unvaccinated without verification, the status was reclassified as vaccinated.

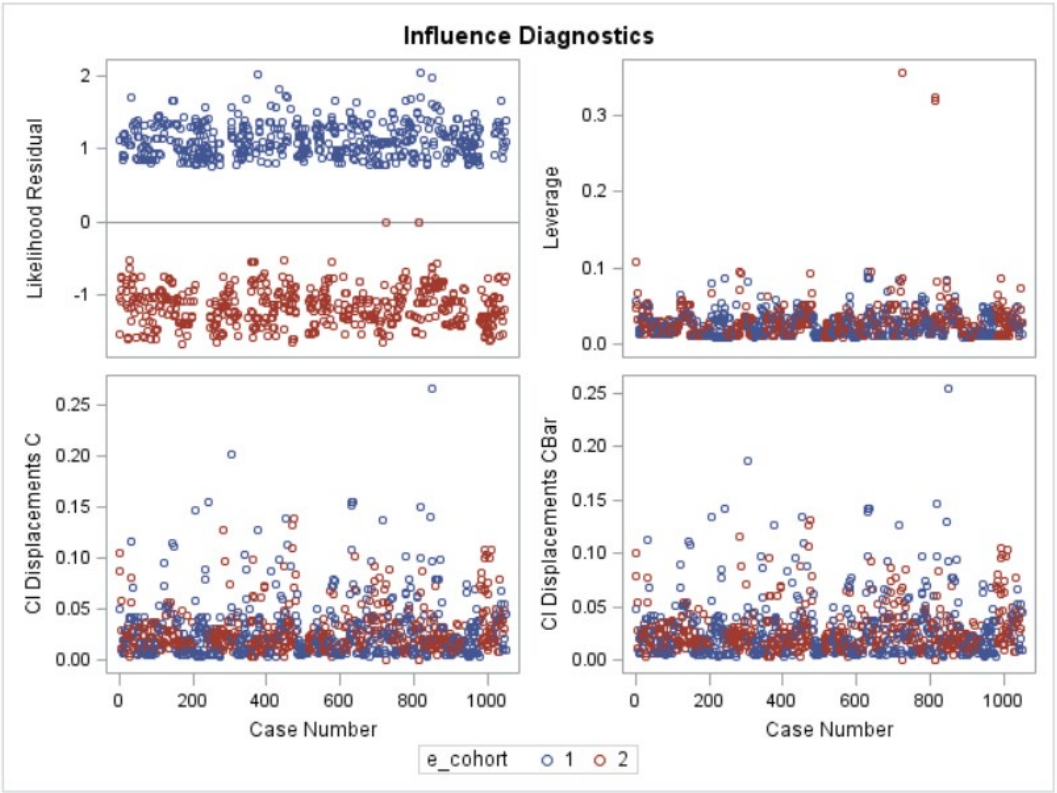
‡A total of 25 infants born to mothers vaccinated before pregnancy were excluded from the primary analysis, but included in this estimate to assess the impact of vaccination prior to pregnancy. The sample size was too small to assess vaccination before pregnancy alone.

§A total of 4 infants were born to mothers vaccinated with the second dose 7-14 days before delivery.

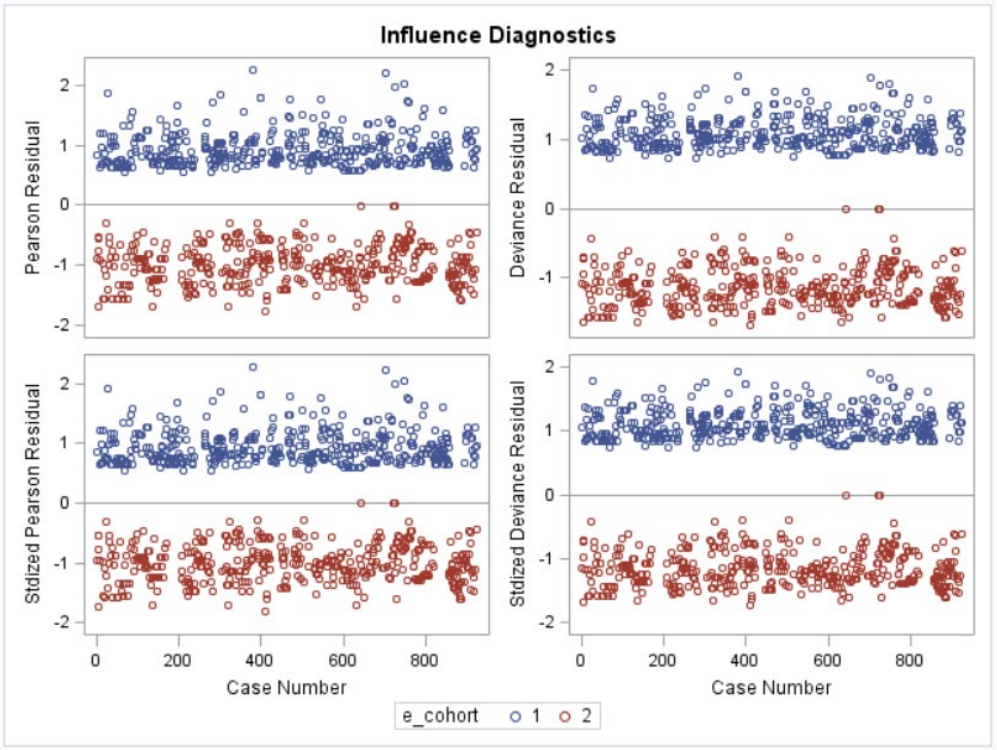
Figure S1. Graph of residuals for fully adjusted vaccine effectiveness models

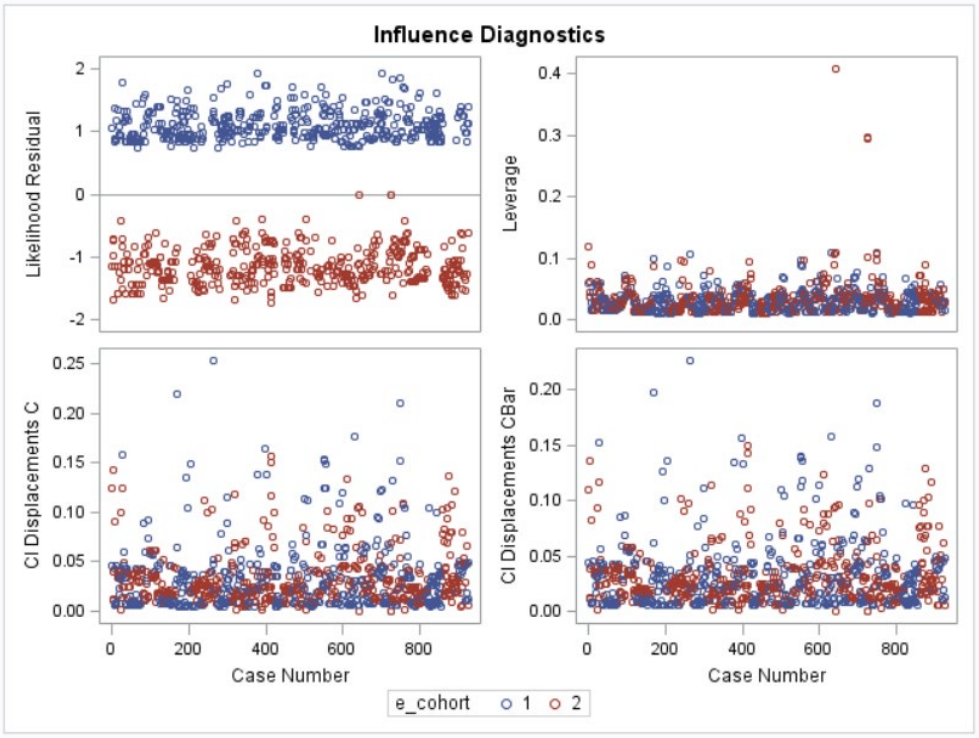
Panel S1A. Residuals for overall vaccine effectiveness model



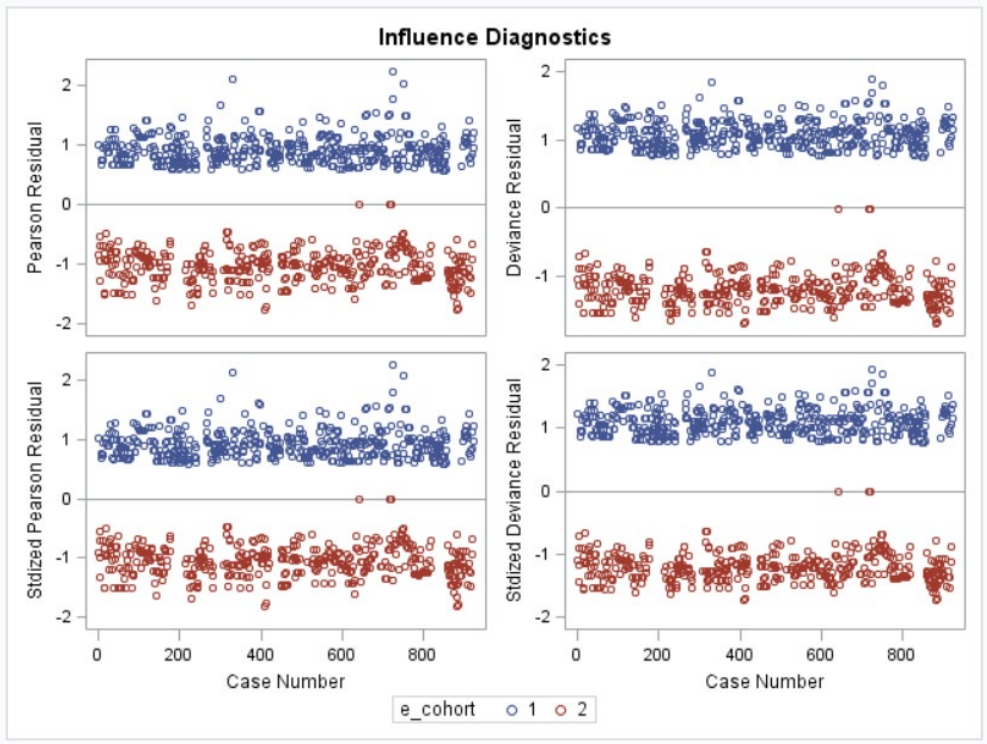


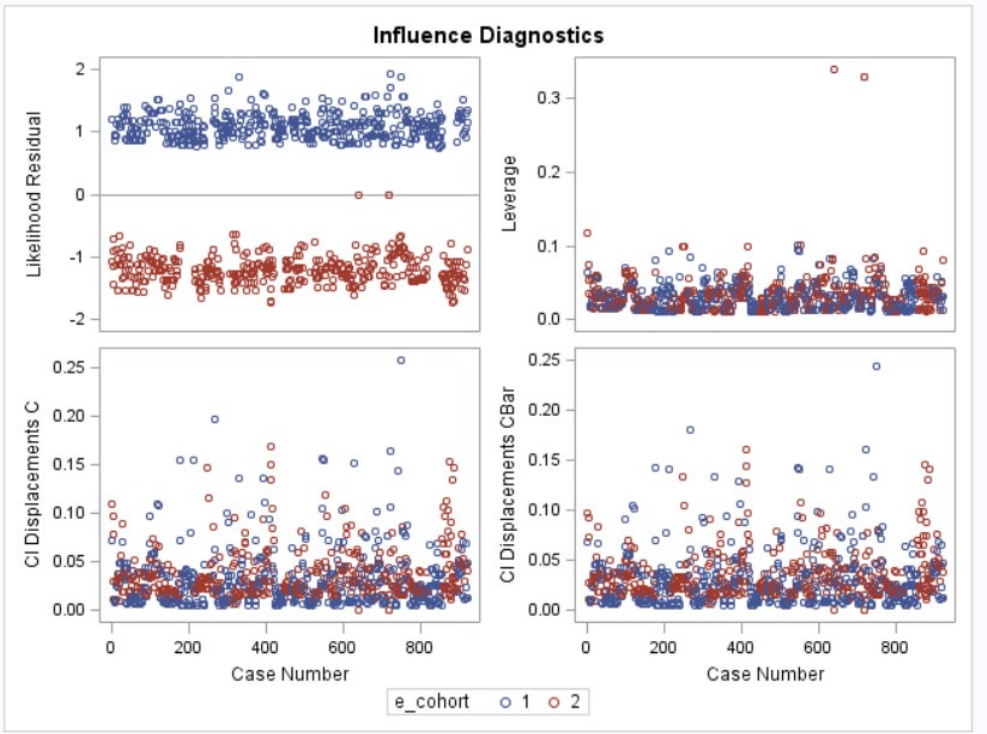
Panel S1B. Residuals for vaccine effectiveness among those vaccinated after 20 weeks of pregnancy model





Panel S1C. Residuals for vaccine effectiveness among those vaccinated 0 to 20 weeks of pregnancy model





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