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Maternal influenza vaccination and associated risk of fetal loss: A claims-based prospective cohort study

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Abstract

Background: Although numerous studies support the safety of influenza vaccination during pregnancy, fewer studies have evaluated the risk of miscarriage or considered the effect of prior immunization.

Methods: Using national de-identified administrative claims data from the Optum Labs Data Warehouse, we conducted a claims-based cohort study of 117,626 pregnancies between January 2009 and December 2018. We identified pandemic A(H1N1)pdm09 and seasonal influenza vaccinations using CPT codes. Fetal loss was defined as miscarriage, medical termination, or stillbirth as identified by ICD-10-CM diagnostic codes. Cox proportional hazard models treating influenza vaccination as a time-varying exposure, weighted for loss-to-follow-up and stratified by baseline probability of vaccination, were used to model the risk of fetal loss by exposure to influenza vaccine.

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CRediT authorship contribution statement

Annette K. Regan: Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Sheena G. Sullivan:** Writing – review & editing, Validation, Methodology. **Onyebuchi A. Arah:** Writing – review & editing, Supervision, Methodology, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126256.

Results: About 31.4 % of the cohort had a record of influenza vaccination; 10.0 % were vaccinated before pregnancy only, 17.8 % during pregnancy only, and 3.6 % before and during pregnancy. The risk of miscarriage was 39 % lower among those vaccinated during pregnancy compared to unvaccinated (adjusted hazard ratio, aHR 0.61; 95 % CI 0.50, 0.74) and was similar for medical termination or stillbirth (HR 0.69; 95 % CI 0.45, 1.03 and aHR 0.99; 95 % CI 0.76, 1.30, respectively). Similar results were observed for women who received the vaccine before and during pregnancy. We observed little to no association between vaccination before pregnancy and risk of miscarriage (HR 0.98; 95 % CI 0.76, 1.26), medical termination (HR 1.02; 95 % CI 0.46, 2.24), or stillbirth (HR 1.14, 95 % CI 0.77, 1.69).

Discussion: Influenza vaccination was not associated with an increased risk of fetal loss. These results support the safety of influenza vaccine administration even when administered before or early during pregnancy.

Keywords

Inactivated influenza vaccine; Miscarriage; Pregnancy; Vaccine safety; Maternal vaccination

1. Background

Pregnant women are a priority group for influenza vaccination. [1–3] More than 44 % of World Health Organization member states currently have a policy recommending influenza vaccine to pregnant women. [4] In the US, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination for women planning pregnancy and women who are pregnant during the influenza season, regardless of their stage of pregnancy. [2] Although several studies have evaluated the safety of the administration of inactivated influenza vaccines during pregnancy, most studies have focused on the safety of vaccines administered in the late second or third trimester. Safety data for vaccines administered early in pregnancy is more limited. [5,6]

As a result, relatively few studies have evaluated the risk of miscarriage, and existing studies have had methodological limitations. A 2023 systematic review of trivalent influenza vaccination during pregnancy identified five studies that examined the occurrence of spontaneous abortion under 20–22 weeks, only two of which were deemed to be at low risk of bias. [7] They concluded that there was very low certainty of evidence in support of an increased risk of spontaneous abortion among vaccinated mothers. Studies published subsequent to this review have confirmed this finding. [8,9]

However, a 2017 case-control study using 2010–12 data from the Vaccine Safety Datalink of 970 matched case-control pregnancies over two consecutive influenza seasons suggested that influenza vaccination was associated with two-fold increased odds of spontaneous abortion. [10] Several issues with the methodology were noted. [11–13] A 2019 update to this study among 1254 matched case-control pregnancies during the 2012/13 to 2014/15 influenza seasons did not replicate the earlier findings and found no association between vaccination and miscarriage. [14] In the intervening period, however, a 2018 survey of US obstetricians indicated that one-in-four were aware of the earlier study, among whom one-in-three said that the study increased their concerns about influenza vaccine safety. [15] Sixteen percent

reported that they either would not recommend vaccination in the first trimester or would consider recommending delaying vaccination until the second trimester. [15]

For any vaccine administered during pregnancy, safety concerns arising from even a single study can severely harm public and provider confidence in immunization programs for pregnant people. Thus, there is a need for additional research conducted in larger samples to permit observation of outcomes raising concern for pregnant people and their healthcare professionals. Moreover, the variable nature of influenza viruses and vaccine components provides a compelling argument for constant monitoring of these vaccines. To this end, we constructed a large, claims-based cohort of 117,626 pregnancies covering a 10-year period to evaluate the safety of influenza vaccines administered during early pregnancy. To address this knowledge gap, this study evaluated the safety of influenza vaccine administered during early pregnancy.

2. Methods

2.1. Study design and data sources

We conducted a de-identified claims-based cohort study using OptumLabs® Data Warehouse (OLDW) claims data for enrollees with a pregnancy record between 1 January 2009 and 31 December 2018. The OLDW includes longitudinal health information on enrollees and patients in the United States. [16]

OptumLabs is an open, collaborative research and innovation center founded in 2013 as a partnership between Optum and Mayo Clinic with its core linked data assets in the OLDW. The database contains de-identified, longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States. The claims data in OLDW include medical and pharmacy claims, laboratory results and enrollment records for commercial insurance enrollees. The electronic health record (EHR)-derived data includes a subset of EHR data that has been normalized and standardized into a single database. This study used de-identified administrative claims and EHR data with linked medical benefit information, a family identifier, and socioeconomic status information from the OLDW. This study involved analysis of pre-existing, de-identified data, and thus, it was exempt from Institutional Review Board approval.

We identified pregnancies using administrative codes indicating a pregnancy detection (i.e., first-trimester ultrasound, Table S1). Pregnancy outcomes and the date of pregnancy end were identified using previously validated *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, ICD-10-CM codes, and Current Procedural Terminology (CPT) codes (Table S1). [17,18] Gestational age codes (i.e., Z3A codes) and information on the pregnancy outcome were used to derive gestational length. [17] We estimated the date of pregnancy start as the date of pregnancy end minus gestational age x 7. We extracted all inpatient and outpatient medical claims records with a service date 365 days before pregnancy start to identify prior vaccination events and pre-existing medical conditions (Fig. S1). We used information from medical claims with a date of service within 294 days following pregnancy start to identify prenatal vaccination and pregnancy

complications (Table S1). Pregnancies where no outcome could be identified were deemed lost to follow-up. Infant records were linked and extracted based on insurance enrollment information for pregnancies included in the cohort.

Influenza vaccination was identified from inpatient and outpatient medical claims information for the 365 days preceding and 294 days following the start of pregnancy using CPT codes (Table S2). Information on maternal age, race/ethnicity, residence, educational attainment, and household income were derived from enrollment data and linked data supplied by an external vendor. Race/ethnicity was defined as Black, Hispanic, Asian, or White. It was assigned by an external vendor based on a structured, rule-based system that combines analysis of first names, middle names, and surnames with geographic reference files. Values were then categorized to comply with data de-identification requirements. Education was estimated based on the median level of education achieved among residents within the census block group. Household income was derived using public and private consumer data for the street address of the enrollee. We identified pre-existing health conditions and pregnancy complications using medical claims records (Table S2). Medical claims information was also used to identify pregnancy complications and outcomes (Table S2).

2.2. Statistical analysis

We evaluated the risk of fetal loss, including miscarriage, medical termination, and stillbirth. We used inverse probability (of vaccination) weighting (IPW) to adjust for loss to follow-up [19] and fine stratification weighting to account for the baseline probability of vaccination. [20] The probability of treatment (vaccination) was estimated using multivariable logistic regression, accounting for maternal age, conception through Assisted Reproductive Technology (ART), pre-existing medical conditions, race/ethnicity, rurality of residence, household income, maternal education, and year and season of conception. Covariate balance was evaluated using standardized mean differences (SMD), with an absolute value >0.1 indicating a concerning difference. Cox proportional hazard models weighted by IPW were used to model the risk of fetal loss by exposure to influenza vaccine before and/or during pregnancy. For those exposed to the influenza vaccine during pregnancy, we treated influenza vaccination as a time-varying exposure in the models. [21]

In sensitivity analyses, we separately evaluated the risks of fetal loss associated with influenza A(H1N1)pdm09 pandemic vaccination (vaccines administered in 2009/10) and seasonal vaccination (vaccines administered after the 2009/10 season). To further restrict the threat of immortal time bias, we conducted additional analyses restricting vaccination status during pregnancy to those receiving the vaccine before 8 weeks of completed gestation.

3. Results

Of the 1,312,076 records with a CPT code indicating early pregnancy identified between January 2009 and December 2018, 127,272 met continuous enrolment criteria; 7215 (5.7 %) pregnancies were lost to follow-up, and 1719 (1.3 %) had a gestational length inconsistent with their identified pregnancy outcome (Fig. S2). Following propensity score estimation, of

the 118,338 pregnancies available for analysis, we excluded data on 712 pregnancies with extreme values; 117,626 pregnancies were included in the final analysis.

A total of 37,954 (31.4 %) women had a record of receiving inactivated influenza vaccine: 11,746 (10.0 %) before pregnancy, 20,917 (17.8 %) during pregnancy, and 4291 (3.6 %) before and during pregnancy (Table 1); 80,672 (68.6 %) women had no record of influenza vaccination. Among those vaccinated during pregnancy, 6511 (25.8 %) received the vaccine during the first trimester of pregnancy, 10,240 (40.6 %) during the second trimester, and 8457 (33.5 %) during the third trimester. Unvaccinated individuals were more commonly younger than 20 years old, non-Hispanic Black or Hispanic, residential in a non-metropolitan area, completing lower educational attainment, and had lower household income. The prevalence of vaccination before or during pregnancy increased from 30.8 % in 2009 to 38.5 % in 2018. Those who became pregnant in Summer were most commonly vaccinated during pregnancy, and those who became pregnant in winter were most commonly vaccinated before pregnancy. ART use was more frequently recorded among those vaccinated before pregnancy than those unvaccinated. Examination of standardized mean differences (SMD) for covariates showed good balance (<0.05 SMD) in the weighted sample (Fig. S3).

The mean gestational length for those vaccinated before pregnancy was 33.1 weeks (SD 9.8); for those vaccinated during pregnancy, 38.0 weeks (SD 3.6); for those vaccinated before and during pregnancy, it was 38.1 (SD 3.3), and for those unvaccinated was 32.9 (SD 10.7) (Fig. 1). Median gestational length was similar based on vaccination status (37–38 weeks). In total, 12,183 (10.4 %) of the cohort experienced a miscarriage, 2537 (2.1 %) a medical termination, and 974 (0.8 %) a stillbirth. The risk of fetal loss was 29 % lower for those vaccinated during pregnancy compared to those unvaccinated (weighted HR 0.71; 95 % CI 0.62, 0.82) (Fig. 2). This was mostly attributed to a decreased risk of miscarriage observed among those vaccinated during pregnancy (weighted HR 0.61; 95 % CI 0.50, 0.74) (Table 2). We observed no differences in the risk of medical termination (weighted HR 0.69; 95 % CI 0.45, 1.03) or stillbirth (weighted HR 0.99; 95 % CI 0.76, 1.30). Vaccination before becoming pregnant was also not associated with the risk of miscarriage (weighted HR 0.98; 95 % CI 0.76, 1.26), medical termination (weighted HR 1.02; 95 % CI 0.46, 2.24), or stillbirth (weighted HR 1.14; 95 % CI 0.66, 1.69).

We observed no difference in fetal outcomes for A(H1N1)pdm09 pandemic influenza vaccination (Fig. S4). The risk of fetal loss was similar for pregnancies exposed to A(H1N1)pdm09 pandemic influenza vaccine and unvaccinated pregnancies (weighted HR 0.92; 95 % CI 0.71, 1.20) (Table S4). However, we observed a 46 % reduction in the risk of miscarriage (weighted HR 0.54; 95 % CI 0.44, 0.66) associated with A (H1N1)pdm09 influenza vaccination during pregnancy.

When we restricted our analysis to those vaccinated during the first 8 weeks of pregnancy (Fig. S5), measures of association between fetal loss and prenatal vaccination were stronger (weighted HR 0.26; 95 % CI 0.21, 0.33) which was mostly attributed to lower incidence of miscarriage (weighted HR 0.24; 95 % CI 0.18, 0.30), medical termination (weighted HR

0.25, 95 % CI 0.14, 0.46) and a non-significant reduction in stillbirth (weighted HR 0.61; 95 % CI 0.36, 1.04).

4. Discussion

Results from this large, national cohort study indicate that administration of an inactivated influenza vaccine during the year before becoming pregnant or during early pregnancy was not associated with an increased risk of miscarriage, medical termination, or stillbirth. While previous clinical trials in Bangladesh, Mali, Nepal, and South Africa have supported the safety of influenza vaccination regarding gestational length, birth weight, and fetal growth, [22] due to eligibility requirements, these trials included only those vaccinated during the second or third trimester and live births, and these trials cannot be used to evaluate the risk of early pregnancy loss or stillbirth. Results from this study, where pregnancies were “recruited” at the date of medical confirmation of the pregnancy and followed through pregnancy end, add to the growing body of evidence supporting the safety of maternal influenza immunization, regardless of trimester. [23–26] These findings support the continuation of existing immunization policies recommending vaccination during any stage of pregnancy. [2]

Our finding that exposure in early pregnancy did not increase the risk of adverse events in early pregnancy is an important contribution. Although the influenza vaccine is widely recommended during pregnancy, [4] some countries continue to recommend vaccination only in the second or third trimester. [27,28] The more limited evidence supporting the safety of vaccination given early in pregnancy has been outlined as one reason for limiting recommendations in these countries to second and third trimesters. [28,29] Of the previous research published evaluating miscarriage after influenza vaccination, at least eight have suggested no association, [8,14,30–35] three suggest a protective association, [34,36,37] and one indicated a harmful association. [10] To our knowledge, six of these studies were prospectively conducted, [8,32–35,37] where pregnancies were not selected into the case-control or cohort study based on there having been a pregnancy outcome to observe. Results from prior prospectively conducted studies align with our findings, indicating no association with vaccination before or during early pregnancy and miscarriage. One prior prospectively cohort study of 1253 healthy nulliparous pregnant women reported a non-significant 58 % reduction in the risk of miscarriage associated with influenza vaccination during pregnancy, [34] and this estimate is similar to the effect estimate observed in our study.

Our results, and the results of several prior studies, indicate a potential protective association between vaccination early in pregnancy and miscarriage. However, we recommend interpreting these findings with caution. First, while medical claims information to estimate gestational length has been shown to be valid, [38–41] they are likely to retain some measurement error. This is especially problematic for pregnancies ending before 8 weeks of gestation, where medical contact may be sparse and ICD and CPT codes are unable to accurately estimate gestational age. [38] Because our follow-up period began at first medical encounter indicating pregnancy, our cohort could not have captured early losses (e.g., before 6–8 weeks) or losses where no medical contact occurred resulting in some left truncation in the cohort. This could introduce selection bias in effect estimates. Second, although we

implemented several techniques to address potential confounding and other biases in our analysis, this study is observational, and we cannot entirely exclude the possible influence of residual confounding in our results.

Our study had several strengths and additional limitations to consider. We could draw from a rich, extensive national medical information database for mothers and their newborns. However, as with most studies relying on administrative databases, it is possible that some vaccination events were not recorded. This may have resulted in some exposure misclassification. Furthermore, these data are restricted to commercially insured individuals. Although we do not expect vaccine effects to differ for uninsured or publicly insured individuals, these results may not necessarily generalize to the general population of pregnancies. Finally, socioeconomic indicators, including educational attainment and household income reflect area-level measures and may not align with individual-level attributes. Furthermore, race and ethnicity were imputed using proprietary algorithms. As a result, we anticipate some measurement error in covariates could have occurred in the study. Despite this, examination of vaccine patterns by race/ethnicity and other socioeconomic indicators align well with previously reported data, [42,43] which would support the validity of our findings.

5. Conclusions

This register-based longitudinal cohort study provides additional evidence supporting the safety of influenza vaccines administered before or during pregnancy—consistent with current Advisory Committee on Immunization Practice recommendations for pregnant women. [2] This information can be used to support the confidence of policymakers and healthcare providers in recommending and providing influenza vaccines during any stage of pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Source

Access to the data was provided under a funded research agreement between University of California Los Angeles and OptumLabs. The funder had no role in the design of the study, interpretation of results or the decision to publish.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Onyebuchi A Arah reports financial support was provided by Optum Labs Inc. Sheena G Sullivan reports a relationship with Seqirus Australia Pty Ltd. that includes: consulting or advisory. Sheena G Sullivan reports a relationship with Moderna Inc. that includes: consulting or advisory. Sheena G Sullivan reports a relationship with Novavax Inc. that includes: consulting or advisory. Sheena G Sullivan reports a relationship with Pfizer Inc. that includes: consulting or advisory. Annette K Regan reports a relationship with Moderna Inc. that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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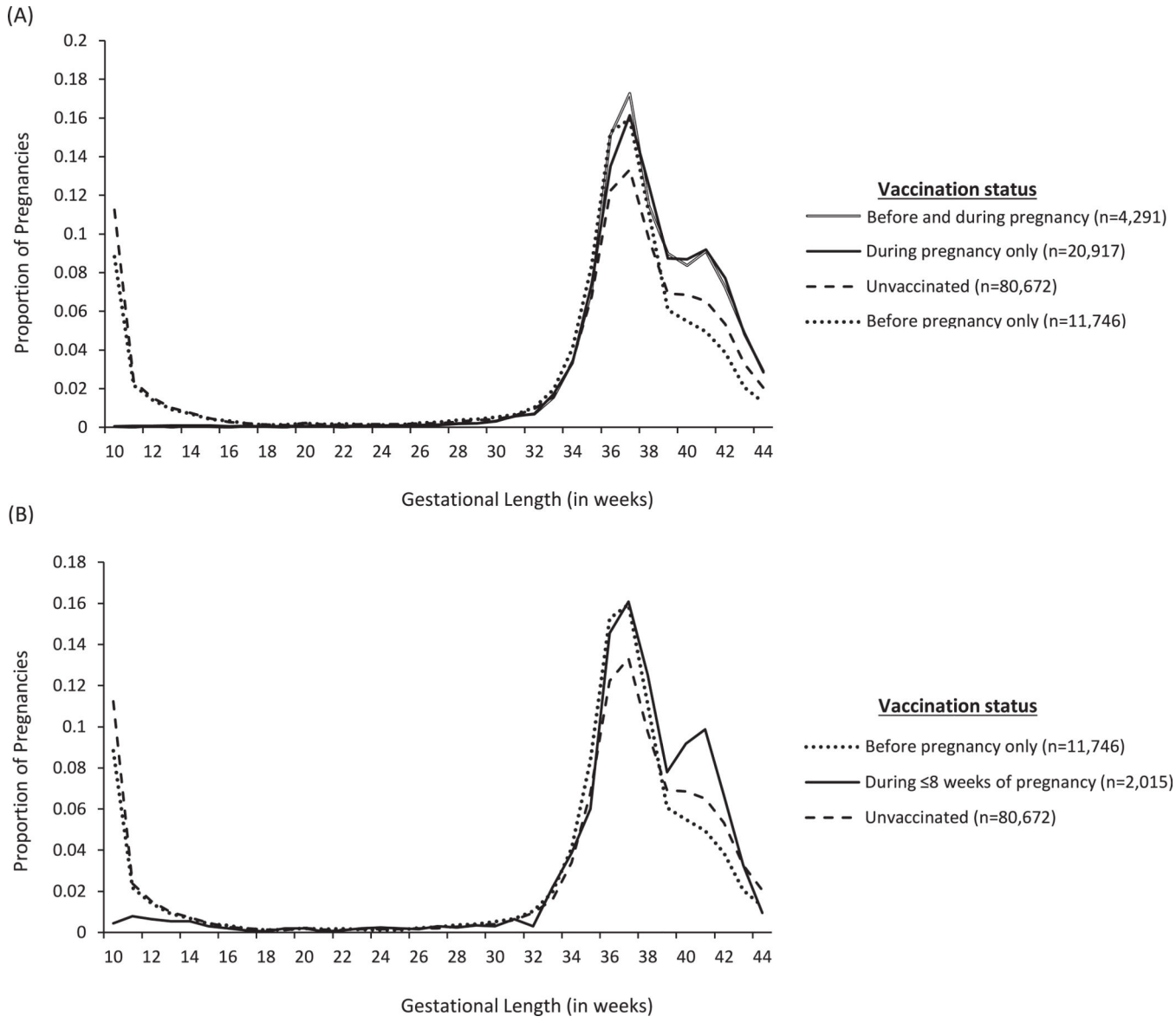

Fig. 1.

Distribution of the gestational length of pregnancies, stratified by maternal vaccination status. Panel A indicates the distribution of gestational length for all pregnancies identified between 2009 and 2018. Panel B demonstrates that the distribution of gestational length was restricted to those vaccinated before week 8 of pregnancy or unvaccinated during pregnancy between 2009 and 2018.

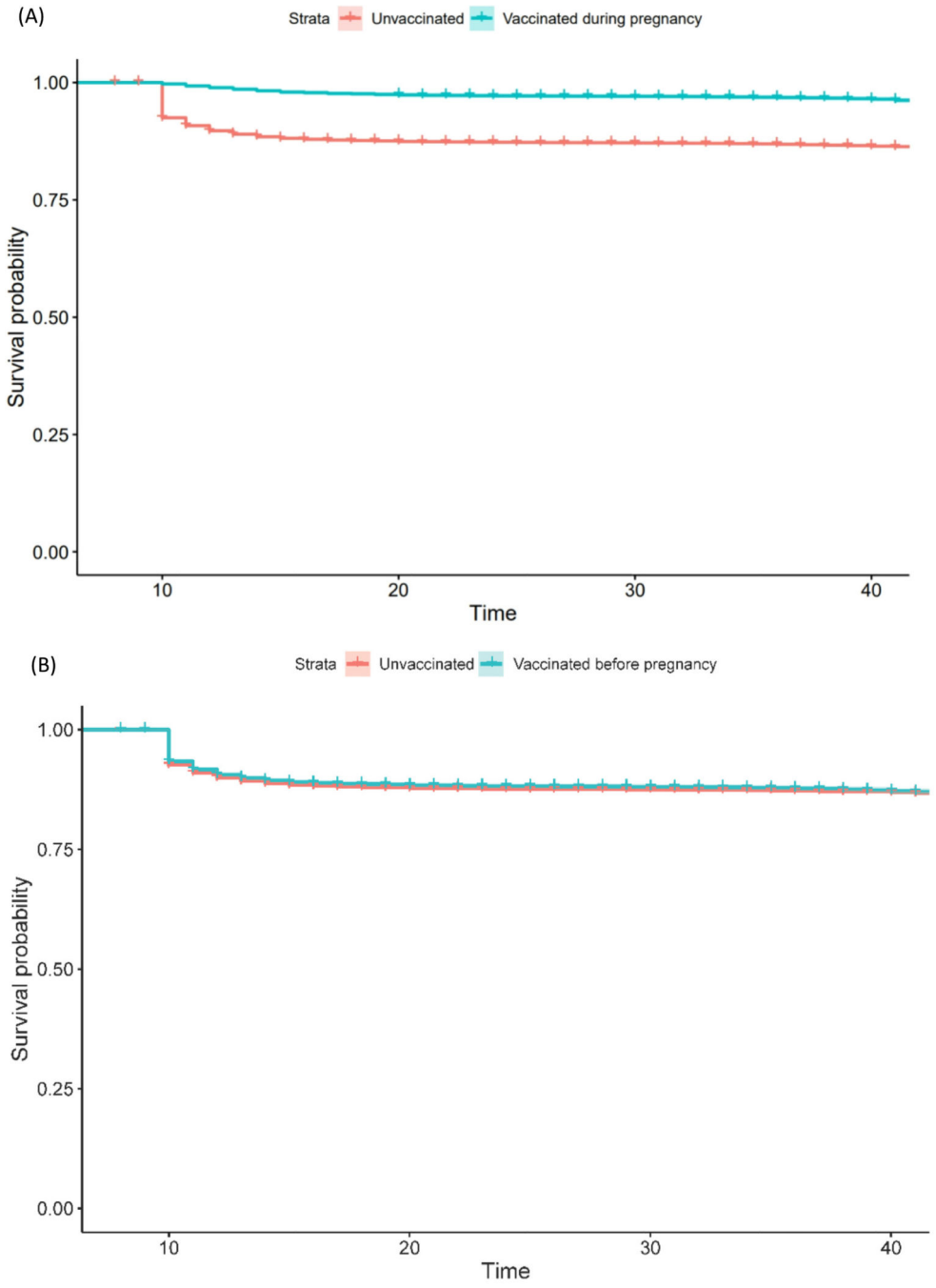

Fig. 2.

Survival curve indicating cumulative survival from week 6 of pregnancy to delivery, stratified by maternal vaccination status. Panel A indicates the probability of survival among those vaccinated during pregnancy compared to unvaccinated pregnancies. Panel B indicates the probability of survival among those vaccinated prior to pregnancy compared to unvaccinated pregnancies.

Table 1

Characteristics of participants whose pregnancies ended between January 2009 and December 2018, grouped by their receipt of influenza vaccination before or during pregnancy (*n* = 117,626).

Characteristic	Vaccinated before pregnancy only (n = 11,746)	Vaccinated during pregnancy only (*n* = 20,917)	Vaccinated before and during pregnancy (*n* = 4291)	Unvaccinated before and during pregnancy (*n* = 80,672)
	n (%)	n (%)	n (%)	n (%)
Age group (years)				
14-19y	262 (2.2)	596 (2.9)	82 (1.9)	2930 (3.6)
20-24y	689 (5.9)	2079 (9.9)	254 (5.9)	9966 (12.3)
25-29y	1881 (16.0)	4112 (19.7)	677 (15.8)	15,767 (19.5)
30-34y	4701 (40.0)	7994 (38.2)	1714 (39.9)	27,162 (33.7)
35-39y	3270 (27.8)	4942 (23.6)	1279 (29.8)	18,681 (23.2)
40-49y	943 (8.0)	1194 (5.7)	285 (6.6)	6166 (7.6)
Race/ethnicity				
White, NH	7781 (66.2)	13,491 (64.5)	2845 (66.3)	49,542 (61.4)
Black, NH	1246 (10.6)	2343 (11.2)	429 (10.0)	10,411 (12.9)
Hispanic	1632 (13.9)	3154 (15.1)	595 (13.9)	13,918 (17.3)
Asian	1087 (9.3)	1929 (9.2)	422 (9.8)	6801 (8.4)
Residence				
Metropolitan	11,168 (95.1)	19,606 (93.7)	4067 (94.8)	74,558 (92.4)
Micropolitan	286 (2.4)	714 (3.4)	139 (3.2)	3595 (4.5)
Small town	185 (1.6)	382 (1.8)	52 (1.2)	1681 (2.1)
Rural	107 (0.9)	215 (1.0)	33 (0.8)	838 (1.0)
Income category				
<$40,000	1772 (15.1)	3396 (16.2)	667 (15.5)	14,529 (18.0)
$40-74,000	2624 (22.3)	4810 (23.0)	925 (21.5)	19,611 (24.3)
$75-124,000	2149 (18.3)	3870 (18.5)	769 (17.9)	14,648 (18.1)
$125-199,000	2669 (22.7)	4569 (21.8)	1024 (23.9)	16,839 (20.9)
≥$200,000	2532 (21.6)	4272 (20.4)	906 (21.1)	15,045 (19.6)
Education level				
High school degree or less	231 (2.0)	422 (2.0)	84 (1.9)	1656 (2.1)

Characteristic	Vaccinated before pregnancy only (n = 11,746)	Vaccinated during pregnancy only (*n* = 20,917)	Vaccinated before and during pregnancy (*n* = 4291)	Unvaccinated before and during pregnancy (*n* = 80,672)
Some college	2120 (18.0)	4294 (20.5)	775 (18.1)	19,193 (23.8)
College degree	5656 (48.1)	10,310 (49.3)	2017 (47.0)	39,771 (49.3)
Graduate degree	3739 (31.8)	5891 (28.2)	1415 (33.0)	20,052 (24.9)
Year of pregnancy				
2009	1080 (9.2)	2847 (13.6)	493 (11.5)	9922 (12.3)
2010	1469 (12.5)	2077 (9.9)	492 (11.5)	9926 (12.3)
2011	1540 (13.1)	2264 (10.8)	468 (10.9)	10,768 (13.3)
2012	1244 (10.6)	2234 (10.7)	420 (9.8)	10,102 (12.5)
2013	1183 (10.1)	1871 (8.9)	389 (9.1)	8045 (10.0)
2014	1220 (10.4)	2120 (10.1)	395 (9.2)	7568 (9.4)
2015	985 (8.4)	2038 (9.7)	360 (8.4)	6853 (8.5)
2016	947 (8.1)	1662 (7.9)	346 (8.1)	5843 (7.2)
2017	976 (8.3)	1835 (8.8)	428 (10.0)	5950 (7.4)
2018	1102 (9.4)	1969 (9.4)	500 (11.7)	5695 (7.1)
Season of pregnancy start				
Spring	2193 (18.7)	5955 (28.5)	1541 (35.9)	20,341 (25.2)
Summer	1254 (10.7)	7676 (36.7)	1694 (39.5)	16,001 (19.8)
Fall	3174 (27.0)	5447 (26.0)	872 (20.3)	16,390 (20.3)
Winter	5125 (43.6)	1839 (8.8)	184 (4.3)	27,940 (34.6)
Pre-existing medical condition				
Any medical condition	2529 (21.5)	3528 (16.9)	870 (20.3)	14,386 (17.8)
Asthma	1281 (10.9)	1710 (8.2)	448 (10.4)	6460 (8.0)
Coronary heart disease	113 (1.0)	169 (0.8)	34 (0.8)	727 (0.9)
Diabetes	412 (3.5)	470 (2.2)	123 (2.9)	2311 (2.9)
Hypertension	908 (7.7)	1297 (6.2)	302 (7.0)	5630 (7.0)
Metabolic disorder	105 (0.9)	145 (0.7)	30 (0.7)	679 (0.8)
No medical condition	9217 (78.5)	17,389 (83.1)	3421 (79.7)	66,286 (82.2)
History of ART use	708 (6.0)	1120 (5.3)	257 (6.0)	3391 (4.2)
Pregnancy complications				
Any complication	5376 (45.8)	9155 (43.8)	1837 (42.8)	39,521 (49.0)

Characteristic	Vaccinated before pregnancy only (n = 11,746)	Vaccinated during pregnancy only (*n* = 20,917)	Vaccinated before and during pregnancy (*n* = 4291)	Unvaccinated before and during pregnancy (*n* = 80,672)
Preeclampsia	1333 (11.3)	2479 (11.9)	508 (11.8)	8940 (11.1)
Gestational diabetes	1366 (11.6)	2494 (11.9)	503 (11.7)	9037 (11.2)
Bleeding condition	1276 (10.9)	2283 (10.9)	455 (10.6)	8888 (11.0)
Hemorrhage during pregnancy	2143 (18.2)	3040 (14.5)	663 (15.5)	18,439 (22.9)
Thyroid condition	645 (5.5)	1126 (5.4)	263 (6.1)	3710 (4.6)
Hyperemesis	569 (4.8)	1297 (6.2)	232 (5.4)	5079 (6.3)
No complication	6370 (54.2)	11,762 (56.2)	2454 (57.2)	41,151 (51.0)

ART, assisted reproductive technology.

Table 2

Unweighted and weighted hazard ratios for the risk of fetal loss, stratified by maternal vaccination status.

Fetal outcome	Vaccinated before pregnancy (*n* = 25,208)	Vaccinated during pregnancy (n = 20,917)	Vaccinated before and during pregnancy (n = 4291)	Unvaccinated before and during pregnancy (n = 80,672)
Any fetal loss				
% (95 % CI)	14.9 (14.2, 15.5)	1.3 (1.2, 1.5)	0.9 (0.7, 1.2)	19.0 (18.7, 19.3)
Unweighted HR (95 % CI)	1.14 (1.12, 1.16)	0.45 (0.40, 0.51)	0.43 (0.31, 0.59)	Reference
Weighted HR* (95 % CI)	1.07 (0.98, 1.17)	0.71 (0.62, 0.82)	0.62 (0.45, 0.86)	Reference
Miscarriage				
% (95 % CI)	5.5 (5.3, 5.8)	0.5 (0.4, 0.6)	0.3 (0.2, 0.5)	13.2 (13.0, 13.5)
Unweighted HR (95 % CI)	0.89 (0.84, 0.94)	0.31 (0.25, 0.37)	0.28 (0.16, 0.49)	Reference
Weighted HR* (95 % CI)	0.98 (0.76, 1.26)	0.61 (0.50, 0.74)	0.56, (0.32, 0.99)	Reference
Medical termination				
% (95 % CI)	0.9 (0.8, 1.0)	0.1 (0.0, 0.2)	–	2.8 (2.7, 2.9)
Unweighted HR (95 % CI)	0.68 (0.60, 0.78)	0.30 (0.20, 0.45)	–	Reference
Weighted HR* (95 % CI)	1.02 (0.46, 2.24)	0.69 (0.45, 1.03)	–	Reference
Stillbirth				
% (95 % CI)	0.5 (0.4, 0.6)	0.7 (0.6, 0.8)	0.6 (0.4, 0.9)	0.8 (0.7, 0.9)
Unweighted HR (95 % CI)	1.23 (1.01, 1.50)	0.89 (0.74, 1.08)	0.78 (0.53, 1.17)	Reference
Weighted HR* (95 % CI)	1.14 (0.77, 1.69)	0.99 (0.76, 1.30)	0.86 (0.56, 1.33)	Reference

HR, hazard ratio; CI, confidence interval.

*Cox proportional hazard models weighted by the inverse probability of treatment (vaccination). Factors contributing to inverse probability treatment weights included: maternal age, residence, race/ethnicity, household income, educational attainment, year and season of pregnancy, pre-existing medical conditions, pregnancy complications, and use of assisted reproductive technology.