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Influenza vaccination during early pregnancy and risk of major birth defects, US Birth Defects Study To Evaluate Pregnancy exposureS, 2014–2019

Veronica Malange [a,1], Tasnim Mohaissen [a,b,1], Kristin M. Conway [c], Anthony Rhoads [c], Joan K. Morris [d], Elizabeth C. Ailes [e], Paula L. Hedley [a,c], Janet D. Cragan [e], Eirini Nestoridi [f], Eleni A. Papadopoulos [g], Thomas D. Scholz [h], Alpa Sidhu [i], Michael Christiansen [a,c,j], Paul A. Romitti [a,c,*], the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)

[a] Department for Congenital Disorders, Danish National Biobank and Biomarkers, Statens Serum Institut, Copenhagen, Denmark
[b] Jagiellonian University, Jagiellonian Center for Experimental Therapeutics (JCET), Krakow, Poland
[c] Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa, USA
[d] School of Health & Medical Sciences, City St George's University of London, London, UK
[e] Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA
[f] Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, MA, USA
[g] Birth Defects Registry, New York State Department of Health, Albany, New York, USA
[h] Division of Pediatric Cardiology, The Stead Family Department of Pediatrics, University of Iowa Health Care, Iowa City, Iowa, USA
[i] Division of Medical Genetics and Genomics, The Stead Family Department of Pediatrics, University of Iowa Health Care, Iowa City, Iowa, USA
[j] Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Purpose: Studies of influenza vaccination during pregnancy and major birth defects generally provide reassuring findings. To maintain public confidence, it is important to continue evaluating the safety of maternal vaccination using well characterized, population-based data. This study extended previous research to examine associations between maternal influenza vaccination and selected birth defects using data from the Birth Defects Study To Evaluate Pregnancy exposureS, a US, multisite case-control study.

Methods: Mothers of case children (diagnosed with a birth defect) and control children (without a birth defect diagnosis) were identified from population-based birth defect surveillance programs and recruited to complete a telephone interview. Data from 2675 case and 1575 control mothers (participants) with deliveries during 2014–2019 were analyzed. Influenza vaccination exposure during the critical exposure period (one month before pregnancy through the first pregnancy month [B1P1] for spina bifida or through the third pregnancy month [B1P3] for other selected birth defects) was assessed controlling for several participant covariates. Logistic regression with propensity score adjustment was used to estimate adjusted odds ratios (aORs) and 95 % confidence intervals (CIs). Several secondary analyses were conducted. A probabilistic bias analysis examined the effect of exposure misclassification.

Results: The aOR observed between B1P1 influenza vaccination exposure and spina bifida was 0.9 (95 % CI: 0.4–2.0). The aORs for B1P3 exposure and other selected birth defects examined ranged from 0.4 to 1.3, with 95 % CIs including the null except those for cleft lip ± cleft palate (aOR: 0.6; 95 % CI: 0.4–0.9) and gastroschisis (aOR: 0.4; 95 % CI: 0.2–0.7). Results from secondary analyses were similar to the primary analyses, and those from probabilistic bias analysis were similar to respective primary and secondary analyses.

Conclusion: Findings showed no statistically significant positive associations between influenza vaccination and the selected birth defects, supporting public health efforts to promote optimal vaccination coverage among pregnant women.

* Corresponding author at: University of Iowa, College of Public Health, Department of Epidemiology, 145 N Riverside Dr, S416 CPHB, Iowa City, IA 52242, USA
E-mail address: paul-romitti@uiowa.edu (P.A. Romitti).
[1] Veronica Malange and Tasnim Mohaissen contributed equally to this work.

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1. Introduction

Influenza infections can pose a significant threat to pregnant women and their newborns, including increased risk of maternal hospitalization and death and potential adverse birth outcomes such as premature birth, low birth weight, stillbirth, and birth defects [1,2]. Consequently, the World Health Organization, United States (US) Advisory Committee on Immunization Practices (ACIP), and the American College of Obstetricians and Gynecologists (ACOG) recommend influenza vaccination for pregnant women in any trimester [3–5]. Vaccination against influenza during pregnancy protects maternal and fetal health. It directly protects the mother from influenza infection, which in turn, protects the fetus from harmful consequences associated with maternal illness [2,6].

Even with global and national recommendations for influenza vaccination during pregnancy, vaccine coverage remains around 60 % [7–9]. Concern regarding the potential risk to fetal safety is one of the most recognized barriers to maternal vaccination [10,11]. Our analyses of 2006–2011 data from the US population-based, National Birth Defects Prevention Study (NBDPS) examining risk for over 30 major birth defects supported the safety of maternal influenza vaccination [12,13]. Influenza vaccine components may change from one year to another, requiring continued evaluation of the safety of seasonal vaccination. Of the 11 published studies identified using data since 2011 [2,14–23], four were summaries of post market surveillance reports of frequencies of several adverse infant events, including birth defects [18–20,23]. Of the remaining seven studies [2,14–17,21,22], none used population-based data to examine risk for individual major birth defects.

To maintain public confidence in vaccine safety and optimize maternal and fetal health outcomes, it is important to continue to evaluate the safety of maternal vaccinations using well-characterized, population-based datasets encompassing children with and without major birth defects. Building upon our prior publications [11,12], we used data for 2014–2019 deliveries enrolled in the US Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), a population-based, case-control study, to investigate potential associations between influenza vaccine exposure during the respective critical exposure period and selected individual birth defects.

2. Methods

2.1. Study population

BD-STEPS, an ongoing multi-site case-control study funded by the US Centers for Disease Control and Prevention (CDC), aims to investigate risk factors for selected major structural birth defects [24]. Data included in the current analyses were for delivery years 2014–2019 to examine influenza vaccine uptake and risk prior to the COVID-19 pandemic. For the delivery years 2014–2019, BD-STEPS eligible birth defects included central nervous system (spina bifida), ear (anotia/microtia), eye (anopthalmos/micropthalmos), heart (coarctation of the aorta, dextro-transposition of the great arteries, hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, tricuspid atresia with or without aortic malposition, truncus arteriosus), orofacial clefts (cleft lip ± cleft palate, cleft palate alone), gastrointestinal (esophageal atresia), limb reduction (transverse limb deficiency), and musculoskeletal (diaphragmatic hernia, gastroschisis) defects diagnosed in live births, stillbirths (20 weeks or greater gestation), and elective terminations (any gestational age). Case children with one or more BD-STEPS eligible defects and a random sample of live-born control children without a major birth defect diagnosis were identified by birth defect surveillance programs statewide in Arkansas and Iowa, and in selected counties in California, Georgia, Massachusetts, New York, and North Carolina. Because of the number of defects included in BD-STEPS, each BD-STEPS site attempted to recruit the number of controls needed per birth year to provide, at a minimum, a 1:1 case:control ratio for each defect.

Data abstracted from medical records for each child diagnosed with a birth defect were reviewed by a clinical geneticist at each birth defect surveillance program to identify those with nonsyndromic presentations of each eligible defect; case children with suspected or confirmed chromosomal or single gene disorders were excluded. A clinical geneticist re-reviewed data abstracted for all children diagnosed with an eligible defect (e.g. spina bifida) to classify the children as presenting with an isolated (single major defect, with or without minor defects or one or more developmentally related major defects), multiple (two or more major unrelated defects in different organ systems), or complex (a pattern of embryologically related defects) phenotype. A pediatric cardiologist re-reviewed data abstracted for all children diagnosed with a congenital heart defect.

2.2. Data collection

Data collection procedures for BD-STEPS were approved by the CDC Institutional Review Board. Mothers were eligible for BD-STEPS if they spoke English or Spanish and had custody of their child and were not incarcerated at the time of recruitment. Mothers who provided verbal informed consent completed a computer-assisted telephone interview within an average of 8.6 months following their child's estimated date of delivery (EDD). The interview included questions on chronic diseases, infections, and medications. Interviews were not conducted for pregnancies with an EDD on or after September 1, 2015 and date of delivery before July 1, 2016.

Participants were asked whether they received a vaccine during the month before pregnancy (B1) through the third pregnancy month (P3) (Question T154; relevant questions are listed in Supplemental Table 1). If they responded in the affirmative, they were asked which vaccines they received (Question T156) and when they received the vaccines (Question T157). Participants were asked to provide the full date (month, day, year) for each vaccine reported; if they did not recall the full date, they were asked to provide a partial date, which could consist of either the pregnancy month or the calendar month and (if the participant recalled) whether the date occurred at the beginning, middle, or end of the reported calendar month.

Reports of influenza vaccines were examined during the relevant embryological periods for organ development, including the month before pregnancy to capture exposures that may continue into early pregnancy. With the development of the neural tube occurring within the first month of pregnancy, we defined the critical exposure period for spina bifida as B1 through the first pregnancy month (P1). For the remainder of eligible BD-STEPS birth defects whose development extended beyond the first month, we defined the critical exposure period as B1P3. For the primary analysis, participants who reported full dates were defined as exposed if they reported receiving an influenza vaccine during the critical exposure period and unexposed if they reported not receiving an influenza vaccine or receiving an influenza vaccine outside the critical exposure period. Participants who reported partial dates (e.g. month and year) were defined as exposed if the entire time period (e.g. month) to which the partial date applied was within the critical exposure period and unexposed if the entire time period (e.g. month) was outside of the critical exposure period. Reports of the "beginning," "middle," or "end" of a calendar month were approximated as the 1st through the 10th, the 11th through the 20th, and the 21st through the end of the month, respectively.

2.3. Analytical sample

Overall, 2675 case participants and 1575 control participants with deliveries during 2014–2019 completed the BD-STEPS interview (Figs. 1 and 2). Of these 2675 case participants, 218 had children diagnosed with spina bifida and 2461 had children diagnosed with birth defects other than spina bifida; 4 of the 2675 children were diagnosed with spina bifida and one or more additional BD-STEPS-eligible defects.

Participants who reported a type 1 or type 2 diabetes diagnosis prior to the index pregnancy or who did not report complete information regarding diabetes were excluded. For analysis of spina bifida, participants who reported use of folate antagonist medications (carbamazepine, cholestyramine resin, methotrexate, oxcarbazepine, sulfasalazine, triamterene, trimethoprim, phenytoin, or phenobarbital) during B1P1 or with unreported timing of use were excluded based on previous findings of associations of these medications with neural tube defects [25]. Participants who did not complete the interview through the questions asking about vaccines, refused to answer the questions about vaccines, or did not recall whether they received a vaccine or which vaccine they received were excluded. Participants who did not report when they received an influenza vaccine with respect to the critical exposure period (e.g., received influenza vaccine on an unreported day of October 2016 with a critical exposure period of October 15, 2016-Febrary 11, 2017) were also excluded from the primary analysis. Any birth defects for which there were fewer than 5 exposed cases (anopthalmos/micropthalmos, pulmonary atresia, tricuspid atresia with or without aortic malposition, truncus arteriosus) were excluded from analysis. For the primary analysis, the final analytical sample for spina bifida included 195 cases (8 exposed, 187 unexposed) and 1333 controls (60 exposed, 1273 unexposed), and the final analytical sample for the 12 eligible birth

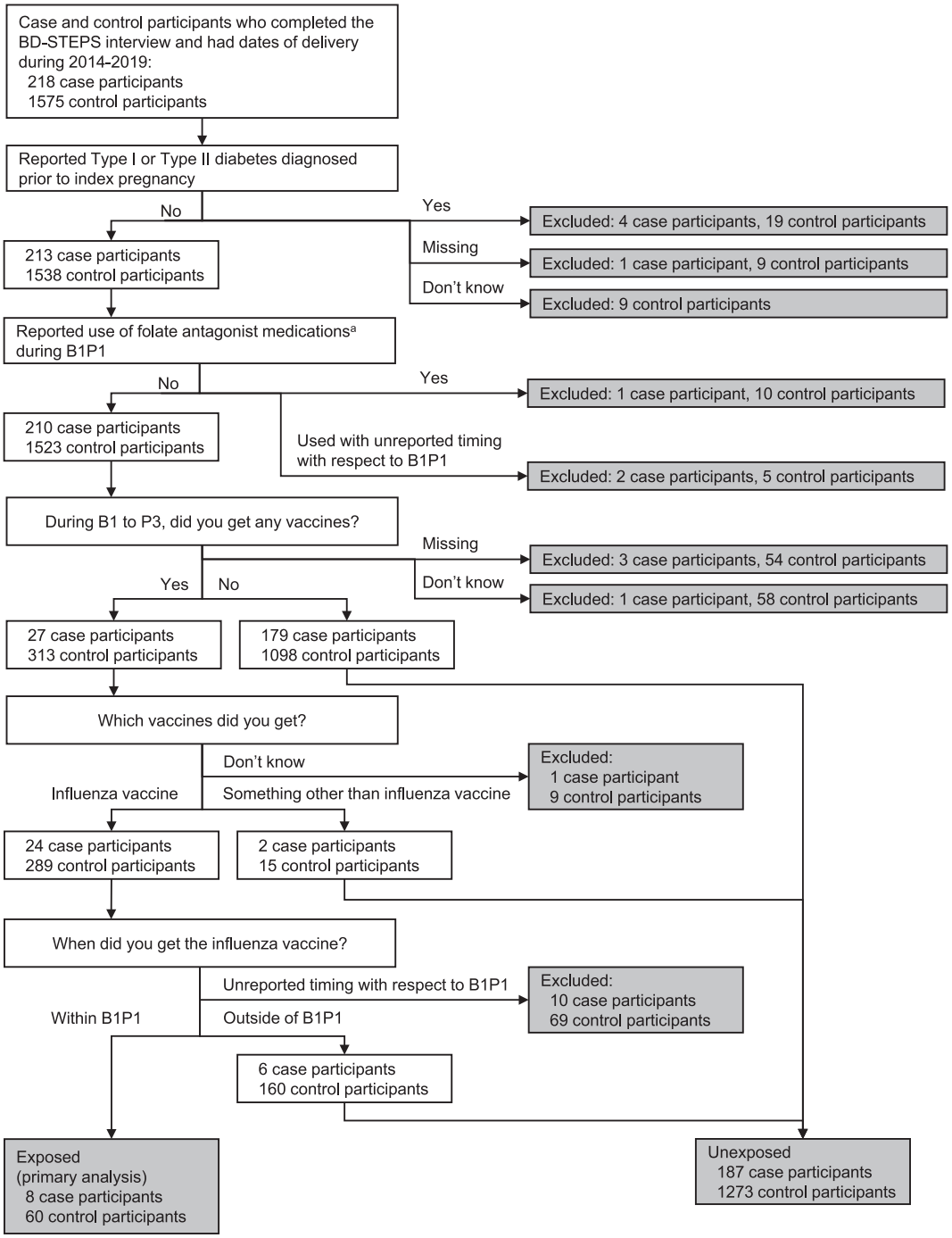

Fig. 1. Exclusion criteria for analysis of spina bifida, BD-STEPS, 2014–2019. Abbreviations: B1, the month before pregnancy; BD-STEPS, Birth Defects Study To Evaluate Pregnancy exposureS; P1, the first pregnancy month; P3, the third pregnancy month. [a] carbamazepine, cholestyramine resin, methotrexate, oxcarbazepine, sulfasalazine, triamterene, trimethoprim, phenytoin, or phenobarbital.

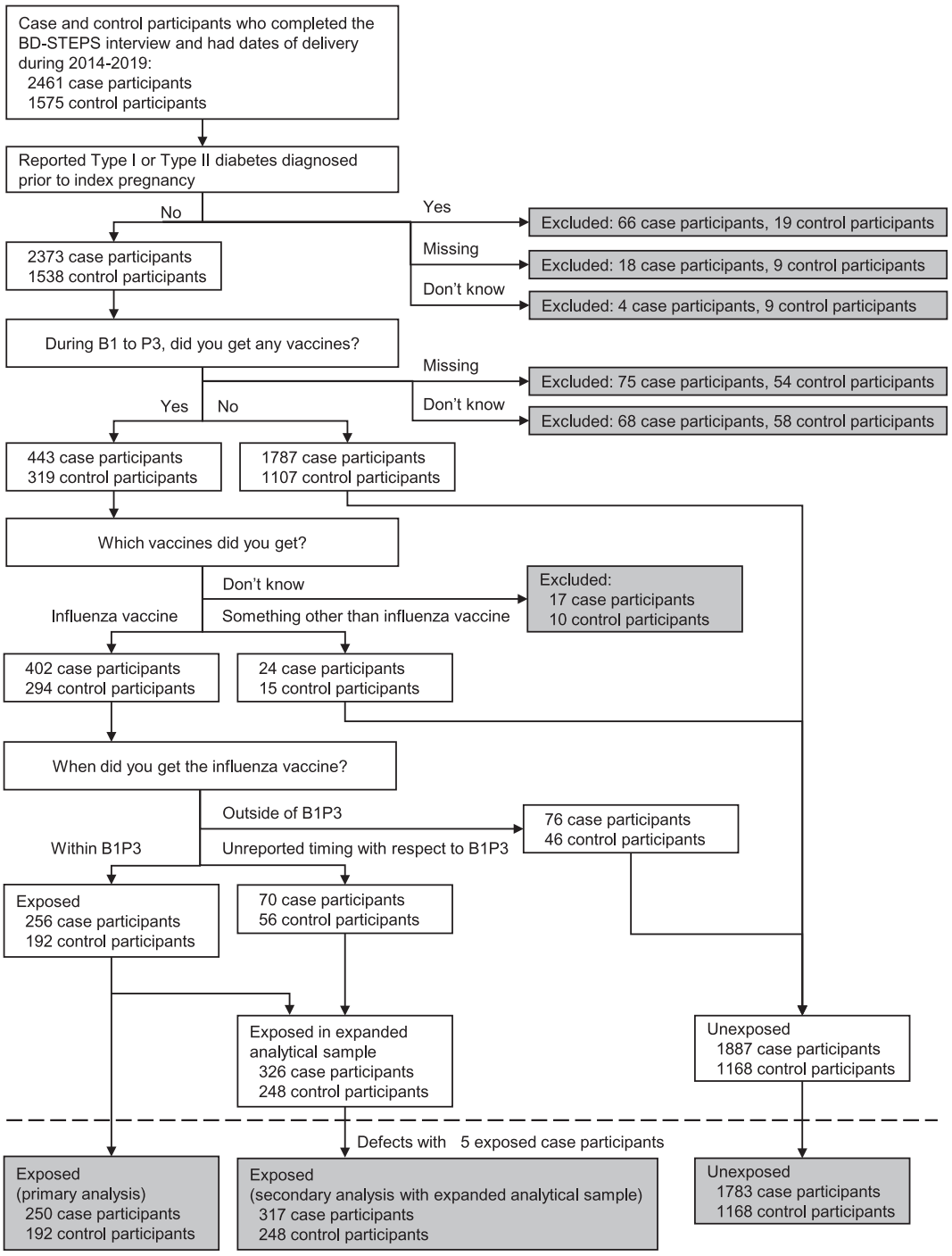

Fig. 2. Exclusion criteria for analysis of birth defects other than spina bifida, BD-STEPS, 2014–2019. Abbreviations: B1, the month before pregnancy; BD-STEPS, Birth Defects Study To Evaluate Pregnancy exposureS; P3, the third pregnancy month.

defects other than spina bifida included 2033 cases (250 exposed, 1783 unexposed) and 1360 controls (192 exposed, 1168 unexposed).

2.4. Covariates

Several participant characteristics and exposures previously shown to be associated with major birth defects were selected as covariates, and proportions of case and control participants with these characteristics and exposures were calculated. These characteristics and exposures included pregnancy plurality (singleton, multiple birth); age at delivery (<20, 20–34, ≥35 years); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); educational attainment at delivery (≤11, 12, ≥13 years); gravidity (0, 1, ≥2); pre-pregnancy body-mass index (BMI) (underweight: <18.5, normal weight: 18.5–24.9, overweight: 25–29.9, obese: ≥30 kg/m2); chronic hypertension (yes, no); asthma diagnosed before or during the first trimester (yes, no); fever during the critical exposure period (yes, no); use of a multivitamin, prenatal vitamin, or folic acid-containing supplement during B1P1 (yes, no); cigarette smoking (yes, no) and alcohol use (yes, no) during the critical exposure period; study center (Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina); and calendar quarter (January 1–March 31, April 1–June 30, July 1–September 30, October 1–December 31) and year (2013–2019) of conception.

2.5. Primary analyses

Crude odds ratios, adjusted odds ratios (aORs), and their corresponding 95 % confidence intervals (CIs) were estimated using unconditional logistic regression. Children with more than one eligible BD-STEPS defect were included in the analysis for each defect. Because of the small numbers for some defects, propensity scores were used to adjust for all covariates [26]. Propensity scores were calculated from the predicted probability of influenza vaccination during the critical exposure period among control participants and included in the logistic regression model as a continuous variable [27]. No violations of model assumptions were observed.

2.6. Secondary analyses

Six secondary analyses were conducted. The first secondary analysis applied standard multivariable adjustment using a limited set of covariates (participant age at delivery, race/ethnicity, pre-pregnancy BMI, quarter and year of conception, and study center) identified a priori that we believed to be the most important for confounding to confirm the propensity score-adjusted estimates. To examine an expanded analytical sample, the second analysis included participants who were defined as exposed in the primary analysis and previously excluded participants who provided an affirmative response to receiving a vaccine during B1P3 (Question T154) that was an influenza vaccine (Question T156), but whose reported timing of vaccination (Question T157) lacked precision with regard to B1P3. Spina bifida was excluded from this secondary analysis because the gateway question (Question T154) was not restricted to B1P1. The third analysis restricted the analytical sample of case children to those classified as isolated, as those with co-occurring major birth defects may exhibit developmental heterogeneity. The fourth analysis included only case and control children without a family history of a same-site birth defect to examine risk independent of potential increased hereditary risk. Twinning is also associated with some birth defects [28]; therefore, the fifth analysis included only singleton births. The final analysis included only participants whose first trimester occurred at least partially during influenza season (approximated as September 1–March 31) to examine only those who would likely have an influenza vaccine available during their first trimester.

2.7. Bias analysis

A probabilistic bias analysis using the methods developed by Fox et al. [29] was conducted to evaluate the effect of non-differential misclassification of influenza vaccine exposure in the primary analysis and first two secondary analyses. Triangular distributions were assigned for the sensitivity and specificity parameters using results for participants aged 18–49 years from a validation study of self-reported influenza vaccination [30]. The estimate was assigned as the mode and the 95 % confidence limits as the minimum and maximum for the respective triangular sensitivity (0.952; 95 % CI: 0.910–0.978) and specificity (0.982; 95 % CI: 0.955–0.995) distributions. To more closely align with the recall time from the current study, the published estimate for previous-season vaccination status for sensitivity was applied. When applying the previous-season specificity estimate (0.876; 95 % CI: 0.818–0.920), a high deletion rate (>10 %) was observed, suggesting that the distribution was insufficiently compatible with the data for the analytic approach used; as an alternative, the published current-season estimate for specificity was applied. Each bias parameter was sampled 30,000 times, and estimates were summarized as the median aOR and 95 % simulation interval, which included both random and systematic error. Estimates were adjusted for the same propensity score or set of covariates as in the respective conventional analysis. All analyses were generated using SAS software v.9.4 Copyright © [2016] SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

The analytical sample for spina bifida included 1333 control children and 195 children with spina bifida (182 isolated case children and 13 with multiple defects); the sample for the other selected major birth defects included 1360 control children and 2033 children with other defects (1779 isolated case children, 253 with multiple defects, and 1 complex case). Characteristics of case and control participants are presented in Table 1, and characteristics of exposed and unexposed control participants are presented in Supplemental Table 2.

Influenza vaccination during B1P1 was reported by 4.5 % of control and 4.1 % (spina bifida) of case participants; reports during B1P3 were 14.1 % for control participants and ranged from 6.8 % (gastroschisis) to 17.5 % (diaphragmatic hernia) for case participants (Table 2). Of note, the analysis also evaluated the overlap between influenza vaccination periods (B1P1, B1P3) and the influenza season in the United States (September–March). For pregnancies with influenza vaccination exposure during the B1P3 period, the first trimester overlapped with the influenza season in 77.9 % of cases and 83.4 % of controls. A similar pattern was observed for pregnancies with influenza vaccination during the B1P1 period (83.3 % of cases and 83.5 % of controls).

In the primary analyses, the aOR for influenza vaccination was near the null for spina bifida (aOR: 0.9; 95 %CI: 0.4–2.0), and those for exposure during B1P3 and the other selected major birth defects ranged from 0.4 (95 %CI: 0.2–0.7) for gastroschisis to 1.3 (95 %CI: 0.9–1.9) for cleft palate alone (Table 2). Estimates greater than the null were observed for dextro-transposition of the great arteries, total anomalous pulmonary venous return, and cleft palate alone; null or inverse estimates were observed for anotia/microtia, coarctation of the aorta, hypoplastic left heart syndrome, tetralogy of Fallot, cleft lip ± cleft palate, esophageal atresia, transverse limb deficiency, diaphragmatic hernia, and gastroschisis. Only the 95 % CIs for cleft lip ± cleft palate (aOR: 0.6; 95 %CI: 0.4–0.9) and gastroschisis (aOR: 0.4; 95 %CI: 0.2–0.7) excluded the null.

The secondary analysis using standard multivariable adjustment and a limited set of covariates produced similar results (Table 2), supporting the propensity score-adjusted estimates produced in the primary analyses. Another secondary analysis using an expanded analytical sample that included participants with incomplete or imprecise influenza vaccination timing data also tended to yield similar results to the primary analyses (Table 3).

Additional secondary analyses that restricted case children to those classified as isolated (Supplemental Table 3), excluded case and control children with a family history of the same site defect (Supplemental Table 4), restricted case and control children to singleton pregnancies (Supplemental Table 5), and restricted participants to those with first trimester of pregnancy overlapping with influenza season (Supplemental Table 6) yielded results similar to those of the primary analysis. Results of our probabilistic bias analysis examining the potential effect of exposure misclassification (Supplemental Table 7) were also similar to those of the respective primary or secondary analysis.

4. Discussion

Our study investigated potential associations between maternal influenza vaccination shortly before or during pregnancy and the risk of major birth defects in offspring. Vaccine uptake during B1P1 was reported to be less than 5.0 %, and uptake during B1P3 across defects

Table 1
Distributions of participant characteristics and exposures for primary analysis, BD-STEPS, 2014–2019.

	Spina Bifida		Birth Defects Other Than Spina Bifida	
	Control Group (*n* = 1333)	Case Group (*n* = 195)	Control Group (*n* = 1360)	Case Group (*n* = 2033)
Characteristic or Exposure	**N (%)** [a]	**N (%)** [a]	**N (%)** [a]	**N (%)** [a]
Pregnancy plurality				
1	1279 (95.9)	185 (94.9)	1308 (96.2)	1927 (94.8)
2+	54 (4.1)	10 (5.1)	52 (3.8)	106 (5.2)
Missing	0	0	0	0
Age at delivery (years)				
<20	41 (3.1)	13 (6.7)	42 (3.1)	108 (5.3)
20–34	994 (74.6)	152 (77.9)	1014 (74.6)	1573 (77.4)
≥35	298 (22.4)	30 (15.4)	304 (22.4)	352 (17.3)
Missing	0	0	0	0
Race/ethnicity				
Non-Hispanic White	708 (53.2)	96 (49.2)	727 (53.5)	1063 (52.4)
Non-Hispanic Black	171 (12.8)	25 (12.8)	174 (12.8)	193 (9.5)
Hispanic	335 (25.2)	63 (32.3)	339 (24.9)	590 (29.1)
Other	118 (8.9)	11 (5.6)	119 (8.8)	184 (9.1)
Missing	1	0	1	3
Educational attainment at delivery (years)				
≤11	133 (10.4)	31 (16.4)	135 (10.3)	249 (12.7)
12	217 (16.9)	40 (21.2)	223 (17.0)	430 (21.9)
≥13	935 (72.8)	118 (62.4)	953 (72.7)	1280 (65.3)
Missing	48	6	49	74
Gravidity				
0	364 (27.3)	49 (25.1)	374 (27.5)	619 (30.4)
1	403 (30.2)	52 (26.7)	408 (30.0)	567 (27.9)
≥2	565 (42.4)	94 (48.2)	577 (42.5)	847 (41.7)
Missing	1	0	1	0
Pre-pregnancy body-mass index (kg/m^2)				
<18.5	29 (2.3)	5 (2.8)	30 (2.4)	69 (3.6)
18.5–24.9	587 (47.2)	72 (39.8)	598 (47.2)	884 (46.6)
25.0–29.9	347 (27.9)	55 (30.4)	351 (27.7)	491 (25.9)
≥30.0	281 (22.6)	49 (27.1)	289 (22.8)	454 (23.9)
Missing	89	14	92	135
Preexisting hypertension				
Yes	45 (3.4)	5 (2.6)	46 (3.4)	70 (3.5)
No	1271 (96.6)	189 (97.4)	1297 (96.6)	1941 (96.5)
Missing	17	1	17	22
Asthma[b]				
Yes	188 (14.1)	27 (13.8)	190 (14.0)	286 (14.1)
No	1144 (85.9)	168 (86.2)	1169 (86.0)	1745 (85.9)
Missing	1	0	1	2
Fever[c]				
Yes	31 (2.4)	7 (3.6)	75 (5.6)	143 (7.1)
No	1286 (97.6)	186 (96.4)	1273 (94.4)	1873 (92.9)
Missing	16	2	12	17
Multivitamin, prenatal vitamin, or folic acid supplement use[d]				
Yes	1006 (77.0)	132 (69.1)	1024 (76.8)	1461 (73.4)
No	300 (23.0)	59 (30.9)	309 (23.2)	529 (26.6)
Missing	27	4	27	43
Cigarette smoking[c]				
Yes	125 (9.7)	17 (8.9)	131 (10.0)	284 (14.4)
No	1164 (90.3)	173 (91.1)	1184 (90.0)	1686 (85.6)
Missing	44	5	45	63
Alcohol use[c]				
Yes	627 (48.9)	80 (42.3)	652 (49.7)	1010 (51.5)
No	655 (51.1)	109 (57.7)	659 (50.3)	953 (48.5)
Missing	51	6	49	70
BD-STEPS study center				
Arkansas	174 (13.1)	23 (11.8)	179 (13.2)	255 (12.5)
California	129 (9.7)	35 (17.9)	131 (9.6)	342 (16.8)
Georgia	194 (14.6)	19 (9.7)	197 (14.5)	213 (10.5)
Iowa	156 (11.7)	23 (11.8)	164 (12.1)	228 (11.2)
Massachusetts	204 (15.3)	26 (13.3)	204 (15.0)	343 (16.9)
New York	293 (22.0)	36 (18.5)	297 (21.8)	397 (19.5)
North Carolina	183 (13.7)	33 (16.9)	188 (13.8)	255 (12.5)
Missing	0	0	0	0
Quarter of estimated date of conception				
January–March	333 (25.0)	52 (26.7)	340 (25.0)	497 (24.4)
April–June	333 (25.0)	55 (28.2)	332 (24.4)	486 (23.9)
July–September	319 (23.9)	38 (19.5)	327 (24.0)	519 (25.5)
October–December	348 (26.1)	50 (25.6)	361 (26.5)	531 (26.1)
Missing	0	0	0	0
Year of estimated date of conception				
2013	198 (14.9)	25 (12.8)	205 (15.1)	361 (17.8)
2014	274 (20.6)	34 (17.4)	279 (20.5)	332 (16.3)
2015	34 (2.6)	5 (2.6)	34 (2.5)	65 (3.2)
2016	239 (17.9)	29 (14.9)	244 (17.9)	348 (17.1)
2017	276 (20.7)	54 (27.7)	284 (20.9)	425 (20.9)
2018	230 (17.3)	38 (19.5)	232 (17.1)	382 (18.8)
2019	82 (6.2)	10 (5.1)	82 (6.0)	120 (5.9)
Missing	0	0	0	0

Abbreviation: BD-STEPS, Birth Defects Study To Evaluate Pregnancy exposureS.

[a] Due to rounding, proportions may not total to 100.

[b] Diagnosed before or during the first trimester.

[c] During the one month before pregnancy through the first pregnancy month for spina bifida; during the one month before pregnancy through the third pregnancy month for birth defects other than spina bifida.

[d] During the one month before pregnancy through the first pregnancy month.

Table 2
Primary and secondary analyses of associations of influenza vaccine exposure and selected birth defects, BD-STEPS, 2014–2019.

	Unexposed	Exposed[a]	Primary Analysis		Secondary Analysis: Standard Adjustment Using Limited Covariates
	N	N (%)	cOR (95 %CI)	aOR[b] (95 %CI)	aOR[d] (95 %CI)
Control group for spina bifida	1273	60 (4.5)			
Spina bifida	187	8 (4.1)	0.9 (0.4–1.9)	0.9 (0.4–2.0)[c]	1.0 (0.5–2.3)
Control group for birth defects other than spina bifida	1168	192 (14.1)			
Ear					
Anotia/microtia	112	12 (9.7)	0.7 (0.4–1.2)	0.7 (0.4–1.4)	0.7 (0.3–1.3)
Heart					
Coarctation of the aorta	152	25 (14.1)	1.0 (0.6–1.6)	0.9 (0.5–1.5)	0.9 (0.6–1.5)
Dextro-transposition of the great arteries	102	18 (15.0)	1.1 (0.6–1.8)	1.2 (0.7–2.0)	1.1 (0.6–1.9)
Hypoplastic left heart syndrome	99	16 (13.9)	1.0 (0.6–1.7)	0.9 (0.5–1.7)	1.0 (0.6–1.8)
Tetralogy of Fallot	161	27 (14.4)	1.0 (0.7–1.6)	1.0 (0.6–1.6)	1.0 (0.6–1.6)
Total anomalous pulmonary venous return	50	8 (13.8)	1.0 (0.5–2.1)	1.1 (0.4–2.5)	1.3 (0.6–2.9)
Orofacial Clefts					
Cleft lip ± palate	425	43 (9.2)	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.7 (0.5–1.0)
Cleft palate alone	200	41 (17.0)	1.2 (0.9–1.8)	1.3 (0.9–1.9)	1.2 (0.8–1.8)
Gastrointestinal					
Esophageal atresia	119	13 (9.8)	0.7 (0.4–1.2)	0.6 (0.3–1.2)	0.6 (0.3–1.2)
Limb reduction					
Transverse limb deficiency	59	8 (11.9)	0.8 (0.4–1.8)	0.8 (0.3–1.7)	0.8 (0.4–1.8)
Musculoskeletal					
Diaphragmatic hernia	127	27 (17.5)	1.3 (0.8–2.0)	0.9 (0.5–1.5)	1.1 (0.7–1.9)
Gastroschisis	207	15 (6.8)	0.4 (0.3–0.8)	0.4 (0.2–0.7)	0.5 (0.3–0.8)

Abbreviations: aOR, adjusted odds ratio; BD-STEPS, Birth Defects Study To Evaluate Pregnancy exposureS; cOR, crude odds ratio; CI, confidence interval.

[a] During the one month before pregnancy through the first pregnancy month for spina bifida; during the one month before pregnancy through the third pregnancy month for birth defects other than spina bifida.

[b] Adjusted for propensity score calculated from the predicted probability of influenza vaccination during the critical exposure period among control participants, which was estimated from a logistic regression model that included pregnancy plurality and participant age at delivery; race/ethnicity; educational attainment at delivery; gravidity; pre-pregnancy body-mass index (BMI); pre-existing hypertension; asthma diagnosed before or during the first trimester; fever during the critical exposure period; multivitamin, prenatal vitamin, or folic acid supplement use during the one month before pregnancy through the first pregnancy month; cigarette smoking during the critical exposure period; alcohol use during the critical exposure period; BD-STEPS study center; and quarter and year of estimated date of conception.

[c] Participant age at delivery and pre-pregnancy BMI were not used in calculating the propensity score for analysis of spina bifida due to lack of control participants with age < 20 or BMI <18.5 who were exposed during the critical exposure period.

[d] Adjusted for participant age at delivery, race/ethnicity, pre-pregnancy BMI, cigarette smoking during the critical exposure period, BD-STEPS study center, and quarter and year of estimated date of conception.

ranged from 6.8 to 17.5 %. Primary adjusted analyses applying propensity scores showed no statistically significant positive associations between maternal influenza vaccination and any of the selected birth defects studied, with most associations being near or below the null. Several secondary analyses applying standard multivariable adjustment with a limited set of covariates, using an expanded analytical sample, or restricting to isolated case children, children with no family history of same site defect, singleton births, and participants whose first trimester of pregnancy overlapped with influenza season tended to yield similar results to the primary analyses. Our probabilistic bias analysis also tended to yield similar results to respective primary or secondary analyses, although we were limited to examining the potential effect of exposure misclassification using an estimate of specificity based on current-year vaccination status rather than a lower but potentially more accurate estimate based on previous-year vaccination status. Together, these analyses strengthen the evidence that influenza vaccination during critical exposure period does not increase the risk of selected major birth defects.

In our six-year BD-STEPS study period (2014–2019), vaccine uptake among participants (control, case) during B1P1 (4.5 %, 4.1 %) and B1P3 (14.1 %, 6.8–17.5 %) exceeded the respective proportions observed during our six-year NBDPS study period (2006–2011) for B1P1 (1.3 %, 1.0 %) and B1P3 (4.3 %, 2.4–8.5 %). We also observed differences (≥10 % absolute change) in the magnitude of the associations estimated in each study, with only the associations for cleft lip ± cleft palate and gastroschisis in BD-STEPS being statistically significant. Positive associations observed for vaccine exposure during B1P3 in NBDPS were attenuated in BD-STEPS for coarctation of the aorta (aOR = 1.3 to 0.9), total anomalous pulmonary venous return (aOR = 2.3 to 1.1), esophageal atresia (aOR = 1.2 to 0.6), and diaphragmatic hernia (aOR = 1.3 to 0.9). Inverse associations observed in NBDPS were strengthened in BD-STEPS for cleft lip ± cleft palate (aOR = 0.9 to 0.6) and gastroschisis (aOR = 0.8 to 0.4) but attenuated for hypoplastic left heart syndrome (aOR = 0.6 to 0.9), tetralogy of Fallot (aOR = 0.7 to 1.0), and transverse limb (aOR = 0.7 to 0.8). Associations in NBDPS for cleft palate strengthened from 1.0 to 1.3 in BD-STEPS. Lastly, associations for anotia/microtia (aOR = 0.7 versus 0.7) and dextro-transposition of the great arteries (aOR = 1.3 versus 1.2) were similar (<10 % absolute change) between the two studies. Our current findings support our earlier conclusions regarding the safety of influenza vaccine during early pregnancy.

Influenza vaccine uptake among case and control participants is not directly comparable to previous studies, as we only had data for vaccination during the first trimester of pregnancy, not all trimesters of pregnancy. Additionally, among the seven studies cited that examined birth defect risk [2,14–17,21,22], only Louik et al. [16] reported findings for individual birth defects. Where data were available, our findings were comparable for the inverse association for cleft lip ± cleft palate and a positive, but nonsignificant, association for cleft palate alone. Conversely, our positive association for anomalous pulmonary venous return differed from the inverse association reported by Louik et al. [16]. Likewise, our inverse association for anotia/microtia and that near the null for diaphragmatic hernia differed from the positive associations reported by Louik et al. [16]. Our findings were not comparable to those for defect groups reported by Louik et al. [16], Kharbanda et al. [15], or Sarna et al. [21], due to the different individual phenotypes included

Table 3
Secondary analyses of associations of influenza vaccine exposure and selected birth defects using an expanded analytical sample, BD-STEPS, 2014–2019.

	Unexposed	Exposed[a]	Secondary Analysis: Expanded Analytical Sample[b]	
	N	N (%)	cOR (95 %CI)	aOR[c] (95 %CI)
Control group for birth defects other than spina bifida	1168	248 (17.5)		
Ear				
Anotia/microtia	112	20 (15.2)	0.8 (0.5–1.4)	0.9 (0.5–1.5)
Heart				
Coarctation of the aorta	152	33 (17.8)	1.0 (0.7–1.5)	1.0 (0.6–1.5)
Dextro-transposition of the great arteries	102	23 (18.4)	1.1 (0.7–1.7)	1.1 (0.6–1.8)
Hypoplastic left heart syndrome	99	20 (16.8)	1.0 (0.6–1.6)	1.0 (0.6–1.7)
Tetralogy of Fallot	161	32 (16.6)	0.9 (0.6–1.4)	0.9 (0.6–1.4)
Total anomalous pulmonary venous return	50	9 (15.3)	0.8 (0.4–1.7)	0.9 (0.4–2.1)
Orofacial Clefts				
Cleft lip ± palate	425	55 (11.5)	0.6 (0.4–0.8)	0.6 (0.4–0.9)
Cleft palate alone	200	49 (19.7)	1.2 (0.8–1.6)	1.2 (0.8–1.8)
Gastrointestinal				
Esophageal atresia	119	17 (12.5)	0.7 (0.4–1.1)	0.6 (0.4–1.1)
Limb reduction				
Transverse limb deficiency	59	10 (14.5)	0.8 (0.4–1.6)	0.7 (0.3–1.5)
Musculoskeletal				
Diaphragmatic hernia	127	32 (20.1)	1.2 (0.8–1.8)	0.9 (0.6–1.5)
Gastroschisis	207	20 (8.8)	0.5 (0.3–0.7)	0.4 (0.3–0.7)

Abbreviations: aOR, adjusted odds ratio; BD-STEPS, Birth Defects Study To Evaluate Pregnancy exposureS; cOR, crude odds ratio; CI, confidence interval.

[a] Exposure during the one month before pregnancy through the third pregnancy month (B1P3).

[b] Included participants who were defined as exposed in the primary analysis and previously excluded participants who provided an affirmative response to receiving a vaccine during B1P3 (Question T154) that was an influenza vaccine (Question T156).

[c] Adjusted for propensity score calculated from the predicted probability of influenza vaccination during the critical exposure period among control participants, which was estimated from a logistic regression model that included pregnancy plurality and participant age at delivery; race/ethnicity; educational attainment at delivery; gravidity; pre-pregnancy body-mass index; pre-existing hypertension; asthma diagnosed before or during the first trimester; fever during the critical exposure period; multivitamin, prenatal vitamin, or folic acid supplement use during the one month before pregnancy through the first pregnancy month; cigarette smoking during the critical exposure period; alcohol use during the critical exposure period; BD-STEPS study center; and quarter and year of estimated date of conception.

within a group (e.g. congenital heart defects).

Our findings are limited to the major birth defects eligible for BD-STEPS. Additionally, our findings do not generalize beyond the US. Defects eligible for BD-STEPS are a reduced number compared to those included in the NBDPS and the study by Louik et al. [16] that examined risk for individual birth defects. An additional limitation was our exclusion of BD-STEPS eligible birth defects that had fewer than five exposed case children. Nonetheless, our use of population-based surveillance programs to identify children diagnosed with birth defects and rigorous, systematic review and classification of eligible BD-STEPS birth defects remained consistent with the approach used in NBDPS. BD-STEPS data also included fetal deaths and elective terminations and used population-based birth data to select control children, consistent with the approaches used in NBDPS. Our case ascertainment approach, however, was unable to systematically ascertain early fetal losses before 20 weeks gestation, a limitation shared with NBDPS.

Use of observational studies to monitor the safety of influenza vaccination during pregnancy poses challenges, such as the potential for influenza vaccine components to change from year to year, varied timing of administration, and low prevalence of outcomes, such as birth defects. As such, these studies require ongoing collection of maternal influenza vaccinations using large study samples. BD-STEPS collection of self-reports of influenza vaccination was conducted using telephone interviews. Although this approach was consistent with NBDPS methods, it may lead to exposure misclassification, particularly given the recall period spanned more than one influenza season. Based on the limited relevant literature identified that evaluated recall for influenza vaccination among reproductive-aged adults, [30] we were unable to determine the potential for differential misclassification for such recall. Compared to results from our primary analysis, our probabilistic bias analysis for non-differential misclassification showed similar aOR estimates with less precise 95 % CIs. Another limitation of our interview data collection was that receipt of influenza vaccine but not type of inactivated vaccine (e.g. egg-based, cell-culture-based, or antigen changes by season,) was requested. To minimize this limitation, we controlled for quarter and year of conception.

To control for confounding, we used propensity score adjustment for several covariates in our primary analyses and conducted a secondary analysis applying standard multivariable adjustment and a limited set of covariates, consistent with the analytical approaches we used with NBDPS data. Findings were similar between our primary analyses using propensity scores and secondary analyses using standard adjusted models, supporting our propensity score-adjusted estimates produced in the primary analyses. We also conducted several secondary analyses using more homogeneous samples (e.g. isolated case children only, singleton births only, etc.); findings from these analyses also tended to support those from our primary analyses. Even with these various analyses, we cannot rule out residual confounding.

5. Conclusion

Influenza infection during pregnancy puts both the mother and the child at increased risk of severe outcomes. As such, the World Health Organization, United States (US) Advisory Committee on Immunization Practices (ACIP), and the American College of Obstetricians and Gynecologists (ACOG) continue to recommend influenza vaccination for pregnant women during pregnancy [2–4]. Addressing vaccine hesitancy among pregnant women can optimize maternal and child health. Future studies would benefit from large, multinational samples and additional types of major birth defects to expand evaluation of the safety of influenza vaccination during pregnancy, although our findings reinforce the safety of influenza vaccination during pregnancy for the birth defects studied, supporting public health efforts to promote vaccination coverage among pregnant women.

CRediT authorship contribution statement

Veronica Malange: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Tasnim Mohaissen:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization. **Kristin M. Conway:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Anthony Rhoads:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Joan K. Morris:** Writing – review & editing, Writing – original draft, Visualization, Validation,

Software, Methodology, Formal analysis, Data curation. **Elizabeth C. Ailes:** Writing – review & editing, Resources, Investigation. **Paula L. Hedley:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Conceptualization. **Janet D. Cragan:** Writing – review & editing, Resources, Investigation. **Eirini Nestoridi:** Writing – review & editing, Resources, Investigation. **Eleni A. Papadopoulos:** Writing – review & editing, Resources, Methodology, Investigation. **Thomas D. Scholz:** Writing – review & editing, Resources, Investigation, Data curation. **Alpa Sidhu:** Writing – review & editing, Resources, Investigation, Data curation. **Michael Christiansen:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Conceptualization. **Paul A. Romitti:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethical approval

All interviewed study participants provided informed consent. The Centers for Disease Control and Prevention Institutional Review Board approved the BD-STEPS study protocol (#2087). The most recent approval date was January 27,2025.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul A Romitti reports financial support was provided by US Centers for Disease Control and Prevention Research Centers. Tasnim Mohaissen reports financial support was provided by Polish National Agency for Academic Exchange. 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127297.

Data availability

We have added a statement at the end of our manuscript draft informing the reader of a web link to review established procedures and approvals needed to access the data.

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