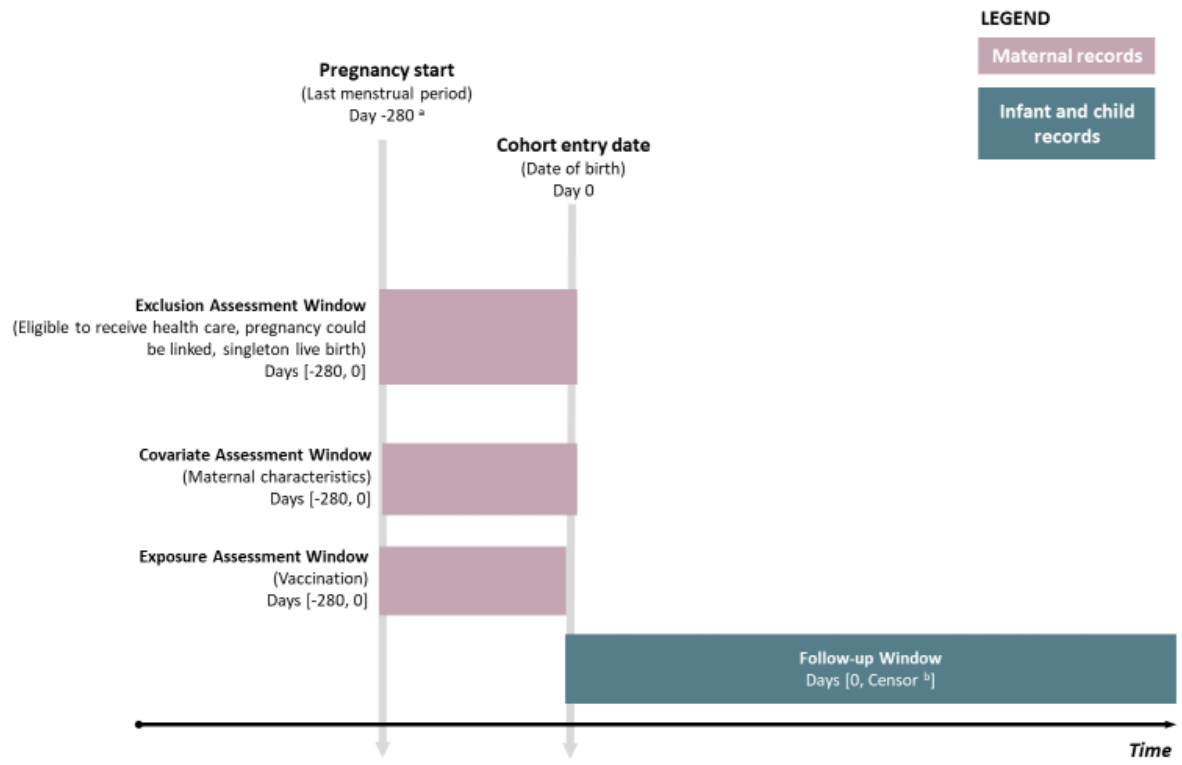
Supplementary Online Content

Mehrabadi A, Dodds L, MacDonald NE, et al. Association of maternal influenza vaccination during pregnancy with early childhood health outcomes. *JAMA*. doi:10.1001/jama.2021.6778

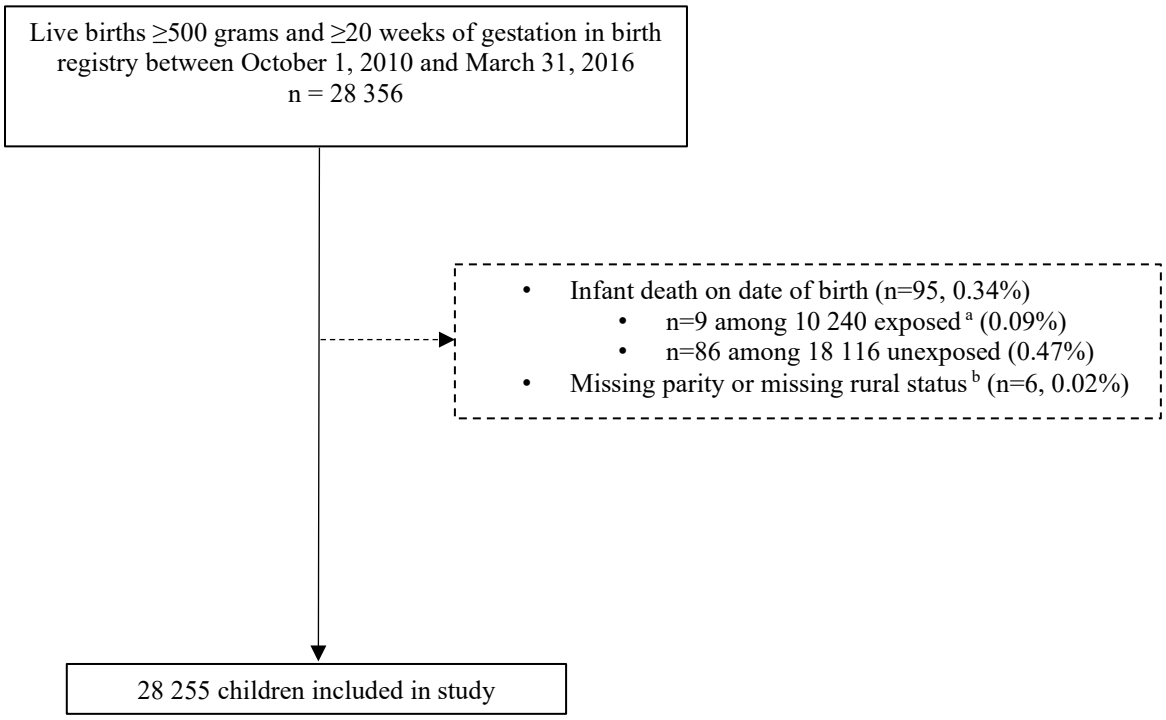
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Study Design



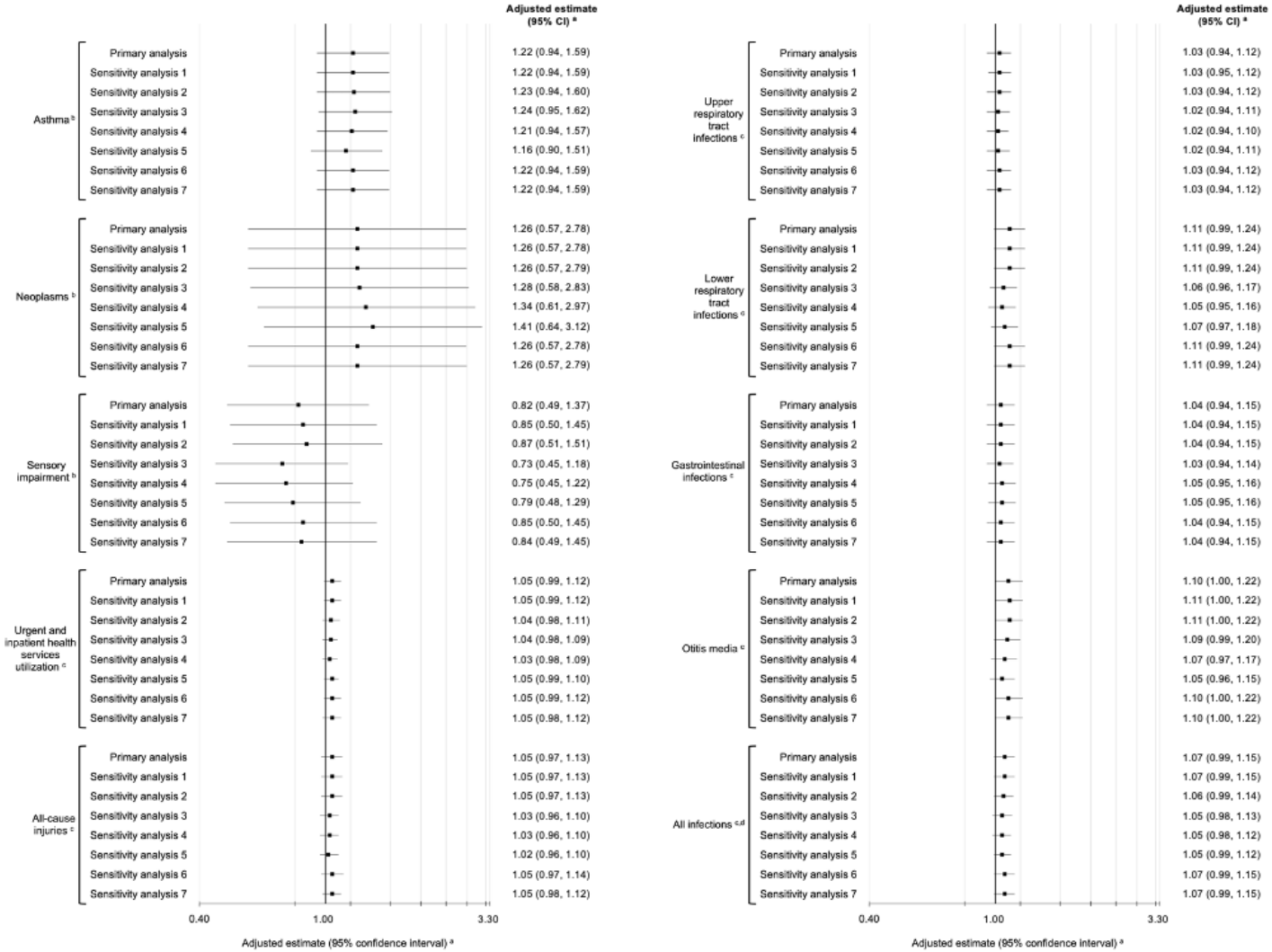
[a] For the purposes of illustrating the temporal relationship between maternal and infant study variables, the date of the last menstrual period (LMP) is shown as day -280 (i.e. 40 completed weeks of gestation). In the study, the length of this interval depends on the actual length of gestation.
[b] Earliest of outcome of interest (for time-to-event analyses), death, disenrollment from provincial health plan, or end of study period (March 31, 2016).

eFigure 2. Study Flow Diagram



[a] Exposure refers to *in utero* seasonal influenza vaccine exposure.
[b] Note that these numbers have been combined as each category was <5 and could not be presented according to data privacy policies.

eFigure 3. Sensitivity Analyses



Sensitivity analysis 1: Primary analysis model additionally adjusted for maternal history of asthma; Sensitivity analysis 2: Primary analysis model additionally adjusted for continuous gestational age; Sensitivity analysis 3: Children with inverse probability of treatment weights ≤0.01 percentile or ≥99.9 percentile were excluded. Analysis includes 28,194 children (10,166 born to vaccinated mothers; 18,028 born to unvaccinated mothers); Sensitivity analysis 4: Children with inverse probability of treatment weights ≤0.5 percentile or ≥99.5 percentile were excluded. Includes 27,949 children (9,922 born to vaccinated mothers; 18,027 born to unvaccinated mothers); Sensitivity analysis 5: Children with inverse probability of treatment weights ≤1 percentile or ≥99 percentile were excluded. Includes 27,668 children (9,642 born to vaccinated mothers; 18,026 born to unvaccinated mothers); Sensitivity analysis 6: Primary analysis model additionally adjusted for obstetric conditions affecting pregnancy; Sensitivity analysis 7: Primary analysis model additionally adjusted for maternal history of medically-attended influenza during pregnancy.

[a] Adjusted using stabilized inverse probability of treatment weights.
[b] Point estimates are hazard ratios generated from a Cox proportional hazards model.
[c] Point estimates are incidence rate ratios generated from a negative binomial regression model.
[d] Composite of upper respiratory tract infections, lower respiratory tract infections, gastrointestinal infections, and otitis media.

eTable 1. Influenza Vaccination Exposure Assessment

Source	Exposure assessment algorithm[a]
Physician billing code	Presence of billing code for Influenza-Inactivated Vaccine (Coded as RO=INFL)
Nova Scotia Atlee Perinatal Database	Documentation of seasonal influenza vaccine on the prenatal record or maternal assessment form

[a] Note that only split or subunit seasonal influenza vaccines (and not whole virus vaccines) are approved for use in Canada.

eTable 2. Individual *ICD-10-CA* Diagnostic Codes to Identify Outcomes

Study outcome	Diagnostic codes or case-finding algorithm
Infectious diseases	
Upper respiratory infections	ICD-10: A36.0 (pharyngeal diphtheria), A36.1 (nasopharyngeal diphtheria), A36.2 (laryngeal diphtheria), A36.8 (other diphtheria: conjunctivitis, myocarditis, polyneuritis), A36.9 (diphtheria, unspecified), J01-J06 (acute upper respiratory infections), J35.0 (chronic tonsillitis), J36 (peritonsillar abscess), J37.0 (chronic laryngitis)
Lower respiratory infections	ICD-10: A37 (whooping cough), A42.0 (pulmonary actinomycosis), A48.1 (other bacterial diseases), A70 (chlamydia psittaci infection), J09-J18 (Influenza and pneumonia), J20-J22 (acute bronchitis, acute bronchiolitis, unspecified acute lower respiratory infection), J85 (abscess of lung and mediastinum), J86 (pyothorax)
Gastrointestinal infections	ICD-10: A00 (cholera), A01 (typhoid and paratyphoid fevers), A02.0 (salmonella enteritis), A02.2-A02.9 (salmonella infections), A03-A09 (bacterial, protozoal, viral and other intestinal infections), A42.1 (abdominal actinomycosis)
Otitis media	ICD-10: H65 to H67
Atopic disease	
Pediatric asthma	ICD-10: J45 (asthma), J46 (status asthmaticus)
Neoplasm	ICD-10: C00-C97 (malignant neoplasms), D00-D48 (in situ neoplasms, benign neoplasms, neoplasms of uncertain or unknown behaviour)
Sensory impairment	
Hearing loss	ICD-10: H90 (conductive and sensorineural hearing loss), H91 (other hearing loss)
Vision loss	ICD-10: H47 & H48.8 (other disorders of optic nerve and visual pathways), H53 (visual disturbances), H54 (visual impairment including blindness)
Rates of urgent and in-patient health services utilization	All-cause hospitalizations and emergency department visits
Negative control outcome	
All-cause injury	ICD-10: S00-S99 and T00-T75

eMethods.

Analytic approach for exposure analyses by pregnancy trimester:

Among 10 227 children exposed *in utero* to seasonal influenza vaccine, 2302 (22.5%) were exposed in trimester 1, 2909 (28.4%) were exposed in trimester 2, 3061 (29.9%) were exposed in trimester 3, and 1955 (19.1%) had missing gestational timing of exposure in pregnancy. Complete case analysis was not appropriate for analyzing seasonal influenza vaccine exposure by trimester as missingness occurred in >5% of the population and the missing observations were likely not missing completely at random (Yang 2016 Int J Stat Med Res). Missing observations included children whose mothers received the vaccine in a setting other than a physician's office, such as at a pharmacy or in an occupational setting; such children may be systematically different than children whose mothers received the vaccine in a physician's office. Complete case analysis could therefore introduce bias.

The main analytic approach was, therefore, to impute missing gestation age in days for 1955 children with missing gestational age at seasonal influenza vaccine exposure *in utero* using multiple imputation by chained equations (fully conditional specification) using predictive mean matching for imputing gestational age in days at seasonal influenza vaccine exposure. The model for imputing missing gestational age at exposure included all covariates used in the propensity score model for influenza vaccination exposure and generated 10 imputed datasets that were then used to calculate stabilized inverse probability of treatment weights used in outcome-specific regression models, as per our primary analyses. We dealt with missing covariates similar to the main analyses (using multiple imputation by chained equations, generating 10 imputed datasets and including all covariates in the imputation model). As extremely large inverse probability of treatment weights were observed in this sub-group analysis, we applied an approach to all the trimester-specific analyses, whereby weights equal or less than the 1st percentile were set to the 1st percentile weight, and weights equal or greater than the 99th percentile weight were set to the 99th percentile weight (Austin 2015 Statistics in Medicine). Following this procedure, the imputed gestational day at seasonal influenza vaccine exposure was then classified into the trimester of exposure.

eTable 3. Description of "Obstetric Conditions Affecting Pregnancy" Covariate

Covariate	Description
Obstetric conditions affecting pregnancy[a]	Any documentation of: • Pruritic urticarial papules and plaques of pregnancy (PUPP) • Impetigo herpetiformis • Dermatitis herpetiformis • Separation of symphysis pubis • Gestational (pregnancy-induced) hypertension without proteinuria, includes: gestational hypertension not otherwise specified, mild pre-eclampsia • Hypertension, unspecified type • Pre-existing hypertension complicating pregnancy, childbirth and the puerperium • Pre-existing hypertensive disorder with superimposed proteinuria[b] • Pre-existing diabetes mellitus, type 1 • Pre-existing diabetes mellitus, type 2 • Pre-existing diabetes mellitus of other specified type present when pregnant during this pregnancy • Pre-existing diabetes mellitus of unspecified type present during this pregnancy • Diabetes mellitus arising in pregnancy, includes gestational diabetes • Diabetes mellitus in pregnancy, unspecified • Anemia in pregnancy (hemoglobin < 10gms% in pregnancy, as recorded before delivery) • Anemia in pregnancy (hemoglobin < 10gms% in pregnancy, as recorded after delivery) • Febrile morbidity (38 degrees or more on 2 or more occasions at least 4 hours apart, in any 48 hour period, excluding the first 24 hours after delivery, regardless of cause.) • Maternal fever > 38 degrees • Gestational hypertension with significant proteinuria • HELLP Syndrome (Hemolysis, elevated liver enzymes, low platelet count)

[a] This covariate was provided as a composite and we were therefore not able to differentiate pre-pregnancy versus pregnancy-related gestational diabetes and gestational hypertension. Due to the fact that these maternal gestational co-morbidities could be on the causal pathway between vaccination and the outcomes, we did not include this composite variable in the main analysis. These obstetric conditions were 22.5% among the vaccine exposed and 22.3% among the vaccine unexposed, and the inclusion of this covariate in the weighted outcome model did not markedly alter the effect estimates or confidence intervals, as shown in the sensitivity analyses.

[b] Proteinuria is defined using the following criteria: 24 hr urine - protein greater than or equal to 0.3g/day, or Urine dipstick (P.O.C.) greater than or equal to 1+ protein, or Protein-Creatinine ratio (PrCr) greater than or equal to 30g/mol.