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Pertussis Immunisation in Pregnancy Safety (PIPS) Study: A retrospective cohort study of safety outcomes in pregnant women vaccinated with Tdap vaccine

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ABSTRACT

Background: New Zealand has funded the administration of tetanus, diphtheria and acellular pertussis (Tdap) vaccine during pregnancy to prevent infant pertussis since 2013. The aim of this study was to assess the safety of Tdap vaccine administered to pregnant women as part of a national maternal immunisation programme.

Methods: We conducted a national retrospective observational study using linked administrative New Zealand datasets. The study population consisted of pregnant women eligible to receive funded Tdap vaccination from 28 to 38 weeks gestation in 2013. Primary study outcomes were based on prioritised adverse events for the assessment of vaccine safety in pregnant women, as defined by WHO and Brighton Collaboration taskforces. We examined the effect of Tdap vaccination on prioritised maternal outcomes using Cox proportional hazard models. Adjusted hazard ratios controlled for key confounding variables.

Results: In the cohort of 68,550 women eligible to receive funded antenatal Tdap vaccination during 2013, 8178 (11.9%) were vaccinated and 60,372 (88.1%) were unvaccinated. The use of Tdap in pregnancy was not associated with an increase in the rate of primary outcomes, including preterm labour; pre-eclampsia; pre-eclampsia with severe features; eclampsia; gestational hypertension; fetal growth restriction; or post-partum haemorrhage. Tdap also did not increase secondary outcomes, including gestational diabetes mellitus; antenatal bleeding; placental abruption; premature rupture of membranes; preterm delivery; fetal distress; chorioamnionitis; or, maternal fever during or after labour. Lactation disorders was the only secondary maternal outcome with a significantly increased hazard ratio. Tdap vaccine had a protective effect on pre-eclampsia with severe features, preterm labour, preterm delivery, and antenatal bleeding.

Conclusion: We did not detect any biologically plausible adverse maternal outcomes following Tdap vaccination during pregnancy. This study provides further assurance that Tdap administration during pregnancy is not associated with unexpected safety risks.

Abbreviations: AHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ID, identifiers; IMMS, Immunisation Subsidies Collection; ICD-10-AM, International Classification of Disease 10, Australian Modification; MAT, National Maternity Collection Dataset; MoH, Ministry of Health; MORT, Mortality Data Set; NHI, National Health Index; NMDS, National Minimum Data Set; NZ, New Zealand; NZDep2013, New Zealand Deprivation Index 2013; PIPS, Pertussis Immunisation in Pregnancy Safety; PROM, pre-labour rupture of membranes; SD, standard deviation; SGA, small for gestational age; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; UK, United Kingdom; US, United States; WHO, World Health Organization.

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1. Introduction

Bordetella pertussis is a highly-contagious, gram-negative bacterium causing respiratory disease. While pertussis infections can be mild or asymptomatic in adults and older children, pertussis can cause severe morbidity and mortality in infants, particularly among those too young to be vaccinated. Pertussis vaccination during pregnancy both protects the mother from pertussis infection and allows for maternal antibody transfer to the fetus, thereby protecting the infant from pertussis infection during the first months of life [1]. In 2011, the United States (US) Advisory Committee on Immunisation Practices recommended that tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine be given to any person, including previously unvaccinated pregnant women, likely to be in close contact with young infants under the age of one year [2]. In 2012, the United Kingdom (UK) Joint Committee on Vaccination and Immunisation recommended a pertussis vaccination program for pregnant women [3].

Until 2014, there were sparse data on the safety of Tdap vaccine during pregnancy. Data from small post-marketing surveillance studies and the US Vaccine Adverse Event Reporting System did not suggest increased adverse events among pregnant women receiving Tdap [4–8]. More recently, larger observational studies have contributed to the safety profile of Tdap during pregnancy [9–14], although Tdap was associated with chorioamnionitis in one study [10]. Other studies have reported Tdap vaccination association with a reduced risk of having preterm delivery, small for gestational age (SGA), length of neonatal hospitalisation [15], and caesarean delivery [16]. While there are currently no concerns about the safety of Tdap in pregnancy, most data come from US populations [8,10,11,14–17] and there are no nationally representative studies in New Zealand.

Between 2011 and 2013, New Zealand (NZ) experienced a large pertussis epidemic. Almost half of notified cases were in infants less than one year and nearly all notified cases in infants under six weeks were hospitalised [18]. In response, a maternal pertussis booster was recommended, and subsequently funded by the NZ Ministry of Health (MoH) from 2013 for pregnant women from 28 to 38 weeks gestation. The Pertussis Immunisation in Pregnancy Safety (PIPS) studies are three observational studies in NZ examining the safety of Tdap immunisation during pregnancy. The first two components were active safety surveillance to evaluate reactogenicity for maternal and infant outcomes among two cohorts totalling 793 pregnant women. There were no serious adverse events attributable to receipt of Tdap [19,20].

The aim of this PIPS study was to assess the safety of Tdap vaccine administered to pregnant women in 2013. This retrospective, data-linking study used national databases from all pregnant women in NZ in 2013 to examine the difference in hospitalisations for prioritised maternal outcomes between Tdap vaccinated and unvaccinated women during pregnancy.

2. Methods

2.1. Study population and variables

There were 107,084 pregnancies ending in delivery in New Zealand in 2013. We excluded pregnancies with gestational age <20 weeks or birthweight <400 g (n = 60); missing maternal age (n = 246); missing gestational age (n = 4863); and live born babies <28 weeks gestation (2 9 9). We did not consider pregnancies that never entered the eligibility window for Tdap vaccination (i.e. 28–38 weeks gestation) in 2013 (n = 33,365). Thus, the analytic study population consisted of all pregnancies resulting in a delivery of a live born baby or stillbirth of at least 20 weeks gestation, and who were eligible to receive NZ MoH-funded Tdap (Boostrix, GSK) vaccination from 28 to 38 weeks gestation in 2013 (n = 68,550). Only outcomes that occurred ≥28 week gestation or after the date of first Tdap vaccination are considered in the analysis.

The main exposure was Tdap vaccination during pregnancy. Study outcomes were based on prioritised adverse events following immunisation, categorised as "priority outcomes", "outcomes", and "suggested outcomes", for the assessment of vaccine safety in pregnant women, as defined by World Health Organisation (WHO) and Brighton Collaboration taskforces [21]. This approach facilitates harmonisation of studies regarding safety assessment of vaccination during pregnancy. Using WHO and Brighton Collaboration prioritised adverse events as a guide, we scanned International Classification of Disease 10, Australian Modification (ICD-10-AM) codes from relevant chapters (O, Z) to identify maternal outcomes potentially associated with Tdap vaccination during pregnancy. Except for duration of pregnancy, outcomes were taken from the National Minimum Data Set (NMDS) and defined dichotomously by the presence of specified ICD-10-AM codes in the primary or other possible diagnosis fields describing an inpatient episode of care. Primary outcomes (including "priority outcomes" and corresponding ICD-10-AM codes) included hospitalisations for: chronic hypertension with superimposed pre-eclampsia (O11); gestational hypertension (O13-O16); pre-eclampsia (O14.0, 9); pre-eclampsia with severe features (O14.1); eclampsia (O15); fetal growth restriction (O36.5); preterm labour (O60.0, 2); and post-partum haemorrhage (O72); maternal death (O95); and, stillbirth (Z37). Secondary outcomes (including "outcomes" and "suggested outcomes") included hospitalisations for: deep vein thrombosis (O22.3); gestational diabetes mellitus (O24.4); pre-labour rupture of membranes (PROM) (O42.0); placental abruption (O45); antenatal bleeding (O46); preterm delivery (O60.1, 3); fetal distress (O68); uterine rupture (O71.0, 1); maternal fever during labour (O75.2); maternal fever after labour (O86.4); maternal cardiomyopathy (O90.3); lactation disorders (agalactia or hypogalactia) (O92.3-5); anaemia during pregnancy and purpura (O99); and, maternal neurologic disorders (O99.3). We did not separate preterm premature rupture of membranes from PROM in our analysis; and, we did not examine the following outcomes and suggested outcomes: mastitis; autoimmune disorders; and maternal seizures.

2.2. Data sources

National Health Index (NHI) Database – contains demographic information for all New Zealanders. NHI identifiers (ID), date of birth, date of death and gender are static; however, remaining data fields may change over time. Data fields relevant to this study include NHI ID (encrypted), date of birth, date of death, prioritised ethnicity, geographic area of residence, and the NZ Deprivation Index 2013 (NZDep2013). NZDep2013 is a validated measure of small-area socioeconomic deprivation based on a combination of census data related to income, home ownership, employment, qualifications, family structure, housing, access to transport and communications [22]. NZDep2013 is measured in deciles with the wealthiest 10% of the population in decile ten and the poorest 10% in decile one.

National Minimum Data Set (NMDS) – contains records of all hospital discharges in NZ following inpatient episodes of care. ICD-10-AM diagnosis codes (up to 100 diagnosis codes are available for each admission event) are contained in the NMDS. Other dataata fields relevant to this study include NHI ID (encrypted), admission event ID, facility code, admission date, discharge date, and length of stay.

Mortality dataset (MORT) – classifies the underlying cause of death for all deaths registered in NZ, including all fetal deaths (stillbirths). MORT data fields related to infants include NHI ID

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