Pertussis Immunisation in Pregnancy Safety (PIPS) Study: A retrospective cohort study of safety outcomes in infants exposed to Tdap vaccine in utero

Helen Petousis-Harris[a], Yannan Jiang[b] Lennex Yu[b], Donna Watson[c], Tony Walls[d], Nikki Turner[c], Anna S Howe[a], Jennifer Griffin[e]

[a] Vaccine Datalink and Research Group, Department of General Practice & Primary Healthcare, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand h.petousis-harris@auckland.ac.nz;

[b] Department of Statistics, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

[c] Immunisation Advisory Centre, Department of General Practice & Primary Healthcare, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

[d] Department of Paediatrics, University of Otago, PO Box 56, Dunedin 9054, New Zealand tony.walls@otago.ac.nz

[e] Social, Statistical, and Environmental Sciences, RTI International, 3040 East Cornwallis Road, Research Triangle Park, NC, USA 27709-2194

Corresponding author.

Dr Helen Petousis-Harris, h.petousis-harris@auckland.ac.nz

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Abstract

We aimed to evaluate the safety of maternal Tdap we assessed health events by examining the difference in birth and hospital-related outcomes of infants with and without fetal exposure to Tdap.

This was a retrospective cohort study using linked administrative datasets. The study population were all live-born infants in New Zealand (NZ) weighing at least 400 grams at delivery and born to women who were eligible for the government funded, national-level vaccination program in 2013. Infants were followed from birth up to one year of age.

There were a total of 69,389 eligible infants in the cohort. Of these, 8,299 infants were born to 8,178 mothers exposed to Tdap (12%), primarily between 28-38 weeks gestation as per the national schedule. Among the outcomes, we found a reduced risk for moderate to late preterm birth, low birth weight, small for gestational age, large for gestational age, respiratory distress syndrome, transient tachypnea of newborn, tachycardia or bradycardia, haemolytic diseases, other neonatal jaundice, anaemia, syndrome of infant of mother with gestational diabetes, and hypoglycemia in infants born to vaccinated mothers. There was no association between maternal Tdap and stillbirth, infant Apgar score at 5 minutes after birth, microcephaly, asphyxia, sepsis or infection, or hypoxic ischemic encephalopathy. Infant exposure to Tdap during pregnancy was associated with a higher mean birthweight (not clinically significant) and higher odds for ankyloglossia and neonatal erythema toxicum diagnoses. There were insufficient observations to allow examination of the effect of Tdap on extreme preterm and very preterm birth, and infant death.

Overall, we found no outcomes of concern associated with the administration of Tdap during pregnancy.

NZ Health and Disability Ethics Committee Approval #14/NTA/169/AM05

Introduction

Pertussis vaccination programmes have had a dramatic impact on pertussis morbidity and mortality, particularly for infants. The burden of severe morbidity and mortality now falls primarily on infants too young to be vaccinated. However, a resurgence in disease is being observed in many countries using acellular vaccines [1] and, to a lesser extent, countries using whole-cell vaccines [2].

Natural immunity to pertussis varies in terms of completeness and duration. Furthermore, immunity via current acellular vaccines, while preventing clinical disease [3], does not prevent carriage or transmission [4, 5]. These issues pose challenges for the control of pertussis.

Maternal immunisation as a strategy to prevent neonatal and infant mortality has been well illustrated with the success of the World Health Organization (WHO)/UNICEF Neonatal Tetanus Elimination programme in low-income settings. Following the implementation of maternal tetanus immunisation programmes in at-risk populations, mortality from neonatal tetanus declined by 94% [95% CI: 80, 98)] [6]. Evidence for the effectiveness of maternal influenza vaccination in preventing influenza for the first months of life has also supported the move to a maternal vaccination approach [7]. Since 2011, some countries, such as the UK, have begun maternal pertussis immunisation [8, 9] and the strategy has proved highly effective [10-13].

While there are no theoretical safety concerns about using inactive or subunit vaccines in pregnant women [14] there were few empirical data available during the early years of these programmes [15].

Between 2011 and 2013, New Zealand (NZ) experienced the largest pertussis epidemic since 2000. The number of notified cases of pertussis rose dramatically from July 2011 and remained high throughout 2012 and 2013, with rates of over 270/100,000 infants under one year of age. Among notified cases in the less than six weeks of age group, 56% were hospitalised, with 23% of these requiring multiple hospitalisations. Because of this disease burden, a booster dose of acellular pertussis vaccine was recommended in 2012 and then funded in 2013 for women between 28–38 weeks gestation.

This is the second paper that reports on outcomes from a retrospective data-linking study that aimed to assess the safety of Tdap vaccine administered to pregnant women in NZ in 2013.

We previously reported the maternal outcomes [16]; here, we report infant outcomes by examining the difference in birth and hospital-related outcomes of infants with and without fetal exposure to Tdap.

Methods

Study population and variables

The study population included all live-born infants in NZ weighing at least 400 grams at delivery and born to women who were eligible for the NZ Ministry of Health (MoH)-funded, national-level vaccination program in 2013 (that is, between 28-38 weeks gestation). Infants were followed from birth up to one year of age (Figure 1.).

The independent binary variable was exposure to Tdap during the mother's pregnancy.

Study outcomes

The study outcomes were prioritized according to the categories presented in the assessment of vaccine safety in pregnant women, as defined by WHO and Brighton Collaboration taskforce, and termed 'priority outcomes', 'outcomes', and 'suggested outcomes' [17]. We used these outcomes as a guide and linked them to International Classification of Disease 10, Australian Modification (ICD-10-AM) codes from relevant chapters A, B, E, F, G, J, P, Q, R and Z to identify outcomes potentially associated with exposure to maternal Tdap vaccination.

Each outcome variable is dichotomous, with possible values of yes or no. Where an infant experienced the same outcome on multiple occasions during the study period, only the first episode was considered. Priority outcomes were stillbirth, perinatal death, neonatal death, infant death, preterm birth, small for gestational age (SGA), congenital anomalies (major and minor), asphyxia, infection, and sudden infant death syndrome. Other outcomes with significant findings are also reported. We included all codes across 99 possible diagnosis fields except the Q-codes (congenital anomalies) where only the primary codes were used.

Additional covariates include demographic and clinical characteristics and the model of care variable (midwife, obstetrician, general practitioner).

Data sources

Our data sources for this study have been previously described in detail [16]. They consisted of: the National Health Index Database of demographic information; National Minimum Data Set of all hospital discharges in NZ following inpatient episodes of care; Mortality Data Set of underlying causes of all deaths registered in NZ, including fetal deaths (stillbirths); National Maternity Collection of data on primary maternity services and inpatient and day-

patient health event data from nine months before and three months after a birth for mothers and infants; and the Immunisation Subsidies Collection of data on the fee-for-service payments made to general practitioners for providing government-funded immunisations.

Statistical methods

For all infants, follow-up began at birth and infants were censored at the first event outcome of: death, first birthday, or loss to follow-up (no record in any of the data sources).

Demographics and clinical characteristics of infants and mothers were first summarised descriptively, overall and by infants who did and did not have fetal exposure to Tdap. Continuous variables were described as mean, standard deviation (SD), median and inter-quartile range (Q1, Q3). Categorical variables were described as frequency and percentage.

Each reported outcome (with at least one event) was next described quantitatively with frequencies and incidence rates, for exposed and unexposed infant groups separately. The median and interquartile range (Q1, Q3) of infants' age at the time of each outcome was also reported.

The relationship between fetal exposure to Tdap and infant outcomes were investigated using adjusted regression models appropriate to the distribution of outcome. Adjusted regression analyses accounted for pre-defined confounding variables and were used to support the main conclusions. Each model was adjusted for: birth status (single live birth, other birth); maternal ethnicity (Māori, Pacific, Asian, NZ European or other); NZ Deprivation Index 2013 (deciles grouped into quintiles); maternal age (in years); history of antenatal care (total number of lead maternity carer visits); maternal body mass index (kg/m2); history of chronic disease (yes, no); parity (0, 1+); model of care (District Health Board (DHB), midwife, obstetrician/general practitioner, no lead maternity carer/other); and influenza vaccination (yes, no) during the same pregnancy. Outcomes were excluded if the proportion of events was <0.1% in either exposed or unexposed group, or the number of events in the exposed group was <10.

Continuous outcomes (birthweight and Apgar score at 5 minutes after birth) were analysed using linear regression models. The effect of fetal Tdap exposure was estimated as mean difference with 95% confidence intervals. Those outcomes diagnosed at delivery with no follow-up time were considered as a binary variable and analysed using logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported accordingly. An

OR of <1 indicated lower odds of having the outcome with fetal exposure to Tdap and was statistically significant if the CI didn't include 1.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided at 5% significance level ($p < 0.05$).

Results

Study cohort

There were a total of 69,389 eligible infants in the cohort. Of these, 8,299 infants were born to 8,178 mothers exposed to Tdap (12%) (Figure 1).

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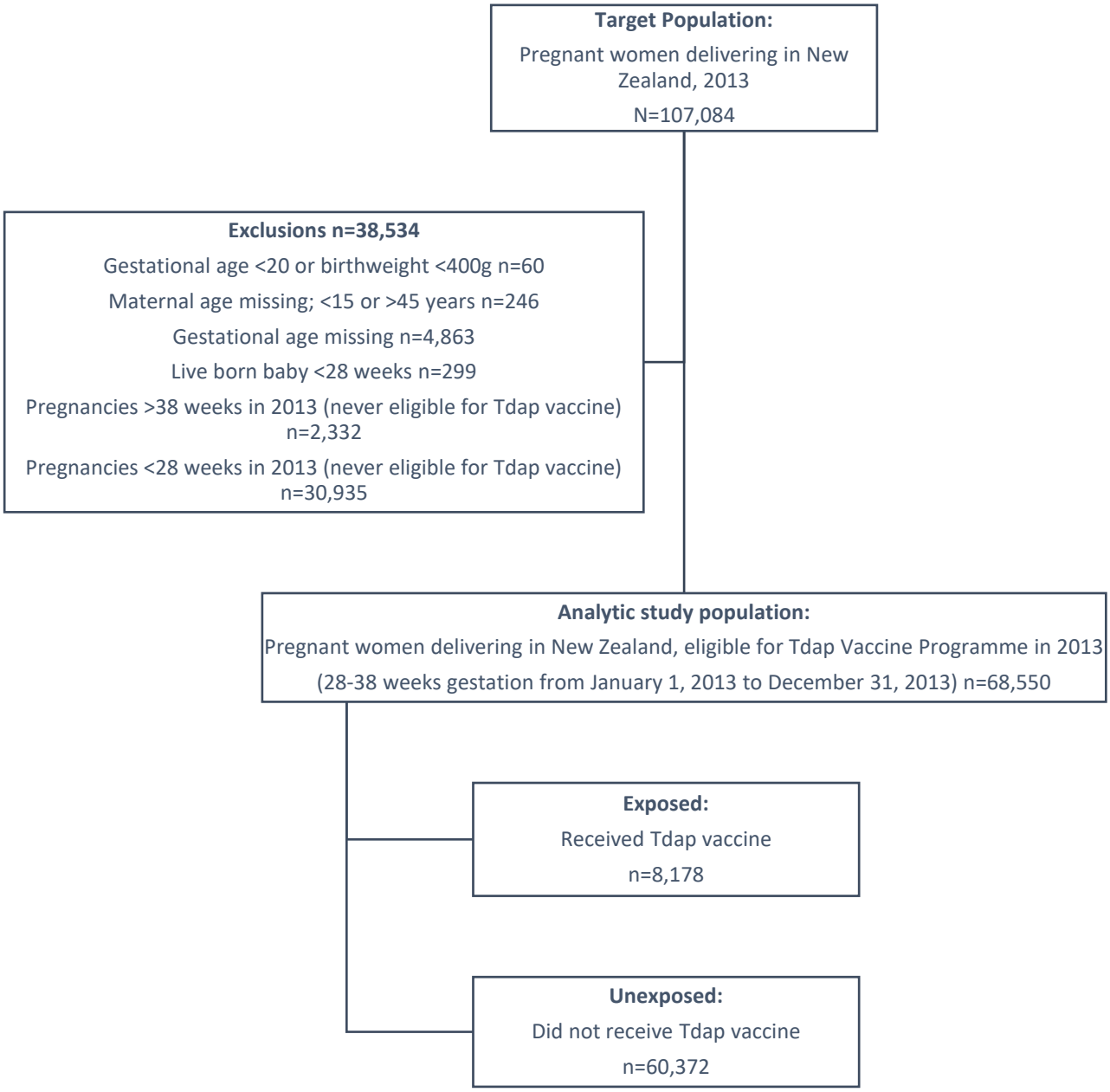

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158 *Figure 1. Flow of study population*

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161 Of infants born to women eligible to receive the vaccine, 51.2% were male. Infants of
162 European ethnicity comprised 67.0% of the vaccine-exposed group, while infants of Māori
163 ethnicity comprised 13.2%. The deprivation quintile of exposed infants ranged between
164 20.4% and 21.7% for the first four deprivation quintiles. The most deprived quintile
165 contributed 15.2% of exposed infants (Table 1).

166 The effect of maternal Tdap on hospital-related infant outcomes diagnosed at birth, on
167 eligible maternities, by Tdap exposure are summarised in Tables 2 and 3.

168

169 **TABLE 1. Demographics of infants born to women* who were eligible† to receive funded vaccination during**
170 **pregnancy between 01 January and 31 December 2013, New Zealand**

	Mother Tdap vaccination					
	Exposed		Unexposed		Total	
	N	%	N	%	N	%
Total	8,299	12.0	61,090	88.0	69,389	100.0
Infant characteristics						
Gender						
Male	4,249	51.2	31,283	51.2	35,532	51.2
Female	4,050	48.8	29,805	48.8	33,855	48.8
Missing	0	0.0	2	0.0	2	0.0
Infant ethnicity						
Maori	1,098	13.2	17,271	28.3	18,369	26.5
Pacific	420	5.1	7,022	11.5	7,442	10.7
Asian	1,216	14.7	8,629	14.1	9,845	14.2
European/Other	5,563	67.0	28,142	46.1	33,705	48.6
Missing	2	0.0	26	0.0	28	0.0
NZ Deprivation Index 2013						
Mean (SD)	5.2 (2.8)		6.4 (2.8)		6.3 (2.8)	
Median (Q1,Q3)	5.0 (3.0,8.0)		7.0 (4.0,9.0)		7.0 (4.0,9.0)	
1–2 (least deprived)	1,805	21.7	7,937	13.0	9,742	14.0
3–4	1,783	21.5	9,216	15.1	10,999	15.9
5–6	1,697	20.4	10,861	17.8	12,558	18.1
7–8	1,751	21.1	14,106	23.1	15,857	22.9
9–10 (most deprived)	1,263	15.2	18,963	31.0	20,226	29.1
Missing	0	0.0	7	0.0	7	0.0
DHB						
Northland	216	2.6	2,293	3.8	2,509	3.6
Waitemata	894	10.8	8,151	13.3	9,045	13.0
Auckland	1,130	13.6	6,253	10.2	7,383	10.6
Counties Manukau	730	8.8	8,773	14.4	9,503	13.7
Waikato	292	3.5	5,858	9.6	6,150	8.9
Lakes	95	1.1	1,582	2.6	1,677	2.4
Bay of Plenty	267	3.2	2,977	4.9	3,244	4.7
Tairawhiti	92	1.1	746	1.2	838	1.2
Hawke's Bay	162	2.0	2,379	3.9	2,541	3.7
Taranaki	145	1.7	1,629	2.7	1,774	2.6
Mid Central	241	2.9	2,257	3.7	2,498	3.6
Whanganui	99	1.2	865	1.4	964	1.4
Capital and Coast	861	10.4	3,479	5.7	4,340	6.3
Hutt	251	3.0	1,997	3.3	2,248	3.2
Wairarapa	79	1.0	474	0.8	553	0.8
Nelson Marlborough	398	4.8	1,404	2.3	1,802	2.6
West Coast	10	0.1	430	0.7	440	0.6
Canterbury	1,511	18.2	5,444	8.9	6,955	10.0
South Canterbury	154	1.9	606	1.0	760	1.1
Southern	667	8.0	3,370	5.5	4,037	5.8
Overseas	5	0.1	123	0.2	128	0.2

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	Mother Tdap vaccination					
	Exposed		Unexposed		Total	
	N	%	N	%	N	%
Apgar score at 5 minutes after birth						
Mean (SD)	9.5 (0.9)		9.5 (0.9)		9.5 (0.9)	
Median (Q1,Q3)	10.0 (9.0,10.0)		10.0 (9.0,10.0)		10.0 (9.0,10.0)	
Poor (Apgar 1–3)	17	0.2	116	0.2	133	0.2
Moderate concern (Apgar 4–6)	109	1.3	720	1.2	829	1.2
Normal (Apgar 7–10)	7,534	90.8	52,969	86.7	60,503	87.2
Missing	639	7.7	7,285	11.9	7,924	11.4
Birth weight (g)						
Mean (SD)	3,467.3 (532.5)		3,429.0 (592.5)		3,433.6 (585.6)	
Median (Q1,Q3)	3,485.0 (3,140.0,3,800.0)		3,450.0 (3,090.0,3,795.0)		3,450.0 (3,100.0,3,800.0)	
Less than 1,000g	1	0.0	31	0.1	32	0.0
1,000 – 2,499g	315	3.8	3,208	5.3	3,523	5.1
2,500g or above	7,747	93.3	55,098	90.2	62,845	90.6
Missing	236	2.8	2,753	4.5	2,989	4.3
Mother characteristics						
Maternal ethnicity						
Maori	955	11.5	16,095	26.3	17,050	24.6
Pacific	394	4.7	7,034	11.5	7,428	10.7
Asian	1,197	14.4	8,484	13.9	9,681	14.0
European/Other	5,751	69.3	29,470	48.2	35,221	50.8
Missing	2	0.0	7	0.0	9	0.0
Age (years) at last menstrual period						
Mean (SD)	30.7 (5.4)		28.3 (6.1)		28.6 (6.1)	
Median (Q1,Q3)	31.0 (27.0,35.0)		28.0 (24.0,33.0)		29.0 (24.0,33.0)	
15–20 years	236	2.8	4,984	8.2	5,220	7.5
20–24 years	850	10.2	12,590	20.6	13,440	19.4
25–29 years	2,168	26.1	16,802	27.5	18,970	27.3
30–34 years	2,951	35.6	16,310	26.7	19,261	27.8
35–39 years	1,763	21.2	8,629	14.1	10,392	15.0
40–45 years	331	4.0	1,775	2.9	2,106	3.0
Gravidity						
Mean (SD)	2.3 (1.4)		2.6 (1.8)		2.6 (1.8)	
Median (Q1,Q3)	2.0 (1.0,3.0)		2.0 (1.0,3.0)		2.0 (1.0,3.0)	
0	1	0.0	3	0.0	4	0.0
1	2,793	33.7	17,030	27.9	19,823	28.6
2	2,597	31.3	16,455	26.9	19,052	27.5
3	1,400	16.9	10,670	17.5	12,070	17.4
4	717	8.6	5,989	9.8	6,706	9.7
5	303	3.7	3,307	5.4	3,610	5.2
6+	269	3.2	4,070	6.7	4,339	6.3
Missing	219	2.6	3,566	5.8	3,785	5.5

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	Mother Tdap vaccination					
	Exposed		Unexposed		Total	
	N	%	N	%	N	%
Parity						
Mean (SD)	0.8 (0.9)		1.1 (1.3)		1.1 (1.3)	
Median (Q1,Q3)	1.0 (0.0,1.0)		1.0 (0.0,2.0)		1.0 (0.0,2.0)	
0	3,642	43.9	21,916	35.9	25,558	36.8
1	2,915	35.1	19,085	31.2	22,000	31.7
2	1,023	12.3	8,840	14.5	9,863	14.2
3	266	3.2	3,652	6.0	3,918	5.6
4	71	0.9	1,529	2.5	1,600	2.3
5	25	0.3	783	1.3	808	1.2
6+	16	0.2	752	1.2	768	1.1
Missing	341	4.1	4,533	7.4	4,874	7.0
History of stillbirth						
Yes	77	0.9	596	1.0	673	1.0
No	8,222	99.1	60,494	99.0	68,716	99.0
History of preterm birth						
Yes	214	2.6	1,961	3.2	2,175	3.1
No	8,085	97.4	59,129	96.8	67,214	96.9
History of chronic disease						
Yes	111	1.3	956	1.6	1,067	1.5
No	8,188	98.7	60,134	98.4	68,322	98.5
History of antenatal care (no. of LMC visits)						
Mean (SD)	9.7 (3.5)		9.2 (3.8)		9.3 (3.8)	
Median (Q1,Q3)	10.0 (7.0,12.0)		9.0 (7.0,12.0)		9.0 (7.0,12.0)	
0 (none)	113	1.4	761	1.2	874	1.3
1–4 (insufficient)	390	4.7	4,439	7.3	4,829	7.0
5–13 (approximately sufficient)	6,175	74.4	42,774	70.0	48,949	70.5
14–16 (greater than sufficient)	694	8.4	3,756	6.1	4,450	6.4
>16 (very high care/complex pregnancy)	342	4.1	2,138	3.5	2,480	3.6
Missing	585	7.0	7,222	11.8	7,807	11.3
Model of care						
DHB	325	3.9	3,388	5.5	3,713	5.4
MWF	6,615	79.7	51,181	83.8	57,796	83.3
GP	111	1.3	442	0.7	553	0.8
OBS	1,024	12.3	2,878	4.7	3,902	5.6
Other	13	0.2	28	0.0	41	0.1
No LMC	211	2.5	3,173	5.2	3,384	4.9
Mother BMI						
Mean (SD)	25.4 (5.4)		26.5 (6.2)		26.3 (6.1)	
Median (Q1,Q3)	24.0 (22.0,28.0)		25.0 (22.0,30.0)		25.0 (22.0,29.0)	
Underweight (<18.5)	209	2.5	1,619	2.7	1,828	2.6
Healthy weight (18.5–24)	4,136	49.8	25,073	41.0	29,209	42.1
Overweight (25–29)	2,308	27.8	16,277	26.6	18,585	26.8
Obese (30+)	1,417	17.1	14,513	23.8	15,930	23.0
Missing	229	2.8	3,608	5.9	3,837	5.5
Current tobacco use						
Yes	550	6.6	11,823	19.4	12,373	17.8
No	7,749	93.4	49,267	80.6	57,016	82.2

	Mother Tdap vaccination					
	Exposed		Unexposed		Total	
	N	%	N	%	N	%
Influenza vaccination						
Yes	3,833	46.2	5,187	8.5	9,020	13.0
No	4,466	53.8	55,903	91.5	60,369	87.0

* Women with a surviving fetus at 20 weeks gestation or who delivered an infant weighing at least 400 grams

† 28–38 weeks gestation during 2013

NOTES: SD = standard deviation; Q1 = first quartile; Q3 = third quartile; DHB = district health board; MWF = midwife; GP = general practitioner; OBS = obstetrician; LMC = lead maternity carer; BMI = body mass index

176 **TABLE 2. Effect of maternal Tdap on hospital-related infant outcomes diagnosed at birth, on eligible maternities, * by Tdap exposure, New Zealand ($N_{Exposed}$ = 8,299;**
177 **$N_{Unexposed}$ = 61,090; N_{Total} = 69,389)**

Outcome†	Description	Tdap (Exposed=1, Unexposed=0)	N (%)	Unadjusted OR‡ (95% CI)	P value	Adjusted OR‡§ (95% CI)	P value
P00	Fetus and newborn affected by maternal conditions	1	14 (0.2)	1.085 (0.619,1.902)	0.7760	1.062 (0.558,2.020)	0.8550
		0	95 (0.2)				
P01	Fetus and newborn affected by maternal complications of pregnancy	1	19 (0.2)	0.999 (0.618,1.614)	0.9968	0.906 (0.526,1.561)	0.7229
		0	140 (0.2)				
P02	Fetus and newborn affected by abnormality of membranes	1	27 (0.3)	1.163 (0.774,1.746)	0.4670	0.911 (0.557,1.490)	0.7112
		0	171 (0.3)				
P03	Fetus and newborn affected by complications of labor and delivery	1	131 (1.6)	1.169 (0.971,1.407)	0.0999	0.931 (0.750,1.155)	0.5141
		0	827 (1.4)				
P05.12	Small for gestational age (SGA)	1	117 (1.4)	0.711 (0.587,0.861)	**0.0005**	0.721 (0.574,0.905)	**0.0047**
		0	1,204 (2.0)				
P05.29	Other fetal malnutrition	1	92 (1.1)	0.832 (0.670,1.034)	0.0969	1.036 (0.807,1.329)	0.7833
		0	812 (1.3)				
P07.13	Low birth weight (LBW): 1500 to <2500 g	1	186 (2.2)	0.755 (0.648,0.880)	**0.0003**	0.784 (0.653,0.941)	**0.0089**
		0	1,800 (2.9)				
P07.323	Moderate to late preterm: 32 to <37 weeks	1	398 (4.8)	0.852 (0.766,0.947)	**0.0031**	0.831 (0.729,0.947)	**0.0055**
		0	3,412 (5.6)				
P08.0	High birth weight	1	45 (0.5)	0.883 (0.647,1.204)	0.4303	1.157 (0.824,1.625)	0.3995
		0	375 (0.6)				
P08.1	Large for gestational age infants	1	31 (0.4)	0.680 (0.470,0.983)	**0.0403**	0.567 (0.359,0.894)	**0.0147**
		0	335 (0.5)				
P12	Scalp injury due to birth trauma	1	84 (1.0)	1.171 (0.929,1.475)	0.1819	0.940 (0.720,1.228)	0.6514
		0	529 (0.9)				
P15.4	Birth trauma to face	1	28 (0.3)	1.079 (0.726,1.606)	0.7063	0.772 (0.484,1.232)	0.2781
		0	191 (0.3)				
P15.8	Other specified birth trauma	1	10 (0.1)	0.775 (0.404,1.487)	0.4430	0.670 (0.308,1.458)	0.3122
		0	95 (0.2)				
P20	Intrauterine hypoxia	1	28 (0.3)	0.698 (0.473,1.029)	0.0692	0.670 (0.429,1.047)	0.0788
		0	295 (0.5)				
P21	Asphyxia	1	49 (0.6)	1.135 (0.839,1.535)	0.4104	1.374 (0.968,1.951)	0.0751
		0	318 (0.5)				
P22.0	Respiratory distress syndrome	1	121 (1.5)	0.635 (0.526,0.765)	**<0.0001**	0.652 (0.524,0.811)	**0.0001**
		0	1,392 (2.3)				
P22.1	Transient tachypnea of newborn	1	247 (3.0)	0.891 (0.779,1.018)	0.0906	0.839 (0.721,0.975)	**0.0224**
		0	2,034 (3.3)				

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Outcome†	Description	Tdap (Exposed=1, Unexposed=0)	N (%)	Unadjusted OR‡ (95% CI)	P value	Adjusted OR‡§ (95% CI)	P value
P22.89_P28.2589	Respiratory distress	1	230 (2.8)	1.060 (0.921,1.219)	0.4165	0.998 (0.850,1.171)	0.9775
		0	1,600 (2.6)				
P23	Congenital pneumonia	1	24 (0.3)	0.870 (0.569,1.329)	0.5192	1.010 (0.629,1.622)	0.9675
		0	203 (0.3)				
P24.0	Meconium aspiration syndrome	1	11 (0.1)	0.736 (0.396,1.369)	0.3330	0.977 (0.497,1.921)	0.9461
		0	110 (0.2)				
P25	Interstitial emphysema and related conditions	1	43 (0.5)	1.344 (0.970,1.861)	0.0754	1.240 (0.860,1.787)	0.2495
		0	236 (0.4)				
P28.34	Apnea	1	70 (0.8)	0.702 (0.549,0.899)	**0.0049**	0.777 (0.585,1.031)	0.0803
		0	731 (1.2)				
P29.1	Tachycardia or bradycardia	1	55 (0.7)	0.785 (0.594,1.037)	0.0888	0.691 (0.501,0.954)	**0.0245**
		0	515 (0.8)				
P29.82	Benign and innocent cardiac murmurs in newborn	1	34 (0.4)	1.193 (0.830,1.715)	0.3415	1.098 (0.724,1.667)	0.6598
		0	210 (0.3)				
P36.89	Bacterial sepsis of newborn, specified or unspecified	1	37 (0.4)	0.803 (0.571,1.128)	0.2052	0.872 (0.599,1.270)	0.4763
		0	339 (0.6)				
P37.5	Candidiasis	1	17 (0.2)	0.702 (0.427,1.156)	0.1645	0.656 (0.381,1.131)	0.1294
		0	178 (0.3)				
P38	Omphalitis	1	29 (0.3)	1.180 (0.797,1.748)	0.4085	1.399 (0.875,2.236)	0.1606
		0	181 (0.3)				
P39.1	Neonatal conjunctivitis and dacryocystitis	1	82 (1.0)	0.961 (0.763,1.211)	0.7383	0.841 (0.641,1.103)	0.2111
		0	628 (1.0)				
P39.4	Neonatal skin infection	1	13 (0.2)	1.153 (0.642,2.070)	0.6329	1.352 (0.706,2.593)	0.3631
		0	83 (0.1)				
P54	Neonatal hemorrhage	1	18 (0.2)	0.914 (0.560,1.492)	0.7180	0.981 (0.571,1.683)	0.9435
		0	145 (0.2)				
P55	Haemolytic diseases	1	39 (0.5)	0.689 (0.496,0.957)	**0.0263**	0.663 (0.444,0.990)	**0.0445**
		0	416 (0.7)				
P59	Other neonatal jaundice	1	308 (3.7)	0.827 (0.733,0.932)	**0.0019**	0.869 (0.757,0.998)	**0.0466**
		0	2,722 (4.5)				
P61.0	Thrombocytopenia	1	13 (0.2)	0.633 (0.359,1.116)	0.1141	0.830 (0.440,1.567)	0.5657
		0	151 (0.2)				
P61.234	Anaemia	1	20 (0.2)	0.574 (0.364,0.905)	**0.0170**	0.461 (0.270,0.786)	**0.0045**
		0	256 (0.4)				
P70.0	Syndrome of infant of mother with gestational diabetes	1	50 (0.6)	0.682 (0.510,0.912)	**0.0099**	0.683 (0.487,0.960)	**0.0281**

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Outcome†	Description	Tdap (Exposed=1, Unexposed=0)	N (%)	Unadjusted OR‡ (95% CI)	P value	Adjusted OR‡§ (95% CI)	P value
		0	538 (0.9)				
P70.1	Syndrome of infant of a diabetic mother	1	18 (0.2)	0.633 (0.391,1.025)	0.0631	0.601 (0.278,1.300)	0.1957
		0	209 (0.3)				
P70.34	Hypoglycemia	1	236 (2.8)	0.792 (0.691,0.907)	**0.0008**	0.795 (0.681,0.929)	**0.0038**
		0	2,178 (3.6)				
P74.1	Dehydration of newborn	1	58 (0.7)	1.155 (0.875,1.525)	0.3091	1.093 (0.794,1.503)	0.5868
		0	370 (0.6)				
P74.23	Electrolyte anomalies (Na, K)	1	57 (0.7)	0.781 (0.594,1.028)	0.0778	0.844 (0.621,1.147)	0.2786
		0	536 (0.9)				
P80	Hypothermia	1	73 (0.9)	0.861 (0.675,1.099)	0.2297	0.964 (0.726,1.279)	0.7996
		0	623 (1.0)				
P81	Other disturbances of temperature regulation of newborn	1	59 (0.7)	1.287 (0.975,1.699)	0.0744	1.297 (0.947,1.775)	0.1052
		0	338 (0.6)				
P83.1	Neonatal erythema toxicum	1	47 (0.6)	1.583 (1.154,2.171)	**0.0044**	1.661 (1.163,2.372)	**0.0052**
		0	219 (0.4)				
P83.5	Congenital hydrocele	1	11 (0.1)	0.771 (0.414,1.436)	0.4123	0.782 (0.396,1.543)	0.4779
		0	105 (0.2)				
P83.89	Other conditions of integument	1	20 (0.2)	0.909 (0.571,1.447)	0.6862	0.986 (0.594,1.637)	0.9572
		0	162 (0.3)				
P90	Seizure	1	18 (0.2)	0.974 (0.596,1.594)	0.9179	1.059 (0.602,1.862)	0.8422
		0	136 (0.2)				
P91.6	Hypoxic Ischemic Encephalopathy	1	12 (0.1)	0.874 (0.480,1.592)	0.6606	0.786 (0.390,1.585)	0.5011
		0	101 (0.2)				
P92.0	Vomiting	1	36 (0.4)	1.228 (0.862,1.749)	0.2549	0.928 (0.612,1.406)	0.7231
		0	216 (0.4)				
P92.123589	Difficulty feeding	1	369 (4.4)	1.239 (1.107,1.386)	**0.0002**	1.054 (0.924,1.203)	0.4344
		0	2,212 (3.6)				
P94.2	Congenital hypotonia	1	15 (0.2)	0.898 (0.525,1.535)	0.6929	0.788 (0.413,1.504)	0.4703
		0	123 (0.2)				
P96.81	Jittery baby	1	32 (0.4)	1.197 (0.823,1.740)	0.3473	1.104 (0.705,1.728)	0.6666
		0	197 (0.3)				
Q38.1	Ankyloglossia	1	221 (2.7)	1.545 (1.334,1.789)	**<0.0001**	1.241 (1.044,1.474)	**0.0143**
		0	1,063 (1.7)				
Q66	Talipes equinovarus, metatarsus varus, or other congenital deformities of feet	1	33 (0.4)	0.880 (0.613,1.263)	0.4873	0.963 (0.612,1.516)	0.8707
		0	276 (0.5)				

178 * 28–38 weeks gestation during 2013

† Table includes outcomes diagnosed at delivery where N ≥ 10 and % ≥ 0.1 (please see Appendix 2 for ICD-10-AM code map).
‡ OR = odds ratio, which compares mothers exposed to Tdap with those unexposed. OR > 1 indicates greater likelihood of exposed group having the outcome if p-value < 0.05.
§ Logistic regression model adjusted for: birth status (single live birth, other birth); maternal ethnicity (Maori, Pacific, Asian, NZ European or other); NZ Deprivation Index 2013 (1-10); maternal age (in years); history of antenatal care (total no. of lead maternity carer visits); body mass index (kg/m2); history of chronic disease (yes, no); parity (0, 1+); model of care (DHB, midwife, obstetrician/general practitioner, no lead maternity carer/other); and influenza vaccination (yes, no)
NOTES: Q1 = first quartile; Q3 = third quartile; CI = confidence interval; ICD-10-AM = International Classification of Diseases, Tenth Revision, Australian Modification

186 **TABLE 3 Effect of maternal Tdap on infant's Apgar score at 5 minutes after birth and birthweight at delivery,**
187 **on eligible maternities,* by Tdap exposure, New Zealand ($N_{Exposed}$ = 8,299; $N_{Unexposed}$ = 61,090; N_{Total} = 69,389)**

Outcome†	Tdap	N	Mean (SD)	Unadjusted mean difference (95% CI)	P value	Adjusted mean difference (95% CI)	P value
Apgar score at 5 minutes after birth	Exposed	7,660	9.537 (0.879)	0.005 (-0.015,0.026)	0.6246	0.000 (-0.022,0.023)	0.9775
	Unexposed	53,810	9.531 (0.870)				
Birthweight (g)	Exposed	8,063	3,467 (532)	38.275 (24.640,51.911)	**<0.0001**	35.585 (21.392,49.778)	**<0.0001**
	Unexposed	58,337	3,429 (592)				

188 * 28–38 weeks gestation during 2013
189 † Generalized linear model adjusted for: birth status (single live birth, other birth); maternal ethnicity (Maori, Pacific, Asian, NZ European
190 or other); NZ Deprivation Index 2013 (1-10); maternal age (in years); history of antenatal care (total no. of lead maternity carer visits);
191 body mass index (kg/m2); history of chronic disease (yes, no); parity (0, 1+); model of care (DHB, midwife, obstetrician/general
192 practitioner, no lead maternity carer/other); and influenza vaccination (yes, no)
193 NOTES: SD = standard deviation; CI = confidence interval
194

Events of delivery

There were insufficient number of cases in the vaccine-exposed group to assess the association between Tdap exposure and stillbirth (n=9); extreme (n=0) and very preterm birth (n=9), and extreme (n=0) and very low birth weight (n=9).

We found a reduced risk associated with exposure to vaccine for moderate to late preterm birth (OR 0.83; 95% CI [0.73, 0.95]).

Physical examination and anthropometric measurements

There were insufficient observations available to allow examination of the effect of Tdap on extreme low birth weight (LBW) and very LBW.

There was no mean difference in Apgar score between vaccine-exposed and unexposed groups (Table 3). A small but significantly higher mean birthweight was observed in the vaccine-exposed group with a mean difference of 35.59g (95% CI [21.39, 49.78]).

We found protective effects of Tdap exposure for LBW (OR=0.78; 95% CI [0.65, 0.94]), SGA (OR=0.721; 95% CI [0.57, 0.91]), and large for gestational age (LGA) (OR=0.567; 95% CI (0.36, 0.89).

Congenital anomalies

Two congenital anomalies that had enough cases to include in the regression models were deformities of feet and ankyloglossia (tongue-tie). There was no association with deformities of feet (OR=0.963; 95% CI [0.61, 1.52]). There was an increased odds associated with ankyloglossia (OR=1.241; 95% CI [1.04, 1.47]). Among the infants in the restricted cohort (eligible to receive the vaccine) born to mothers eligible to receive Tdap, there were three infants in the cohort with microcephaly, none was born to mothers exposed to Tdap. There were insufficient observations in both the exposed and unexposed groups to explore other congenital anomalies

Neonatal conditions classified by organ system

There were insufficient observations available to allow examination of the effect of Tdap on neonatal sepsis due to Streptococcus, group B, other and unspecified streptococci, *Staphylococcus aureus*, other and unspecified staphylococci, *Escherichia coli*, anaerobes, congenital viral infections, congenital infectious and parasitic diseases, neonatal infective

mastitis, and neonatal urinary tract infection or infection specific to the perinatal period, specified or unspecified.

We found no association between exposure to vaccine and asphyxia, specified or unspecified sepsis, candidiasis, omphalitis, neonatal conjunctivitis and dacryocystitis, neonatal skin infection, or hypoxic ischemic encephalopathy. We found a protective effect of Tdap vaccine for respiratory distress syndrome (OR=0.65; 95% CI [0.52, 0.81]), transient tachypnea of newborn (OR=0.84; 95% CI [0.72, 0.98]), tachycardia or bradycardia (OR=0.69; 95% CI [0.50,0.95]), haemolytic diseases (OR= 0.66; 95% CI [0.44, 0.99]), other neonatal jaundice (OR=0.87; 95% CI [0.76, 0.10]), syndrome of infant of mother with gestational diabetes (OR=0.68; 95% CI [0.49, 0.96]), and hypoglycaemia OR=0.80; 95% CI [0.68, 0.93]).

There was one other infant outcome not elsewhere described that was significantly associated with exposure to Tdap, neonatal erythema toxicum. After adjustment the association r emained significant (OR=1.66; 95% CI [1.16, 2.37]).

Infant death

There were insufficient events (n=4) in the exposed group of the restricted cohort to allow examination of the effect of Tdap on infant death.

Discussion

This study sought to examine the safety for the infant after their mothers received Tdap during the pregnancy. We examined the difference in rates of key outcomes between those infants exposed and not exposed. Among the outcomes we found a reduced risk for moderate to late preterm birth, LBW, SGA, LGA, respiratory distress syndrome, transient tachypnea of newborn, tachycardia or bradycardia, haemolytic diseases, other neonatal jaundice, anaemia, syndrome of infant of mother with gestational diabetes, and hypoglycemia in infants born to vaccinated mothers. There was no association between maternal Tdap and stillbirth, infant Apgar score at 5 minutes after birth, microcephaly, asphyxia, sepsis or infection, or hypoxic ischemic encephalopathy. Infant exposure to Tdap during pregnancy was associated with a higher mean birthweight (not clinically significant) and higher odds for ankyloglossia and neonatal erythema toxicum diagnoses. There were insufficient observations to allow examination of the effect of Tdap on extreme preterm and very preterm birth, and infant death. Overall, we found no outcomes of concern associated with the administration of Tdap during pregnancy.

Interpretation

Since the implementation of maternal Tdap programmes internationally there are limited data on infants beyond birth outcomes. Most recently a Vaccine Safety Datalink (VSD) study assessed 413,034 live births from 2004 to 2014 for the risk of hospitalisation and showed no overall increased risk (adjusted OR=0.94; 95% CI [0.88, 1.01]) or death (adjusted OR=0.44; 95% CI [0.17, 1.13]) in the first six months of life associated with maternal pertussis [18]. While we did not measure overall hospitalisation, our findings support this study.

We found no increased risk for stillbirth among our cohort of infants exposed to maternal Tdap, consistent with other cohort studies [19, 20] from Texas, USA and the UK. While we had insufficient observations for infants born extremely preterm or very preterm, we found no increased risk for moderate to late preterm birth. The previous evidence regarding the relationship between Tdap vaccination and preterm birth is mixed. Several VSD studies have found no relationship between Tdap vaccination during pregnancy and preterm birth [21, 22]. The Texas-based study reported a non-significant trend towards a protective effect against preterm birth (>37 weeks) with an adjusted OR for preterm delivery of 0.68 (95% CI: 0.45, 1.03)) [23], and a retrospective cohort study found infants from unvaccinated mothers were more likely to be born preterm (<37 weeks), 6% compared with 12% (p=0.001) [19].

While we had insufficient observations available to allow examination of the effect of Tdap on extreme LBW and very LBW, we found a reduced risk for LBW associated with exposure to Tdap in pregnancy. In the Texas retrospective record review study, the adjusted OR for LBW was 0.76 (0.51–1.14) and very LBW was 0.24 (0.05–1.20) [23]. Likewise a VSD study found no association with LBW with an adjusted RR of 0.92 (0.78–1.09) [22]. In contrast the Texan study found greater risk for lower birthweights among decliners for Tdap in the third, fifth and tenth percentiles (p=0.004, 0.002, and 0.032 respectively) [19].

We found a significant association with reduction in SGA, in line with a maternal influenza study in which the protective effect remained even after consideration of time-dependent biases and confounding from baseline [24]. Unlike preterm birth, for which the protective effect of the vaccine disappeared after adjustments, the associations between vaccination and SGA remained consistent in all analytical approaches [24]. Previous published studies have not shown any association between maternal Tdap vaccination and SGA [21-23]. Our finding of no association between Tdap and 5-minute Apgar score is consistent with other studies [19, 26, 23].

While we examined many birth defects, all but two were too rare for analysis. Other studies have not identified any increased risk for birth defects associated with maternal Tdap [19, 23]. Due to the increased cases of microcephaly reported in Brazil and their temporal association with the recommendations for maternal Tdap we specifically assessed this as an outcome. As with a VSD analysis that assessed this [25], we found no association between maternal Tdap and microcephaly, with no cases in the Tdap-exposed group.

While most of our outcomes had a reduced risk or no association with maternal Tdap, we did find increased odds of ankyloglossia and neonatal erythema toxicum diagnoses among infants born to vaccinated mothers. Both are likely a result of residual confounding, or spurious association to the large number of endpoints. In NZ, both the diagnosis and management of ankyloglossia is controversial with opposing views on the need for treatment and a strong link to the diagnosis and management approaches for lactation disorders. The reported incidence in NZ has increased more than five-fold between 2007 and 2013 with variability in rates of diagnosis and management by region, ethnicity and socioeconomic group. This suggests an inconsistent diagnostic approach, which therefore impacts the reliability of these results. Erythema toxicum is a common rash in neonates and a diagnosis is strongly linked to

health-seeking behaviour. We did not consider either of these outcomes to be related to maternal Tdap.

While we adjusted for important confounding variables, including maternal age, ethnicity, socioeconomic status, ANC history, BMI, history of chronic disease, and parity, there may be residual confounding due to important variables not being included in administrative health datasets, such as maternal educational level or other provider/patient characteristics. For example, provider recommendation is an important predictor of a woman receiving Tdap vaccination during pregnancy [26]. Providers that recommend Tdap vaccination during pregnancy are likely to have other differences, such as the characteristics of their patients, type of patient selection and patient care. Measurement error and misclassification of binary confounders can also contribute to residual confounding. Further, we examined many exposures and did not consider confounders on an outcome-by-outcome basis. This analysis approach may have contributed to residual confounding leading to biased estimates.

There are other limitations of health administrative datasets. The NZ National Minimum Data Set is limited to hospital inpatient diagnostic codes for which the validity cannot be assessed, with the risk of a false positive and bias towards the null hypothesis; as such, the incidence rates of adverse infant outcomes may be underestimated. Additionally, a hospitalization diagnosis code does not necessarily reflect an incident outcome, as some outcomes may have occurred or presented earlier in pregnancy and only present in later pregnancy with severity requiring hospitalization. As previously reported [16], we conducted a small validation study of the Tdap exposure variable, comparing and primary healthcare organisation (PHO) data and found the immunisation dataset Tdap exposure had high specificity (98.8–99.7%), but low sensitivity (9–61%) among 22,710 pregnant women across seven PHOs, indicating 64% of pregnant women receiving Tdap were incorrectly classified as unvaccinated in the immunisation dataset. In the current study, differential misclassification of the Tdap exposure could be caused by differential quality of data across PHOs and hospitals and could lead to either over- or under-estimation of the effects of Tdap on neonatal outcomes. This potential exposure misclassification means that study results should be cautiously interpreted. In the current study, we only examined data for the first year after implementation (2013), which led to small numbers of outcomes. In addition, we did not account for infant primary vaccinations in our analysis for the longer-term follow-up period. However, the current approach will allow for repeated analyses in future years using the same databases, which are expected to improve over time.

Conclusions

Results from this study of adverse outcomes following exposure to maternal Tdap vaccination among the infants of pregnant women in NZ are consistent with other studies and provide further support for the safety of Tdap vaccination during pregnancy. This study evaluated a comprehensive range of infant outcomes in a national population cohort with up to one year follow up. Our findings support the safety of administration of pertussis immunisation during pregnancy.

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Contributions

Conceptualization, HPH, and TW; Methodology, HPH, JBG, LY, and YJ; Validation, JBG, and AH.; Formal Analysis, JBG, LY, and YJ; Investigation, HPH, JBG, LY, DW, and YJ; Resources, University of Auckland.; Data Curation, HPH, TW, NT, JBG, LY, DW, YJ, and AH.; Writing – Original Draft Preparation, HPH.; Writing – Review & Editing, JBG, TW, LY, YJ, NT, AH, and DW.; Visualization, LY, YJ, and DW.; Supervision, HPH, YJ, and DW.; Project Administration, DW; Funding Acquisition, HPH.

HPH and TW conceptualized the study. HPH acquired funding and developed metho, JBG, LY, and YJ conducted the data analyses. HPH, TW, AH, NT and DW were involved in outcome definition and/or data acquisition, and or outcome definitions, HPH drafted the manuscript. All authors participated in the interpretation of data, critically revised the manuscript, and approved the final version submitted.

Conflict of interest statement

HPH has served on advisory groups for GSK, Merck, and Pfizer, but does not personally receive honoraria. All other authors confirm that there are no known conflicts of interest associated with this publication.

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