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Maternal Pertussis Vaccination, Infant Immunization, and Risk of Pertussis

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abstract

OBJECTIVES: Following the introduction of jurisdictional maternal pertussis vaccination programs in Australia, we estimated maternal vaccine effectiveness (VE) and whether maternal pertussis vaccination modified the effectiveness of the first 3 primary doses of pertussis-containing vaccines.

METHODS: We conducted a population-based cohort study of 279 418 mother–infant pairs using probabilistic linkage of administrative health records in 3 Australian jurisdictions. Infants were maternally vaccinated if their mother had a documented pertussis vaccination ≥14 days before birth. Jurisdictional immunization records were used to identify receipt of the first 3 infant doses of pertussis-containing vaccines. Infant pertussis infections were identified using notifiable disease records. VE was estimated using Cox proportional hazard models.

RESULTS: Pertussis was administered during 51.7% (n = 144 429/279 418) of pregnancies, predominantly at 28–31 weeks' gestation. VE of maternal pertussis vaccination declined from 70.4% (95% confidence interval [CI], 50.5–82.3) among infants <2 months old to 43.3% (95% CI, 6.8–65.6) among infants 7–8 months old and was not significant after 8 months of age. Although we observed slightly lower VE point estimates for the third dose of infant pertussis vaccine among maternally vaccinated compared with unvaccinated infants (76.5% vs 92.9%, P = .002), we did not observe higher rates of pertussis infection (hazard ratio, 0.70; 95% CI, 0.61–3.39).

CONCLUSIONS: Pertussis vaccination near 28 weeks' gestation was associated with lower risk of infection among infants through 8 months of age. Although there was some evidence of lower effectiveness of infant vaccination among maternally vaccinated infants, this did not appear to translate to greater risk of disease.

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WHAT'S KNOWN ON THIS SUBJECT: Pertussis vaccination during pregnancy protects against pertussis infection during the first 6 months of age. However, the possible "blunting" effects of maternal antibodies on infants' response to primary immunization remains an important clinical question.

WHAT THIS STUDY ADDS: Despite evidence for lower effectiveness of the third infant dose of acellular pertussis vaccine among maternally vaccinated infants, this was not associated with a higher incidence of pertussis compared with infants with no history of maternal pertussis vaccination.

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Pertussis is a highly contagious, potentially severe respiratory illness. Despite a reduction in the burden of pertussis since the introduction of whole cell and acellular childhood vaccines, morbidity and mortality remain high in young infants, who account for 70% to 90% of all pertussis-attributable hospitalizations and deaths.[1,2] High morbidity and mortality in infants have led to the introduction of maternal vaccination programs to prevent infant infection in many high-income countries. Following pertussis epidemics between 2012 and 2013, the United States and United Kingdom introduced recommendations for vaccinating pregnant women against pertussis (maternal vaccination).[3,4] Between 2014 and 2015, Australian states and territories adopted maternal pertussis vaccination programs, implementing jurisdictional-funded programs for diphtheria-tetanus-acellular pertussis (dTpa) booster vaccinations at approximately 28 weeks' gestation.[5] In July 2018, maternal vaccination became federally funded in Australia under the National Immunization Program.[6]

Although there are strong data to support the effectiveness of maternal pertussis vaccination programs, there remains debate about the duration of protection, the importance of gestational age at vaccination, and potential effects on infant immune response to primary pertussis vaccination. Previous studies in the United Kingdom,[7,8] United States,[9–13] and Australia[14] have demonstrated that maternal dTpa vaccination is 43% to 93% effective against pertussis infection among infants <2 months old. However, few of these studies considered the impact of gestational timing of vaccination during pregnancy on vaccine effectiveness (VE) and few population-based studies have assessed the impact of maternal vaccination by receipt of infant vaccines.

Prior research has identified concerns about the potential for maternal antibodies to interfere with infants' responses to primary immunization with pertussis-containing and other vaccines, a mechanism referred to as "blunting."[15–18] Although several clinical trials and prospective cohort studies have observed lower immunologic responses and seroconversion among infants who were maternally vaccinated compared with maternally unvaccinated infants,[16,17,19] few large-scale observational studies have investigated the impacts of maternal vaccination on the effectiveness of infant pertussis immunization against clinical disease.

Our aim was (1) to provide robust estimates of maternal pertussis VE for preventing pertussis infection among infants, overall, by infant age, and by gestational age at vaccination and (2) to investigate possible blunting effects at the population level using real-world data.

METHODS

The Links2HealthierBubs cohort is a population-based cohort of mother–infant dyads in 3 Australian jurisdictions: Northern Territory (NT), Queensland (QLD), and Western Australia (WA), representing one-third of all Australian births. The study protocol is published elsewhere.[20] In brief, probabilistic record linkage of maternal and infant administrative data sources was used to establish the population-based cohorts within each participating jurisdiction. All mothers and their infants with a gestational age ≥20 weeks and/or a birth weight ≥400 g who were born after the introduction of the jurisdictional maternal pertussis vaccination program were eligible for inclusion in the cohort (NT, WA: after April 1, 2015; QLD: after August 1, 2014).[5]

Data Sources and Variable Measurement

Data sources for measuring maternal dTpa vaccination, pertussis infection, and covariates were linked with the maternal–infant cohort, including perinatal, birth and death register, hospital inpatient, immunization, and notifiable disease data for each jurisdiction. With exception to immunization data, these jurisdictional databases each feed into national data collections and apply standardized data collection procedures.

Perinatal data collections are statutorily mandated databases summarizing information related to all births in each jurisdiction.[21] We estimated the year and month of conception from the infant's date of birth minus the best clinical estimate of gestational age in days. Socioeconomic status was assigned based on the mother's residence at birth using the Index of Relative Socioeconomic Advantage and Disadvantage.[22]

During the study period, maternal pertussis vaccination was recommended during every pregnancy between 28 and 32 weeks of gestational age.[5] Maternal vaccination information was obtained from jurisdictional immunization registers and databases summarizing provider-reported immunization data (2014–2016) in addition to perinatal data collections (≥2016). These data sources were used to determine dTpa vaccination status (yes/no) and the gestation at vaccination during pregnancy (<28 weeks, 28–31 weeks, ≥32 weeks). We also extracted information on influenza vaccination status during pregnancy (yes/no) and whether influenza vaccine was coadministered with dTpa or at a separate appointment. In NT and QLD, where infant immunization data were available, we additionally extracted information on pertussis-containing vaccines (diphtheria-tetanus-acellular pertussis [DTaP]) administered to the child up to 18 months of age.[23] Under the National Immunization Program, children in Australia receive their first dose of hexavalent pertussis–containing vaccine (diphtheria-tetanus-pertussis-hepatitis B-polio-*Haemophilus influenzae* type b vaccine [Infanrix hexa]) at 2 months of age, their second dose at 4 months of age, and their third dose at 6 months of age.[24] A booster dose of diphtheria-tetanus-pertussis vaccine (Infanrix or Tripacel) is recommended at 18 months of age.[24] We used the date

of vaccination to assign the infant's age in months at the time of vaccination with the first, second, and third doses of the primary series of DTaP vaccine.

In Australia, pertussis is a nationally notifiable disease, and information on medically notified or laboratory-diagnosed pertussis cases are collected and summarized in jurisdictional notifiable disease databases.[25] The criteria for notification includes a combination of clinical, epidemiologic, or laboratory evidence, with laboratory definitive evidence (ie, isolation of *Bordetella pertussis* in cell culture, detection by nucleic acid testing, or seroconversion) serving as a confirmed pertussis case[26]; ≥94% of infant pertussis cases are notified following detection by polymerase chain reaction.[27] We identified notified pertussis infections and diagnosis date for infants through age 18 months. Pertussis cases included confirmed cases with definitive laboratory evidence or suggestive laboratory evidence coinciding with clinical evidence and probable cases with clinical and epidemiologic evidence.[26]

Hospital inpatient records and death registrations were used to evaluate pertussis severity. Hospital inpatient records summarize public and private hospital admissions within the jurisdiction.[28] We used hospital admission date and date of pertussis diagnosis to assess whether the pertussis case was temporally associated with a hospitalization or ICU admission (admission date ≤10 days following diagnosis). Deaths, identified from the death register, coincided with the date of diagnosis (death date ≤10 days following diagnosis or diagnosed postmortem).

First Nations mothers and infants were identified using a previously validated algorithm combining information across multiple administrative data sources to avoid incomplete and inaccurate data.[29]

Statistical Analysis

We restricted the primary analysis to live, singleton births with complete covariate information. We excluded mother-infant pairs with a record of vaccination <14 days prior to delivery (classed as "indeterminate vaccination status") (Supplemental Fig 3). We performed descriptive analyses using χ^2 tests for categorical variables and Wilcoxon rank sum tests for nonnormally distributed continuous variables to examine cohort characteristics by maternal vaccination status and pertussis infection.

We used a mixed effects Cox model to compare pertussis infection rates among maternally vaccinated infants and infants with no record of maternal vaccination, with infant age (in months) as the underlying time variable. We included 2 random intercepts for (1) state/territory to account for clustering within region and (2) mothers to account for clustering among infants sharing the same mother. Infants were censored at either the (1) date of their first pertussis notification, (2) date of death, or (3) end of data availability. We used inverse probability of treatment (vaccination) weights to account for confounding. Treatment weights were derived from the predicted probability of pertussis vaccination during pregnancy, based on a fitted multivariable logistic regression model with maternal age, ethnicity, preexisting health conditions, pregnancy complications, parity, smoking status, initiation of prenatal care, year and season of conception, Socioeconomic Index for Areas quintile, and receipt of influenza vaccine during pregnancy as predictor variables. In additional analyses, we considered models adjusting for these variables rather than applying inverse probability of treatment weights. We evaluated the balance between maternally vaccinated and maternally unvaccinated groups by examining the absolute standardized mean differences in maternal characteristics before and after application of the weights (Supplemental Fig 4).

Vaccine effectiveness was estimated as one minus the inverse probability of treatment weighted hazard ratio (HR) from the Cox model × 100. We fit separate models to estimate VE against notified infection and hospitalization. Because of small numbers, we were unable to fit VE models against death or ICU admission. We fit additional models to evaluate VE by gestational age at vaccination (<28 weeks, 28–31 weeks, or ≥32 weeks versus unvaccinated) and the time between vaccination and birth (2–6 weeks, 7–11 weeks, or ≥12 weeks versus unvaccinated). To estimate VE of maternal pertussis vaccination before the possible influence of childhood immunization (and in the age group with highest incidence of severe pertussis), we conducted a sensitivity analysis, restricted to infants <2 months old.

For NT and QLD only, where childhood immunization data were available, we fit models to estimate infant VE against pertussis infection associated with receipt of the 3-dose series of DTaP immunization through 12 months of age to evaluate possible effect modification by maternal vaccination status (ie, "blunting" effects). We compared rates of pertussis infection by infant DTaP dose using Cox proportional hazard models with infant age as the time variable and DTaP dose number as the time-varying exposure. For each DTaP dose, infants were censored at either the (1) date of their first pertussis infection (outcome of interest), (2) date of death, (3) date of receipt of additional DTaP dose, (4) age 12 months, or (5) end of data availability. DTaP VE was estimated as 1 minus the HR adjusted for child covariates, including maternal socioeconomic status, the infant's First Nations status, degree of prematurity, mother's initiation of prenatal care (used as a proxy measure for family's access to health services), and year of birth × 100. To evaluate potential effect modification, we included maternal vaccination status as a hospitalization term with DTaP dose. to compare rates of pertussis at each infant DTaP dose by maternal pertussis vaccination status, we constructed additional Cox proportional hazard

TABLE 1 Characteristics of Included Pregnancies, by Maternal Pertussis Vaccination Status

			Received a Pertussis Vaccine During Pregnancy			
	Total (N = 279 418)	Unvaccinated (n = 134 989)	All Vaccinated (n = 144 429)	Vaccinated <28 wk (n = 14 028)	Vaccinated 28–31 wk (n = 80 327)	Vaccinated ≥32 wk (n = 48 629)
Characteristic	***N***	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
State/territory of residence						
Northern Territory	9996	7375 (5.5)	2621 (1.8)	301 (2.1)	1420 (1.7)	900 (1.9)
Queensland	194 373	86 917 (64.4)	107 456 (74.4)	9672 (68.9)	57 369 (67.5)	40 415 (83.1)
Western Australia[a]	75 049	40 697 (30.1)	34 352 (23.8)	4055 (28.9)	21 538 (26.8)	7314 (15.0)
Maternal age						
<20 y	9590	5500 (4.1)	4090 (2.8)	454 (3.2)	2074 (2.6)	1523 (3.1)
20–24 y	41 052	21 298 (15.8)	19 754 (13.7)	2092 (14.9)	10 613 (13.2)	6918 (14.2)
25–29 y	79 509	37 636 (27.9)	41 873 (29.0)	4196 (29.9)	23 447 (29.2)	13 845 (28.5)
30–34 y	93 123	43 089 (31.9)	50 034 (34.6)	4677 (33.3)	28 070 (34.9)	16 697 (34.3)
≥35 y	56 144	27 466 (20.3)	28 678 (19.9)	2609 (18.6)	16 123 (20.1)	9646 (19.8)
Maternal ethnicity						
First Nations	19 892	12 497 (9.3)	7395 (5.1)	773 (5.5)	3898 (4.9)	2657 (5.5)
Non-Indigenous	25 9526	122 492 (90.7)	137 034 (94.9)	13 255 (94.5)	76 429 (95.1)	45 972 (94.5)
Preexisting health conditions						
Any preexisting health condition	24 076	12 064 (8.9)	12 012 (8.3)	1247 (8.9)	7034 (8.8)	3542 (7.3)
Asthma	14 428	7274 (5.4)	7154 (5.0)	728 (5.2)	4153 (5.2)	2155 (4.4)
Diabetes	2397	1249 (0.9)	1148 (0.8)	138 (1.0)	714 (0.9)	275 (0.6)
Essential hypertension	3927	1909 (1.4)	2018 (1.4)	211 (1.5)	1228 (1.5)	543 (1.1)
Coronary heart disease	4559	2276 (1.7)	2283 (1.6)	236 (1.7)	1310 (1.6)	714 (1.5)
No preexisting health condition	255 342	122 925 (91.1)	132 417 (91.7)	12 781 (91.1)	73 293 (91.2)	45 087 (92.7)
Pregnancy complications						
Any diagnosed pregnancy complication	48 002	23 464 (17.4)	24 538 (17.0)	2581 (18.4)	14 183 (17.7)	7520 (15.5)
Gestational diabetes	24 978	12 227 (9.1)	12 751 (8.8)	1284 (9.2)	7515 (9.4)	3817 (7.8)
Gestational hypertension	9255	4292 (3.2)	4963 (3.4)	572 (4.1)	2940 (3.7)	1377 (2.8)
Preeclampsia	6678	3414 (2.5)	3264 (2.3)	397 (2.8)	1954 (2.4)	877 (1.8)
Anemia	11 461	5361 (4.0)	6100 (4.2)	611 (4.4)	3275 (4.1)	2214 (4.6)
Threatened preterm labor	1459	958 (0.7)	501 (0.3)	57 (0.4)	319 (0.4)	101 (0.2)
Threatened abortion	1112	727 (0.5)	385 (0.3)	42 (0.3)	240 (0.3)	90 (0.2)
No diagnosed pregnancy complication	231 416	111 525 (82.6)	119 891 (83.0)	11 447 (81.6)	66 144 (82.3)	41 109 (84.5)
Tobacco smoking status						
Yes	31 950	19 345 (14.3)	12 605 (8.7)	1236 (8.8)	6556 (8.2)	4712 (9.7)
No	247 468	115 644 (85.7)	131 824 (91.3)	12 792 (91.2)	73 771 (91.8)	43 917 (90.3)
Parity						
0	115 611	47 237 (35.0)	68 374 (47.3)	7012 (50.0)	38 780 (48.3)	21 938 (45.1)
1	96 200	48 810 (36.2)	47 390 (32.8)	4355 (31.0)	26 140 (32.5)	16 403 (33.7)
2	40 948	22 210 (16.5)	18 738 (13.0)	1725 (12.3)	10 109 (12.6)	6699 (13.8)
3	15 295	9101 (6.7)	6194 (4.3)	579 (4.1)	3334 (4.2)	2210 (4.5)
≥4	11 364	7631 (5.7)	3733 (2.6)	357 (2.5)	1964 (2.4)	1379 (2.8)
Initiation of prenatal care (PNC)						
First trimester	204 632	93 061 (68.9)	111 571 (77.2)	10 882 (77.6)	62 492 (77.8)	37 202 (76.5)
Second trimester	68 134	37 290 (27.6)	30 844 (21.4)	2966 (21.1)	16 844 (21.0)	10 627 (21.9)
Third trimester or no PNC[b]	6652	4638 (3.4)	2014 (1.4)	180 (1.3)	991 (1.2)	800 (1.6)
Year of conception[c]						
2013	9678	9501 (7.0)	177 (0.1)	—	—	—
2014	74 886	55 784 (41.3)	19 102 (13.2)	—	—	—
2015	92 452	39 540 (29.3)	52 912 (36.6)	4843 (34.5)	27 991 (34.8)	19 848 (40.8)
2016	87 907	26 857 (19.9)	61 050 (42.3)	6709 (47.8)	37 970 (47.3)	15 158 (31.2)
2017	14 495	3307 (2.4)	11 188 (7.7)	1236 (8.8)	6797 (8.5)	3153 (6.5)

TABLE 1 Continued

Characteristic	Total (N = 279 418)	Unvaccinated (n = 134 989)	Received a Pertussis Vaccine During Pregnancy			
			All Vaccinated (n = 144 429)	Vaccinated <28 wk (n = 14 028)	Vaccinated 28–31 wk (n = 80 327)	Vaccinated ≥32 wk (n = 48 629)
	N	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Season of conception[c]						
Autumn	64 466	32 890 (24.4)	31 576 (21.9)	3021 (21.5)	17 308 (21.5)	10 895 (22.4)
Spring	73 285	32 181 (23.8)	41 104 (28.5)	4142 (29.5)	24 175 (30.1)	12 328 (25.4)
Summer	74 139	35 341 (26.2)	38 798 (26.9)	4045 (28.8)	21 628 (26.9)	12 839 (26.4)
Winter	67 528	34 577 (25.6)	32 951 (22.8)	2820 (20.1)	17 216 (21.4)	12 567 (25.8)
Socioeconomic status[d]						
≤20th percentile (most disadvantaged)	58 602	32 313 (23.9)	26 289 (18.2)	2741 (19.5)	14 493 (18.0)	8799 (18.1)
21st–40th percentile	52 737	25 985 (19.2)	26 752 (18.5)	2725 (19.4)	14 786 (18.4)	8976 (18.5)
41st–60th percentile	55 234	25 848 (19.1)	29 386 (20.3)	2875 (20.5)	16 197 (20.2)	9973 (20.5)
61st–80th percentile	59 447	26 892 (19.9)	32 555 (22.5)	3124 (22.3)	18 307 (22.8)	10 802 (22.2)
>80th percentile (least disadvantaged)	53 398	23 951 (17.7)	29 447 (20.4)	2563 (18.3)	16 544 (20.6)	10.079 (20.7)
Received influenza vaccine						
Yes	69 021	7831 (5.8)	61 190 (42.4)	6984 (49.8)	36 912 (46.0)	16 551 (34.0)
Received at different encounter as dTpa[e]	40 170	—	40 170 (27.8)	4744 (33.8)	24 440 (30.4)	10 986 (22.6)
Received at same encounter as dTpa[e]	19 679	—	19 679 (13.6)	2174 (15.5)	11 998 (14.9)	5507 (11.3)
No	210 397	127 158 (94.2)	83 239 (57.6)	7044 (50.2)	43 415 (54.0)	32 078 (66.0)
Receipt of childhood vaccines on time[f]						
Received ≥1 DTaP dose	198 766	90 104 (95.6)	108 662 (98.7)	9866 (98.9)	58 162 (98.9)	40 634 (98.4)
Received ≥2 DTaP doses	168 952	74 632 (79.1)	94 320 (85.7)	8726 (87.5)	51 025 (86.8)	34 569 (83.7)

DTaP, diphtheria-tetanus-acellular pertussis-containing vaccine; dTpa, diphtheria-tetanus-acellular pertussis vaccine; PNC, prenatal care.
[a] For 2017 pregnancies, the gestational age at vaccination could not be determined.
[b] 103 pregnancies did not receive prenatal care.
[c] Year and month of conception (used to determine season of conception) were estimated from the infant's date of birth minus the best clinical estimate of gestational age in days.
[d] Area-level socioeconomic status was derived using the Index for Relative Socioeconomic Advantage and Disadvantage from the Socioeconomic Indices for Economic Areas based on the mother's residence at Statistical Area 1 (https://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa).
[e] Information on the gestational age of influenza vaccination or dTpa vaccination was missing for 10 351 pregnancies.
[f] Information on receipt of childhood vaccines was only available for pregnancies in Northern Territory and Queensland.

models with maternal vaccination status as the exposure variable stratified by infant DTaP dose.

RESULTS

The cohort included 279 418 infants born to 252 444 mothers: 9996 mother–infant pairs in NT, 75 049 in WA, and 194 373 in QLD (Supplemental Fig 3). Of these, 51.7% (n = 144 429/279 418) had a record of pertussis vaccination during pregnancy: 5.0% (n = 14 028/279 418) before 28 weeks of gestation, 28.7% (n = 80 327/279 418) at 28–31 weeks of gestation, and 17.4% (n = 48 629/279 418) at ≥32 weeks of gestation (Supplemental Fig 5). For 1445 (0.5%) infants, the timing of maternal vaccination could not be determined. The characteristics of mother–infant pairs by pertussis vaccination during pregnancy are presented in Table 1.

A total of 331 notified pertussis cases were Identified in the cohort up to 18 months of age, equating to 118 cases per 100 000 infants; 119 cases were identified among infants of vaccinated mothers (82 per 100 000 infants) and 212 cases were identified among infants of unvaccinated mothers (157 per 100 000 infants). Among the 331 pertussis cases, 49 (14.8%) were diagnosed among infants <2 months old, and 124 (37.5%) were diagnosed among infants <6 months old (Supplemental Fig 6); 12.9% (n = 16/124) of cases among infants <6 months old coincided with a hospital admission, 4.8% (n = 6/124) coincided with an ICU admission, and 1.6% (n = 2/124) had a subsequent death recorded.

Maternal dTpa VE among infants <6 months of age was 65.1% (95% confidence interval [CI], 49.5–76.0) against notified pertussis infection and 60.2% (95% CI, −18.3 to 86.6) against hospitalized pertussis infection (Table 2; Fig 1; Supplemental Fig 7). There were insufficient data to estimate VE against ICU admission with pertussis and death. Results of analyses restricted to infants <2 months of age were similar to those for infants <6 months of age (Supplemental Table 4).

TABLE 2 Estimated effectiveness of pertussis vaccination during pregnancy among infants <6 months of age, by severity, site, and immunization characteristics

	Total	Vaccinated Cases per 100 000 Infants	Unvaccinated Cases per 100 000 Infants	VE (95% CI)[a]	IPTW VE (95% CI)[b]
Overall	279 418	22.8	67.4	65.9 (49.1–77.1)	65.1 (49.5–76.0)
By severity of disease					
Hospitalization	279 418	2.8	8.9	55.5 (–40.3 to 85.9)	60.2 (–18.3 to 86.6)
Admission to ICU	279 418	1.4	3.0	—	—
Pertussis-related death	279 418	0.7	0.7	—	—
By jurisdiction of maternal residence					
Northern Territory	9996	76.3	122.0	37.7 (–188 to 86.5)	12.2 (–208 to 75.0)
Queensland	194 373	19.5	74.8	74.0 (57.4–84.1)	76.0 (63.6–84.2)
Western Australia	75 049	29.1	41.8	27.1 (–56.2 to 66.6)	11.6 (–57.9 to 50.5)
By infant immunization[c]					
Received ≥1 dose of DTaP					
Yes	198 766	19.3	71.0	72.1 (54.3–83.0)	71.7 (56.7–81.5)
No	5603	141.3	238.8	40.9 (–169 to 87.1)	58.8 (–183 to 94.0)
Received ≥2 doses of DTaP					
Yes	168 952	17.0	72.3	75.4 (56.9–86.0)	75.1 (59.7–84.6)
No	35 417	44.4	101.7	56.3 (–3.2 to 81.5)	59.3 (–11.8 to 85.2)
By vaccination characteristics					
Gestational age at vaccination					
<28 wk	14 028	14.3	67.4	78.4 (12.3–94.7)	69.9 (3.2–90.6)
28–31 wk	80 327	24.9	67.4	62.2 (76.8–38.7)	61.5 (60.8–75.6)
≥32 wk	48 629	20.6	67.4	70.5 (43.2–84.7)	71.4 (48.8–84.0)
Time from vaccination to birth					
2–6 wk	39 975	17.5	67.4	74.8 (45.6–88.3)	73.5 (48.9–86.2)
7–11 wk	81 377	25.8	67.4	61.7 (38.3–76.2)	62.7 (41.4–76.3)
≥12 wk	21 632	18.5	67.4	70.6 (20.0–89.2)	62.1 (8.0–84.4)

CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis-containing vaccine; IPTQ, inverse probability of treatment weighted; VE, vaccine effectiveness.

[a] VE was estimated as 1 – hazard ratio derived from a Cox proportional hazard model with infant age in months as the underlying time variable.

[b] IPTW vaccine effectiveness estimates were weighted by the inverse probability of receiving diphtheria-tetanus-acellular pertussis-containing vaccine during pregnancy. Probabilities were derived from multivariable logistic regressions predicting the odds of vaccination by maternal age, First Nations status, asthma, diabetes, hypertension, coronary heart disease, diagnosis of a pregnancy complication, parity, smoking status, trimester of prenatal care initiation, year of conception, socioeconomic status, and receipt of influenza vaccine.

[c] Childhood immunizations were assessed using regional immunization register data. Because only Northern Territory and Queensland had such information available, these analyses were restricted to these jurisdictions (ie, excluded Western Australia).

By age group, maternal dTpa VE was 70.4% (95% CI, 50.5–82.3) among infants <2 months old, 65.7% (95% CI, 41.8–79.8) among infants 3 to 4 months of age, 61.6% (95% CI, 37.5–76.4) among infants 5 to 6 months of age, and 43.3% (95% CI, 6.8–65.6) among infants 7 to 8 months of age (Fig 1). VE was not significant after 8 months of age (9–12 months: VE, 21.8% [95% CI, −31.8 to 53.6%]; 13–18 months: 34.1% [95% CI, 18.1–63.2]; 19–24 months: 44.0% [95% CI, −5.0 to 70.1]). The median age at notified pertussis infection among maternally vaccinated infants (median: 11 months; interquartile range, 8.75 months) was greater than the median age at pertussis infection among maternally unvaccinated infants (median: 7.5 months; interquartile range, 10 months; $P < .001$), although this was predominantly observed in QLD (Supplemental Fig 8). The VE for infants <6 months of age ranged from 11.6% (95% CI, –57.9 to 50.5) in WA to 76.0% (95% CI, 63.6–84.2) in QLD (Table 2). VE among infants <6 months of age was similar regardless of the gestational age at vaccination and the time between vaccination and birth.

A total of 171 840 infants were born in NT and QLD with immunization records available. Of these, 85 166 (49.6%) were exposed to maternal vaccine in utero and 86 674 (50.4%) had no record of maternal vaccination. The majority of infants who were either exposed to maternal vaccination or not received at least 1 infant dose of a pertussis-containing vaccine (93.4% and 84.8%, respectively); 87.3% of maternally vaccinated infants completed the 3-dose DTaP series and 76.6% of infants with no maternal vaccination completed the 3-dose series (Table 3).

Although the infant VE of 1 and 2 doses of DTaP was similar for maternally vaccinated and infants with no maternal vaccination (dose 1: 62.5% vs 71.2%, P value for interaction = .32; dose 2: 83.2% vs 83.6%, P value for interaction = .46), infant VE of the third dose of DTaP was lower (dose 3: 76.5% vs 92.9%, P value for interaction = .002) (Table 3).

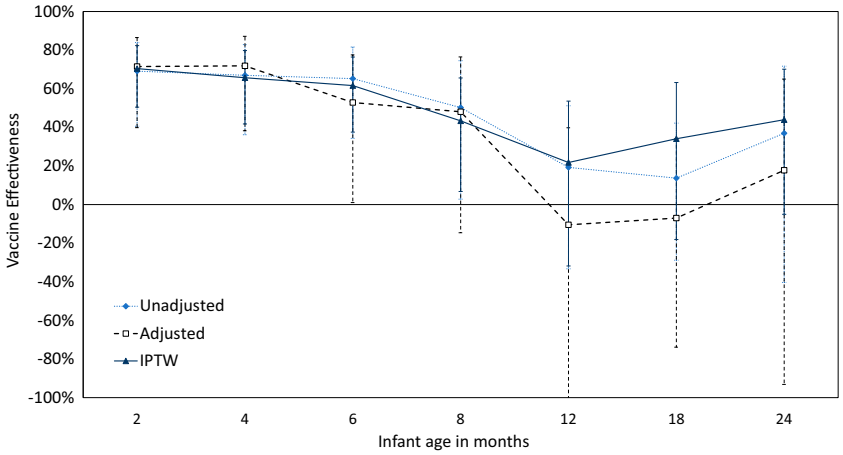

FIGURE 1

Effectiveness of pertussis vaccination during pregnancy against notified pertussis infection, by infant age in months. Dashed lines indicate 95% confidence intervals. Adjusted estimates controlled for maternal age, First Nations status, asthma, diabetes, hypertension, coronary heart disease, diagnosis of a pregnancy complication, parity, smoking status, trimester of prenatal care initiation, year of conception, socioeconomic status, and receipt of influenza vaccine; inverse probability of treatment weighted (IPTW) estimates were weighted by the inverse probability of receiving diphtheria-tetanus-acellular pertussis vaccine during pregnancy. Probabilities were derived from multivariable logistic regressions predicting the odds of vaccination by maternal age, First Nations status, asthma, diabetes, hypertension, coronary heart disease, diagnosis of a pregnancy complication, parity, smoking status, trimester of prenatal care initiation, year of conception, socioeconomic status, and receipt of influenza vaccine.

Despite this, the incidence of pertussis among those who received 3 DTaP doses was similar for maternally vaccinated infants and infants with no maternal vaccination (20.7 cases per 100 000 infants versus 23.1 cases per 100 000 infants; adjusted HR 0.70; 95% CI, 0.61–3.39). Survival curves indicate earlier and more frequent pertussis infection among infants with no record of maternal vaccination, regardless of DTaP immunization (Fig 2).

DISCUSSION

During the first 3 years of maternal pertussis immunization programs implemented in 3 Australian jurisdictions, we estimate that 52% of pregnant individuals received an acellular pertussis vaccine, and vaccination was associated with a 66% overall decrease in infant pertussis infection through 6 months of age. This protective effect of maternal pertussis vaccination was significant through to 8 months of age. Although we observed some evidence to support a reduced infant VE for 3 doses of DTaP immunization among maternally vaccinated infants, this did not appear to translate to greater risk of disease compared with infants with no record of maternal immunization. These results support ongoing pertussis vaccination during pregnancy to prevent pertussis-related morbidity among young infants.

Because of the size of our cohort, we were able to specifically evaluate VE against pertussis by the gestational timing of vaccination and the age of the infant. Although immunogenicity studies have observed higher antibody avidity in the cord blood of infants born to mothers vaccinated between 27 and 30 weeks of pregnancy (compared with later in pregnancy)[15,30] and recent studies have reported increased half-life of maternal antibodies following longer intervals between vaccination and delivery,[31] we did not observe significant differences in VE by timing of vaccination. Similarly, a recent open-label randomized controlled trial in the United Kingdom comparing pertussis vaccination at 16 to 23 weeks, 24 to 27 weeks, and 28 to 31 weeks found no effect of gestational timing of vaccination on infant antibodies at birth.[32] Other surveillance-based studies of maternal pertussis vaccination at ≥17 weeks, 13 to 16 weeks, 8 to 12 weeks, 1 to 7 weeks before birth also suggested that timing has a limited effect on VE against infant disease.[33] Although our findings support the potential effectiveness of administering acellular pertussis vaccines during late second and third trimesters, it is worth noting that because of the recommendation in place during the study period (ie, vaccination at 28 weeks of pregnancy), few mothers were vaccinated before 25 weeks of completed gestation.

We assessed VE through to 18 months of age to evaluate the duration of protection against pertussis attributed to maternal vaccination as well as possible blunting of infants' responses to primary pertussis vaccination. We observed significant protection against disease until at least 8 months of age; 2 months longer than reported in previous studies. We observed some evidence suggesting a lower VE for the third dose of infant DTaP vaccine for maternally vaccinated infants compared with infants with no maternal vaccine exposure. This finding aligns with results from previous randomized controlled trials[17,34,35] and nonrandomized studies,[16,36] that have consistently documented lower immunologic responses to infant pertussis

TABLE 3 Estimated Effectiveness of Infant Pertussis Vaccination, by Maternal Pertussis Immunization Status

Number of Infant Doses of Pertussis-Containing Vaccines Received	Maternally vaccinated infants (n = 85 166)			Infants With No Record of Maternal Vaccination (n = 86 674)			Pertussis Infection Among Maternally Vaccinated Versus No Maternal Vaccination aHR (95% CI)[b]
		Pertussis Infection			Pertussis Infection		
	N (%)	*n*/Total (Cases per 100 000 Infants)	VE (95% CI)[a]	*N* (%)	*n*/Total (Cases per 100 000 Infants)	VE (95% CI)[a]	
Never vaccinated	5594 (6.6%)	9/85 124 (10.6)	Reference	13 202 (15.2%)	80/86 353 (92.6)	Reference	0.21 (0.10–0.45)
Dose 1	79 572 (93.4%)	8/79 548 (10.1)	62.5% (15.5–83.3)	73 472 (84.9%)	22/73 389 (30.0)	71.2% (52.7–82.4)	0.34 (0.12–0.97)
Dose 2	77 641 (91.2%)	4/77 367 (5.2)	83.2% (43.7–95.0)	70 692 (81.6%)	11/70 416 (15.6)	83.6% (67.7–91.7)	0.19 (0.05–0.71)
Dose 3	74 358 (87.3%)	14/67 518 (20.7)	76.5% (32.8–91.8)	66 432 (76.6%)	15/64 835 (23.1)	92.9% (86.4–96.3)	0.70 (0.61–3.39)

aHR, adjusted hazard ratio; CI, confidence interval; VE, vaccine effectiveness.

[a] Vaccine effectiveness was estimated as 1 − hazard ratio derived from a Cox proportional hazard model with infant age in months as the underlying time variable and infant pertussis vaccination as a time-varying exposure variable. Models adjusted for maternal socioeconomic status, the child's First Nations status, prematurity, mother's initiation of prenatal care (used as a proxy measure for family's access to health services), and year of birth.

[b] Hazard ratio comparing the rate of pertussis infection by maternal pertussis vaccine exposure for each dose of infant pertussis vaccine with infant age in months as the underlying time variable. Models adjusted for maternal socioeconomic status, the child's First Nations status, prematurity, mother's initiation of prenatal care (used as a proxy measure for family's access to health services), and year of birth.

vaccines among infants previously exposed to maternal pertussis immunization.

Few studies have directly measured the VE of infant immunization by maternal vaccination status. A recently published multicenter surveillance study of 376 infants 2 to 11 months old showed that VE of at least 1 dose of pertussis-containing vaccine against hospitalized pertussis infection was 74% among maternally vaccinated infants and 68% for infants with no history of maternal vaccination.[37] However, the authors acknowledge they were limited by small sample size and were unable to perform stratified analyses to formally investigate whether maternal vaccination modifies VE.[37] In our larger population-based study, we identified effect modification at third dose of DTaP, but lower incidence of pertussis through 18 months of age. Our interpretation of these findings, in combination with the published literature, is that maternal antibodies may "blunt" the response of infants to primary immunization, but maternal and/or infant antibodies are sufficient to protect maternally vaccinated infants from infection. However, further research is needed to confirm our findings.

Strengths and Weaknesses

Our study had several strengths and limitations. First, using data linkage systems in Australia, we were able to construct a large, population-based cohort of mother–infant pairs across multiple jurisdictions with comprehensive longitudinal information on maternal and infant health, helping to improve generalizability of findings and reduce selection bias. However, these data are observational and, as with any such study, results may be influenced by confounding. To restrict this influence, we applied several techniques, including adjustment for a range of available covariates and fitting weighted models by inverse probability of treatment (vaccination). Despite this, we cannot entirely exclude the possibility of uncontrolled confounding, especially for unobserved or latent variables. Another important limitation to our study was the method of outcome identification and the small number of infant pertussis cases, which precluded us from undertaking some analyses for infants <2 months, generating VE estimates against ICU admission and death, performing adjusted sensitivity analyses, and reduced the precision of our estimates by jurisdiction. Although cases were identified using a national, legally mandated data collection employing a standardized case definition,[26] we cannot exclude the possibility that some asymptomatic cases were not identified in the cohort, resulting in some outcome misclassification. Despite this, given most cases were polymerase chain reaction detected (with high specificity and sensitivity),[38] false positives in our cohort are unlikely and we do not expect that outcome misclassification would have occurred differentially across maternal vaccinated and unvaccinated infants. Finally, although

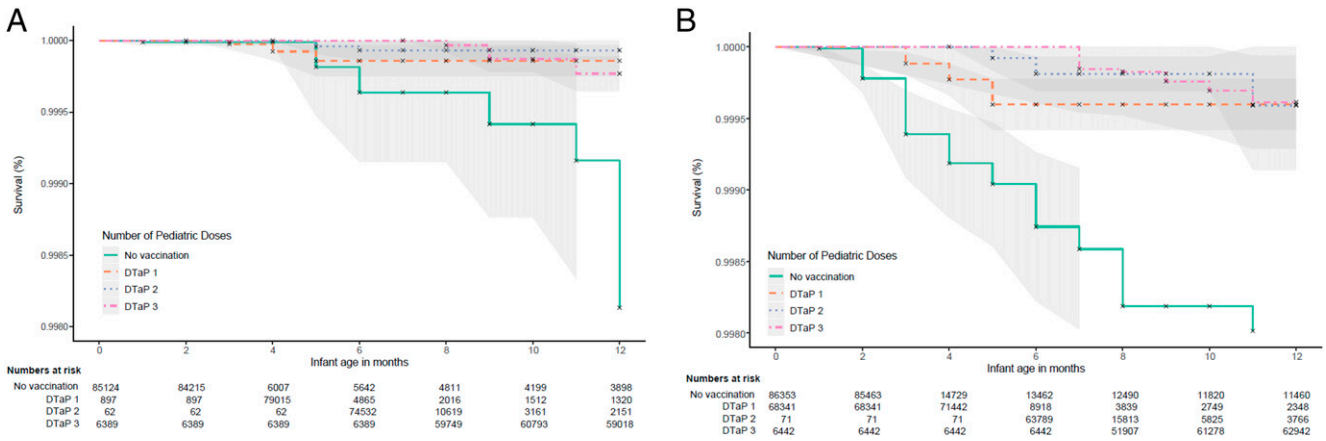

FIGURE 2

Survival against pertussis infection among (A) maternally vaccinated infants and (B) infants with no record of maternal vaccination, by number of diphtheria-tetanus-acellular pertussis (DTaP) vaccine doses.

our sources of data for immunization drew from medical records and registers that have high specificity,[39] it is possible that some vaccinated individuals were misclassified as unvaccinated. Because we have no reason to believe this misclassification would be differential by outcome, this could have biased our VE estimates toward the null, suggesting our estimates may underestimate the true VE.

Conclusions

From this large, population-based cohort, we estimate that immunization with acellular pertussis vaccine during pregnancy prevented 65% of pertussis infections through 6 months of age. Although the VE of the third DTaP dose may be lower for maternally vaccinated infants, we did not observe evidence supporting higher rates of pertussis infection associated with maternal vaccination through 18 months of age. These results indicate that maternal pertussis vaccination protects infants from pertussis infection during a period of greatest vulnerability to severe morbidity and mortality. Our findings support the infant health benefits of recommendations to administer a booster dose of pertussis vaccine near 28 weeks of gestational age.

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ABBREVIATIONS

CI: confidence interval
DTaP: diphtheria-tetanus-acellular pertussis-containing vaccine
dTpa: diphtheria-tetanus-acellular pertussis vaccine
HR: hazard ratio
QLD: Queensland
NT: Northern Territory
VE: vaccine effectiveness
WA: Western Australia

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