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ORIGINAL ARTICLE

Timing and temporal trends of influenza and pertussis vaccinations during pregnancy in three Australian jurisdictions: The Links2HealthierBubs population-based linked cohort study, 2012–2017

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Background: Antenatal inactivated influenza (IIV) and pertussis-containing vaccines (dTpa) offer protection against severe respiratory infections for pregnant women and infants <6 months of age. Both vaccines are recommended in pregnancy; however, little is known about temporal or jurisdictional trends and predictors of uptake.
Aims: To identify gaps and predictors of IIV and/or dTpa vaccinations in Australian pregnancies from 2012 to 2017.
Materials and Methods: We conducted a probabilistically linked, multi-jurisdictional population-based cohort study, drawing from perinatal data collections and immunisation databases. We used a generalised linear mixed model with a random effect term to account for clustering of multiple pregnancies within mothers, to calculate vaccination uptake, and identify predictors of uptake by maternal demographic, pregnancy, and health characteristics.
Results: Of 591 868 unique pregnancies, IIV uptake was 15%, dTpa 27% and 12% received both vaccines. Pertussis vaccinations in First Nations pregnancies were 20% lower than non-Indigenous pregnancies; dTpa was strongly associated with IIV uptake (risk ratio (RR): 8.60, 95% CI 8.48–8.73). This trend was temporally and jurisdictionally consistent. First Nations women were more likely to have had IIV in pregnancy before the introduction of dTpa in the pregnancy program: (RR: 1.48, 95% CI 1.40–1.57), but less likely after dTpa implementation (RR: 0.78, 95% CI 0.76–0.80).
Conclusions: Inequity in vaccine uptake between First Nations and non-Indigenous pregnancies, and dismal rates of vaccination in pregnancy overall need urgent review, particularly before the next influenza pandemic or pertussis outbreak. If antenatal dTpa is driving IIV uptake, changes in antenatal healthcare practices are needed to ensure vaccines are offered equitably and optimally to protect against infection.

KEYWORDS
uptake, influenza, pertussis, vaccination, pregnancy

INTRODUCTION

Inactivated influenza vaccines (IIV) and pertussis-containing vaccines (dTpa) given in pregnancy offer protection against severe respiratory infections for pregnant women and their infants in the first six months of life.[1] In Australia, seasonal IIV has been recommended during pregnancy since 2000,[2] and dTpa since 2014 in Queensland and 2015 in remaining Australian jurisdictions.[3] From 2014–2018 (throughout the duration of our study), dTpa was recommended for the third trimester of every pregnancy (≥28 completed weeks gestation).[3] Despite both vaccines being recommended and free in pregnancy,[4] uptake varies considerably between the states and territories but remains historically low.[5]

Trends in antenatal vaccination uptake have only been evaluated in a few observational studies,[6,7] showing sub-optimal acceptance for IIV (~37–60%) and dTpa (~25–70%), depending on the jurisdiction.[8] Healthcare provider (HCP) recommendation and previous administration of seasonal IIV have been identified as predictors of vaccine uptake in pregnancy,[6] but no Australian study has examined the uptake or temporal trend of both IIV and dTpa vaccines in pregnancy across multiple jurisdictions and consecutive influenza seasons using whole of population data. Also, the influence of other demographic and health characteristics on IIV and dTpa uptake in pregnancy has not been examined on such a large scale, particularly the effect of the introduction of dTpa vaccination in pregnancy on the uptake and timing of seasonal IIV in pregnancy. These data are essential to evaluate national immunisation policy and recommendations.

Using multiple linked, population-based datasets from three Australian jurisdictions, we aimed to: ascertain the proportion of women who received IIV and/or dTpa vaccinations in pregnancy; describe trends in vaccine uptake by year, jurisdiction, and timing of vaccination by gestation; IIV uptake in pre- and post-maternal dTpa program implementation periods; and identify predictors of IIV and dTpa vaccine uptake in pregnancy.

MATERIALS AND METHODS

Study design and population

The Links2HealthierBubs (Links2HB) study,[9] is an observational cohort of mother-infant pairs involving record linkage of multiple, population-based health administrative datasets from three Australian jurisdictions, Northern Territory (NT), Queensland (Qld), and Western Australia (WA), which collectively account for 32% of Australia's birth cohort. The Links2HB cohort includes all mothers and their infants (live and stillborn) ≥20 weeks gestation, born between 1 January 2012 to 31 December 2017.

Data collection methods and sources

Data were sourced from perinatal data collections (PDCs) and immunisation registers/databases for each jurisdiction. The PDCs contain demographic and clinical information for all registered births ≥20 weeks gestation. Immunisation registers capture participant names, dates of birth, and vaccine details (product, date/s given, dose and batch number). Sources of immunisation data used in our study were: the NT Immunisation Register (NTIR), Qld Vaccination Information and Vaccination Administration System (VIVAS), and WA Antenatal Vaccination Database (WAAVD) (Box S1).

Data linkage

A combination of deterministic and probabilistic record linkage was used to identify individual pregnancies from PDCs in each jurisdiction. Infants were then linked to their mothers, creating a birth cohort of unique mother-infant pairs. Pairs were linked to respective jurisdictional immunisation registers to identify any IIV and/or dTpa vaccinations during pregnancy. Antenatal IIV and dTpa vaccinations were also recorded in Qld and WA PDCs following the decommissioning of their respective immunisation registers (Box S2).

Vaccination status

Vaccination status was indicated by PDCs and/or by documented dates in immunisation registers. Variables in PDCs used to calculate the uptake of IIV and dTpa vaccines in pregnancy included: infant date of birth, gestation in weeks at infant birth, and gestation in weeks and trimester of pregnancy at the time of vaccination. Variables in the immunisation registers that were used in conjunction with the PDCs to calculate IIV and dTpa vaccine uptake in pregnancy included name/s and date/s of each vaccination.

'Vaccinated in pregnancy' was defined as receipt of an IIV and/or dTpa vaccine between the estimated date of conception (EDOC) and the date of infant birth. The EDOC was calculated by subtracting the best clinical estimate of gestational age from infant date of birth. 'Unvaccinated in pregnancy' was defined as any participant without a vaccination record in any immunisation register/database, *or* with a vaccination record outside of the defined pregnancy period *or* with missing data for IIV and/or dTpa vaccination fields in the Qld and WA PDCs post-2015.

Sources of maternal demographic, pregnancy and health factors associated with predictors of vaccination in pregnancy are listed in Box S3. Medical conditions were identified from information in PDCs and hospital admissions data using variables and Classification of Disease 10th edition Australian Modification (ICD-10-AM) codes.

Data analysis

Age- and time-related data were presented as medians with interquartile ranges (IQR). Numbers and proportions of unique pregnancies were calculated overall and by study year and jurisdiction.

Antenatal vaccination status was calculated for each unique pregnancy based on: (i) those who received an IIV vaccine in pregnancy; (ii) those who received a dTpa vaccine in pregnancy; and (iii) those who received both IIV and dTpa vaccines in the same pregnancy. A generalised linear mixed model (GLMM), log-binomial regression with a random intercept for the mother's ID was used to account for clustering of multiple pregnancies within mothers, to calculate vaccination uptake, and identify predictors of uptake by maternal demographic, pregnancy, and health characteristics. We estimated the unadjusted relative risk of vaccination for each maternal demographic, pregnancy, and health characteristic. Data are reported as risk ratios (RR) and 95% compatibility intervals (95% CIs). Variables significantly associated with maternal vaccination uptake (RR not equal to one and 95% CIs not crossing one) were included in the final GLMM. Data were analysed using Stata statistical software v.17.1 (StataCorp, College Station, TX, USA).

Ethics committee approvals were obtained from WA Department of Health (HREC 2016/56), Curtin University (HRE2017-0808), Menzies School of Health Research (HREC 2018–3199), Queensland Health and Royal Brisbane and Women's Hospital (HREC/2018/QRBW/47660), and WA Aboriginal Health Ethics Committees (HREC 889).[10]

RESULTS

There were 591 868 eligible pregnancies in the final Links2HB cohort (Fig. 1), and these were evenly distributed throughout the study period with ~99 000 pregnancies/year.

Demographic characteristics

The median maternal age at infant birth was 30 years (IQR 26–34), and 7% of the cohort identified as a First Nations person. Maternal demographic and pregnancy characteristics were similar by jurisdiction (Table S1). Notable differences between the NT cohort and the Qld and WA cohorts respectively were a higher proportion of First Nations women (32% vs 6%, 5%), attending antenatal care in the first trimester (76% vs 66%, 64%), smoking in pregnancy (24% vs 13%, 10%), and anaemia NT vs Qld (18% vs 4%).

Vaccination status

Most women were unvaccinated (69%); 15% had received an IIV, 27% had received dTpa (2015–2017), and 12% had received both vaccines (2015–2017). Vaccine uptake varied by jurisdiction (Table 1). Compared to Qld and WA, a higher proportion of NT women were unvaccinated (81% vs 67%, 72%), received IIV (10% vs 14%, 17%), dTpa (12% vs 31%, 22%) and both IIV and dTpa vaccines during pregnancy (4% vs 12%, 11%). Compared to those vaccinated in pregnancy, women who were unvaccinated in pregnancy were more likely to smoke during pregnancy (14% vs 9%, 8%), and less likely to attend for antenatal care in the first trimester (63% vs 73–75%).

Temporal trends

There was an upward temporal trend in the proportion of all women who had received any vaccine in pregnancy (Fig. S1). Although this trend was consistent between non-Indigenous and First Nations women, the proportion of all vaccinations in First Nations pregnancies were consistently lower than non-Indigenous pregnancies, particularly dTpa (~13–20%). This trend was also consistent in each jurisdiction (data not shown).

Timing of vaccination

The median gestation at IIV administration was 27 weeks (IQR 17–31) and this varied by jurisdiction. In the NT, the median gestation was 23 weeks (IQR 14–31) compared to 28 weeks (IQR 18–31) in Qld, and 26 weeks (IQR 16–32) in WA. The median gestation at dTpa vaccination was 31 weeks (IQR 29–33), and this did not differ by jurisdiction. The median gestation of IIV in pregnancy was impacted by the introduction of the dTpa vaccine program, where IIV increased from 22 weeks (IQR 14–30) in 2012–2014, to 28 weeks (IQR 18–31) in 2015–2017 (Fig. 2). This trend was consistent by jurisdiction (Fig. S2).

For women who received concomitant IIV and dTpa vaccination in the same pregnancy, there was a shift toward third trimester vaccination from 2015–2017 compared to previous years. By 2017, 24%

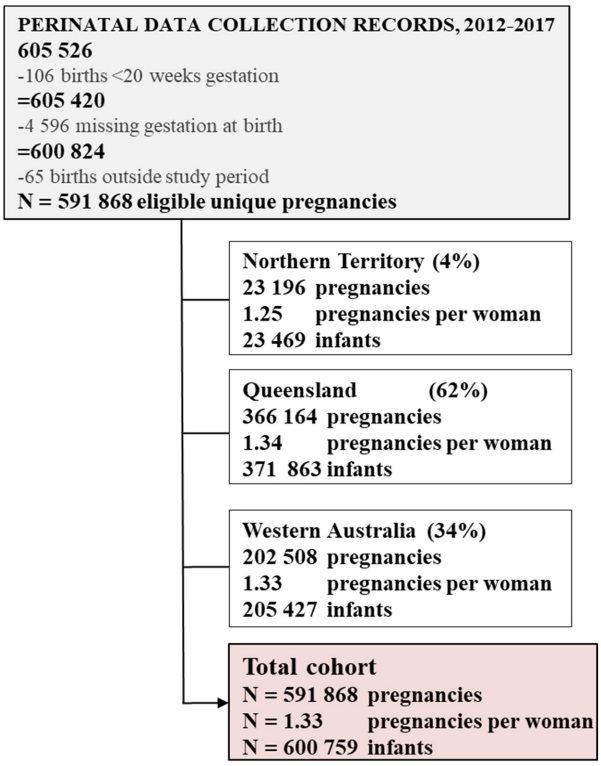

FIGURE 1 Flow diagram of Links2HealthierBubs study participants by study site, Australia, 2012–2017.

of women had received both IIV and dTpa vaccines in the third trimester (range 9–24%). The proportion of women who received IIV only during pregnancy remained consistently low across all trimesters and study years, ranging from 0% to 3% (Fig. S3).

Factors affecting IIV vaccine uptake in pregnancy

Compared to other mothers, those <20 years of age (RR: 0.77, 95% CI 0.74–0.80), who birthed in a public hospital (RR: 0.67, 95% CI 0.66–0.68), or who smoked during pregnancy (RR: 0.75, 95% CI 0.74–0.77) were less likely to have had IIV in pregnancy. These results were consistent in pre- and post-dTpa implementation periods (Table 2), and by jurisdiction (Table S2). Women who attended antenatal care in the first trimester (RR: 1.41, 95% CI 1.39–1.43) and primiparous women (RR: 1.22, 95% CI 1.20–1.23) were more likely to have had IIV in pregnancy before and after dTpa implementation. First Nations women were more likely to have had IIV in pregnancy before the dTpa in pregnancy program commenced (RR: 1.48, 95% CI 1.40–1.57), and less likely after dTpa implementation (RR: 0.78, 95% CI 0.76–0.80), and this was consistent by jurisdiction (Table S2). Pertussis vaccination in pregnancy was the strongest predictor of IIV uptake in pregnancy overall (RR: 8.60, 95% CI 8.48–8.73), in pre- (RR: 1.51, 95% CI 1.26–1.82) and post-dTpa implementation periods (RR: 6.77, 95% CI 6.56–6.99), and by jurisdiction (Table S2).

TABLE 1 Demographic, pregnancy and health characteristics of Links2HealthierBubs pregnancies by vaccination status, for infants born between 2012–2017 inclusive.

	Unvaccinated	IIV[†]	dTpa[‡]	Both IIV and dTpa
Characteristics (% = yes)	***N* = 408 975 (69%)**	***N* = 90 123 (15%)**	***N* = 161 620 (27%)**	***N* = 68 851 (12%)**
Jurisdiction:				
Northern Territory	18 753 (81)	2422 (10)	2879 (12)	858 (4)
Queensland	243 856 (67)	52 924 (14)	114 957 (31)	45 573 (12)
Western Australia	146 366 (72)	34 777 (17)	43 784 (22)	22 420 (11)
Maternal age group at infant birth:				
<20 years	17 559 (4)	2714 (3)	4550 (3)	1806 (3)
20–34 years	310 114 (76)	68 695 (76)	124 780 (77)	52 823 (77)
≥35 years	81 302 (20)	18 714 (21)	32 290 (20)	14 222 (21)
Pregnancy-based characteristics:				
Identified as a First Nations mother	31 097 (8)	5666 (6)	8324 (5)	3397 (5)
Attended antenatal care in 1st trimester	248 346 (63)	65 062 (74)	116 623 (73)	50 821 (75)
Public hospital birth[‡]	160 711 (65)	29 070 (54)	71 861 (63)	24 691 (54)
Primiparous	161 665 (40)	42 551 (47)	75 998 (47)	33 463 (49)
Multiple birth	6470 (1)	1184 (1)	2026 (1)	820 (1)
Smoked during pregnancy	56 029 (14)	7874 (9)	14 279 (9)	5381 (8)
Body mass index in obese category (>30)[§,¶]	79 680 (21)	17 158 (20)	31 672 (20)	13 060 (19)
Anaemia[^]	11 429 (3)	3269 (4)	6621 (4)	2636 (4)
Caesarean section	137 620 (34)	31 131 (34)	54 927 (34)	23 577 (34)
Pre-existing medical risk factors:				
Asthma	22 479 (6)	5282 (6)	8214 (5)	3662 (5)
Hypertension	5149 (1)	1798 (2)	2806 (2)	1382 (2)
Diabetes (types 1 and II)	3098 (<1)	944 (1)	1406 (<1)	675 (1)
Cardiac disease	5764 (1)	1428 (2)	2484 (2)	1007 (1)
Renal disease	1137 (<1)	316 (<1)	542 (<1)	233 (<1)

Note: Denominators differ due to missing data. Pertussis-containing vaccines (dTpa) in pregnancy was recommended from 2014 in Qld, and 2015 in WA and NT.
[†]Results based on any inactivated influenza virus (IIV) or any dTpa vaccine given in pregnancy, regardless of uptake of the other vaccine.
[‡]Qld data only.
[§]No data for NT.
[^]No data for WA.
[¶]Derived from body mass index variable and using standard Australian categories.

Factors affecting dTpa vaccine uptake in pregnancy

Overall, and across all jurisdictions, women who were less likely to have received dTpa in pregnancy than other women were: <20 years of age, First Nations, or smoked during pregnancy (Table S3), and more women received dTpa during pregnancy if they were primiparous, had antenatal care in the first trimester, and had received IIV during pregnancy. Factors affecting concomitant IIV and dTpa vaccine uptake in the same pregnancy were similar overall and by jurisdiction (Table S4).

DISCUSSION

Between 2012–2017, we identified poor uptake of IIV in pregnancy across three jurisdictions, particularly in the first trimester (3%). There was no obvious pattern of IIV uptake in pregnancy by gestation or trimester until the introduction of the antenatal dTpa program in 2015, which shifted the timing of IIV uptake to the third trimester in line with the recommendation for dTpa. We confirmed that receiving one vaccine in pregnancy was strongly associated with the uptake of another. We found that attending antenatal care in the first trimester of pregnancy and being a primiparous woman were factors that consistently predicted the uptake of IIV, dTpa and concomitant IIV and dTpa vaccines in pregnancy over time and across all jurisdictions. Factors that consistently detracted from vaccination uptake in pregnancy were being a First Nations woman, aged less than 20 years of age, and smoking during pregnancy.

The disparity in vaccine uptake between First Nations and non-Indigenous women overall and across all jurisdictions is concerning. Compared to non-Indigenous women, First Nations women were significantly less likely to have received dTpa, or both IIV and dTpa vaccines in pregnancy, which has also been seen in jurisdictions not included in our study.[11] Further, there was a decrease in First Nations women receiving IIV in pregnancy after the implementation of the dTpa in pregnancy program compared to a pre-dTpa program period. This was in contrast to non-Indigenous women, where IIV uptake increased after the introduction of dTpa. Reasons for this disparity and decrease in IIV uptake in pregnancy among First Nations women needs further investigation, because they are a priority group for vaccination,[12] due to significantly higher rates of influenza infections. Previous studies conducted in the NT prior to the antenatal dTpa program found remote-living, pregnant First Nations women had very low uptake of IIV (3%) despite recommendations.[13] This requires further investigation for all remote-living women in other jurisdictions. Also, First Nations infants and First Nations women of child-bearing and caring age are disproportionately affected by pertussis infections,[14] so it is unclear at what stage these vaccine programs/policies are failing.

Strengths and limitations

Our study incorporates the largest mother-infant pair cohort in Australia to examine multi-jurisdictional vaccination status in pregnancy over time, and the predictors of vaccine uptake. Our whole of population-based linked health datasets includes the highest proportion of First Nations mother-infant pairs, and captures stillbirths as well as livebirths, ensuring our results are generalisable to the whole Australian pregnant population. Our record linkage processes enabled us to accurately ascertain

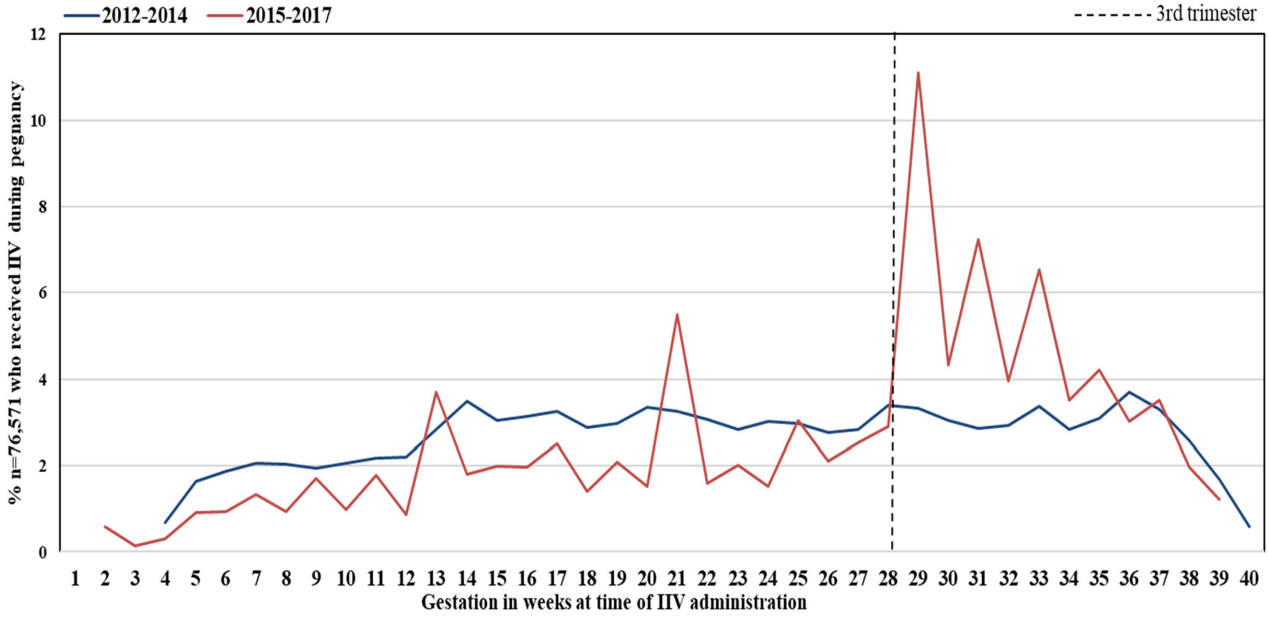

FIGURE 2 Weeks gestation at time of inactivated influenza (IIV) administration in pre- and post-pertussis-containing vaccines (dTpa) implementation periods (*N* = 76 571).

TABLE 2 Factors affecting antenatal IIV uptake in Links2HealthierBubs study participants by year of antenatal dTpa introduction, 2012–2017.

	Overall	Pre-dTpa program	Post-dTpa program
Study years (inclusive)	**2012–2017**	**2012–2014**	**2015–2017**
Characteristics	RR[†] (95% CI)	RR[†] (95% CI)	RR[†] (95% CI)
Maternal age (category) <20 years	0.77 (0.74–0.80)	0.85 (0.78–0.93)	0.84 (0.81–0.88)
20–34 years	1.00 (0.99–1.02)	0.92 (0.89–0.96)	1.01 (1.00–1.02)
≥35 years	1.05 (1.04–1.07)	1.10 (1.06–1.15)	1.02 (1.01–1.04)
Identified as a First Nations mother	0.89 (0.86–0.91)	1.48 (1.40–1.57)	0.78 (0.76–0.80)
Attended antenatal care in 1st trimester	1.41 (1.39–1.43)	1.29 (1.24–1.34)	1.23 (1.21–1.25)
Public hospital birth[‡]	0.67 (0.66–0.68)	0.99 (0.92–1.05)	0.68 (0.67–0.69)
Primiparous	1.22 (1.20–1.23)	1.19 (1.15–1.23)	1.25 (1.24–1.27)
Multiple birth	0.85 (0.80–0.90)	1.04 (0.90–1.19)	0.84 (0.80–0.89)
Smoked during pregnancy	0.75 (0.74–0.77)	0.84 (0.79–0.88)	0.79 (0.77–0.81)
Body mass index in obese category (>30)[§,¶]	1.00 (0.98–1.02)	0.98 (0.90–1.07)	1.00 (0.98–1.01)
Anaemia[^]	1.07 (1.04–1.10)	0.97 (0.79–1.18)	1.05 (1.02–1.09)
Caesarean section	0.97 (0.95–0.98)	1.03 (0.96–1.11)	0.96 (0.95–0.98)
Pertussis vaccination in pregnancy	8.60 (8.48–8.73)	1.51 (1.26–1.82)	6.77 (6.56–6.99)
Pre-existing maternal risk factor:			
Asthma	1.03 (0.99–1.06)	1.03 (0.85–1.25)	1.02 (0.98–1.06)
Hypertension	1.04 (0.98–1.10)	0.87 (0.61–1.24)	1.03 (0.97–1.10)
Diabetes (types 1 and II)	1.09 (1.01–1.18)	1.25 (0.82–1.90)	1.07 (0.99–1.15)
Cardiac disease	1.05 (0.99–1.10)	1.45 (0.13–1.86)	1.02 (0.97–1.08)
Renal disease	1.15 (1.03–1.27)	1.26 (0.66–2.41)	1.13 (1.02–1.26)

[†]Risk ratios; 95% CI, 95% compatibility intervals.
[‡]Qld data only.
[§]No data for NT.
[¶]Derived from body mass index variable and using standard Australian categories.
[^]No data for WA.
IIV, inactivated influenza virus; dTpa, pertussis-containing vaccine.

antenatal vaccination status, and identify concerning potential inequities in First Nations women. These important findings will be used to inform state and territory government-managed antenatal vaccination programs, and Commonwealth government-funded immunisation policy.

Our study captured data for pregnancies ≥20 weeks gestation, so our understanding of vaccination status in women who experienced earlier pregnancy loss was limited. Other limitations we could not control for were potential biases. There are no consistent data collection processes for maternal vaccination information in Australia, so data sources, and potentially data quality, varied across jurisdictions. In the NT, multiple data entry processes are required because this information is not captured in NT PDC forms. Vaccine and HCPs in private and public practice are required to manually send vaccination data to the Australian Immunisation Register and the NT Department of Health. Most women in the NT (~84%),[15] birth at one of the five public hospitals, capturing the majority of women who are eligible for antenatal vaccinations; however, there are currently no plans to add antenatal vaccination information to NT PDC forms. This is a monitoring systems limitation, posing a potential risk for misclassification bias of vaccination status for NT pregnancies. Misclassification bias was also a risk for Qld and WA data following the transition of capturing maternal vaccination information from PDCs. Although vaccination status is recorded in PDCs by the medical professional attending the birth, this system may miss a proportion of vaccinations and gestations may not be entirely accurate. Previous studies have examined the proportion of agreement between HCP-recorded and confirmed dates of antenatal vaccination. Although these studies were small ($N = 421$, $N = 212$, $N = 831$),[7,16,17] one study found ~88% agreement for IIV.[17]

Public health implications

The concerning gap we observed in vaccination uptake between First Nations and non-Indigenous pregnancies, and the dismal rates of vaccination in pregnancy overall, require an urgent review of vaccination strategies before the next influenza pandemic or pertussis outbreak. Determining whether there has been a shift in antenatal vaccine uptake away from women who are traditionally at

risk of infection toward those who have better access to and more affordability of vaccination options and health care is essential. If administration of dTpa in pregnancy is driving IIV uptake in pregnancy rather than national immunisation policy recommendations, changes in practice are required to ensure IIV is distributed equitably and timed to provide optimal protection to pregnant women and infants against influenza infection. Early engagement of young and First Nations women in culturally appropriate antenatal services may improve equity and increase uptake of both vaccines in pregnancy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Box S1: Vaccination sources by jurisdiction and year.
Box S2: Description of immunisation data sources.
Box S3: Data sources for demographic, health and medical factors associated with vaccination in pregnancy and corresponding International Classification of Disease 10th edition Australian Modification (ICD-10-AM) codes.
Table S1: Demographic and health characteristics of LinksHealthierBubs pregnancies by study site, Australia 2012–2017.
Table S2: Factors affecting IIV vaccine uptake in pregnancy in Links2HealthierBubs study participants by year and jurisdiction, 2012–2017.
Table S3: Factors affecting dTpa vaccine uptake in pregnant Links2HealthierBubs study participants overall and by jurisdiction, 2015–2017.
Table S4: Factors affecting uptake of both IIV and dTpa vaccines in the same pregnancy in Links2HealthierBubs mothers overall and by jurisdiction, 2015–2017.
Figure S1: Vaccination status by study year and Indigenous status, Australia, 2012–2017.
Figure S2: Gestation of IIV administration by jurisdiction.
Figure S3: Timing of IIV and dTpa by trimester of pregnancy.