National predictors of influenza vaccine uptake in pregnancy: the FluMum prospective cohort study, Australia, 2012–2015

Lisa McHugh,[1,2] Kerry-Ann F. O'Grady,[3] Terry Nolan,[4] Peter C. Richmond,[5] Nicholas Wood,[6] Helen S. Marshall,[7] Stephen B. Lambert,[8] Mark D. Chatfield,[1,9] Kirsten P. Perrett,[10] Paula Binks,[1] Michael J. Binks,[1] Ross M. Andrews[1,8]

Abstract

Objective: Ascertain predictors of inactivated influenza vaccine (IIV) uptake in pregnancy in mother–infant pairs from six Australian sites over four consecutive influenza seasons (2012–2015).

Methods: Prospective observational cohort study calculating proportions of unvaccinated and vaccinated pregnancies. Multivariable logistic regression calculating adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) to determine demographic, pregnancy and birth characteristics as predictors of IIV uptake in pregnancy.

Results: Uptake of IIV was 36% (n=3,651/9,878) with only 3–4% during the first trimester. Validation of IIV receipt was obtained for 77% of vaccinated participants. Predictors of IIV uptake in pregnancy were: healthcare provider recommendation to have IIV during pregnancy (aOR 7.04 [95%CI 5.83-8.50]): GP (aOR 4.12 [95%CI 3.43-4.98]), obstetrician (aOR 4.41 [95%CI 3.45-5.64]), midwife (aOR 1.88 [95%CI 1.51-2.36]); previous IIV within 12 months of their current pregnancy (aOR 2.87 [95%CI 2.36-3.50]); and pertussis vaccination during the current pregnancy (aOR 4.88 [95%CI 4.08-5.83]).

Conclusions and implications for public health: Healthcare provider discussions with pregnant women about the risks associated with influenza infection during pregnancy and early infancy and evidence about the safety and effectiveness of IIV are required. Recommending and offering IIV in pregnancy needs to be included in these discussions to improve uptake.

Key words: influenza, vaccination, pregnancy, predictors

Pregnant women and infants younger than six months of age (<6m) have a higher risk of being infected by influenza viruses than the general population.[1] Reasons for this heightened risk are multifactorial: pregnancy-induced changes in immune function;[2] age-associated immaturity of the infant's immune system; high exposure to and transmission of pathogens from others; or being unvaccinated, either by age preclusion or choice.[1]

Pregnant women bore a disproportionately high burden of illness during the 2009 H1N1 influenza pandemic, where 30–50% of deaths that occurred among women of child-bearing age were in pregnant women.[3] Studies have shown that influenza infection during pregnancy is associated with a two-fold increase in the risk of foetal death.[4] In Australia, infants <6m also bear a high disease burden from influenza infection, with up to 320 hospitalisations per 100,000 population per year, and from these hospitalisations, up to 10% requiring ICU admission.[5] In Australia, inactivated influenza vaccine (IIV) is not licensed or recommended for use in infants <6m of age, therefore this age group remains vulnerable to the severe effects of infection. To protect young infants and pregnant women from severe morbidity and mortality associated with influenza infection, the routine use of seasonal IIV antenatally has been recommended in Australia since 2000.[6]

Although vaccination programs for IIV in pregnancy have been implemented in all Australian states and territories, there is no systematic process in place to monitor and evaluate the impact of the program at a national level. Although the Australian Immunisation Register (AIR) encompasses a 'whole of life' register, pregnancy status

1. Menzies School of Health Research, Charles Darwin University, Northern Territory
2. School of Public Health, The University of Queensland
3. Australian Centre for Health Services Innovation, Centre for Healthcare Transformation, Queensland University of Technology
4. Peter Doherty Institute for Infection and Immunity, The University of Melbourne, and Murdoch Children's Research Institute
5. Perth Children's Hospital, Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute and Division of Paediatrics, University of Western Australia,
6. National Centre for Immunisation Research and Surveillance (NCIRS) and The Faculty of Medicine and Health, University of Sydney, New South Wales
7. Women's and Children's Health Network and Robinson Research Institute and Adelaide Medical School, The University of Adelaide, South Australia
8. Research School of Population Health, Australian National University, Australian Capital Territory
9. Faculty of Medicine, The University of Queensland
10. Murdoch Children's Research Institute, Royal Children's Hospital and Department of Paediatrics, The University of Melbourne, Victoria
Correspondence to: Dr Lisa McHugh, School of Public Health, Division of Medicine, University of Queensland; e-mail: l.mchugh@uq.edu.au
Submitted: January 2021; Revision requested: April 2021; Accepted: May 2021
The authors have stated the following conflicts of interest: HM is an investigator on industry sponsored studies of investigational vaccines. Her institution has received funding for investigator-led research from GSK, Pfizer and Sanofi-Pasteur. She receives no personal payments from Industry. KPP is an investigator on industry sponsored studies of investigational vaccines. Her institution has received funding from GSK, MedImmune and Novavax outside the submitted work. She receives no personal payments from Industry. PCR is an investigator on industry sponsored studies of Investigational vaccines. His institution has received funding for investigator-led research from GSK and Novartis outside the submitted work and for his participation in advisory boards for Astra Zeneca, GSK, Novavax, Pfizer and Sanofi. He receives no personal payments from Industry.

Aust NZ J Public Health. 2021; 45:455-61; doi: 10.1111/1753-6405.13130

is not recorded.[7] As such, well-conducted observational studies remain critical to assess vaccine uptake and identify predictors of vaccine uptake, particularly in preparation for inevitable future influenza pandemics. We aimed to ascertain the uptake and the predictors of uptake of IIV in pregnancy in participants from six major cities in Australia over four consecutive years, and by gestational timing of vaccination. A secondary aim was to ascertain whether the introduction of the maternal diphtheria-tetanus-acellular pertussis (dTpa) vaccination program in 2014 in Queensland, and in 2015 in the remaining states and territories,[8] affected the uptake of IIV in pregnancy.

Methods

Study design and population

This study formed part of the FluMum study, which was a prospective observational cohort of mother–infants pairs recruited from six sites in mainland Australia (Darwin, Brisbane, Sydney, Melbourne, Adelaide and Perth) over four consecutive years (2012–2015 inclusive). The primary aim of the FluMum study was to assess the effectiveness of IIV in pregnancy in preventing influenza infections in early infancy.[9] This study assesses the uptake of IIV in pregnancy and its predictors, which was a key secondary outcome. Changes from the original published protocol in 2014 (amended and approved by the relevant ethics committees), included adding questions about the uptake of dTpa during pregnancy to the participant questionnaire.

Study participants

Participants were recruited from maternity units and primary healthcare settings by trained study personnel who sought written, informed consent to participate. Eligible participants were women aged 17 years or older at the time of consent who were at least 38 weeks gestation or had delivered a live-born infant within 55 days of enrolment and had sufficient verbal English to permit questionnaire completion.

Data collection methods and sources

Data collection/enrolment each year began from the start to the finish of each respective site's individual influenza season, determined by using real-time surveillance data as they became available.[10] There was year-round recruitment at the Darwin site due to year-round circulating influenza and bimodal peaks of influenza in the tropics.[10] Participants were asked whether they received a flu vaccine in pregnancy, and if yes, "Who gave you the flu vaccine?" The receipt of IIV in pregnancy was based on self-reported dates. Where the date of IIV in pregnancy was unknown, confirmation by the participant's vaccine provider was obtained. For the years 2014–2015 inclusive, information was also sought for self-reported dTpa status in pregnancy. Information for known and potential confounders such as sociodemographic characteristics, co-morbidities and risk factors for infection was collected through an interviewer-administered questionnaire at study entry. Information for barriers/influences affecting the uptake of IIV in pregnancy was obtained through closed questions with fixed responses.

Sample size

As defined in our study protocol,[9] the recruitment target was 10,106 mother–infant pairs: a sample size of 422 participants per year, per site, with estimates of vaccine uptake accurate to within ±5%, for example, 35% uptake=95% confidence interval (95%CI) 30.6-39.5%.

Data analysis

Numbers and proportions of study participants were calculated overall and by antenatal vaccination status, year of study, and study site. Vaccination status in pregnancy was the primary outcome measure, with the following explanatory variables investigated: demographics, comorbidities, risk factors, pregnancy and birth indicators, and attitudes and beliefs towards vaccination in pregnancy. We identified predictors of IIV in pregnancy over time and by site at a univariable level using chi-square tests for binary and categorical variables. Predictors significant at the 5% level in the univariable analysis were included in the multivariable logistic regression model, and adjusted odds ratios (aORs) and 95%CI are reported. Variables that were no longer significant in the multivariable logistic regression model were dropped and not reported in the tables. Participants were excluded from further analysis if IIV vaccination status during pregnancy was unconfirmed. Trimester of pregnancy at the time of IIV administration was calculated using maternal self-reported gestation at infant birth (or date of last menstrual period), date of infant birth and the recorded IIV date in pregnancy. The calendar month of IIV administration was also calculated and summarised based on the recorded date of IIV in pregnancy to assess whether IIV in pregnancy was clustered relative to the typical 'flu season'.

Ethics committee approvals were gained for all jurisdictional participating sites and affiliated research institutions with written informed consent obtained from all participants. This study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) number: 12612000175875.

Results

Of 14,190 mother–infant pairs who were screened, 9,874 were enrolled (71% consent rate), and 6,223/9,874 (63%) of the cohort were unvaccinated for IIV (Figure 1). Among the 3,651/9,874 (37%) participants who self-reported IIV in pregnancy, the date of IIV receipt was obtained for 77%. There were 830 participants for whom a date of IIV was not able to be confirmed by a healthcare provider (HCP). The 830 'unconfirmed' IIV recipients were not clustered in time: n=108 (7.2%) in 2012; n=238 (8.7%) in 2013; n=246 (8.6%) in 2014; and n=236 (8.6%) in 2015.

Participants were evenly distributed throughout the six Australian study sites over the four-year study period (range 1,578–1,758 participants per site). Approximately 50% of IIV received during pregnancy throughout the four-year study period was administered over a seven-week interval: calendar weeks 14– 21 (Supplementary Figure 1).

Demographic characteristics

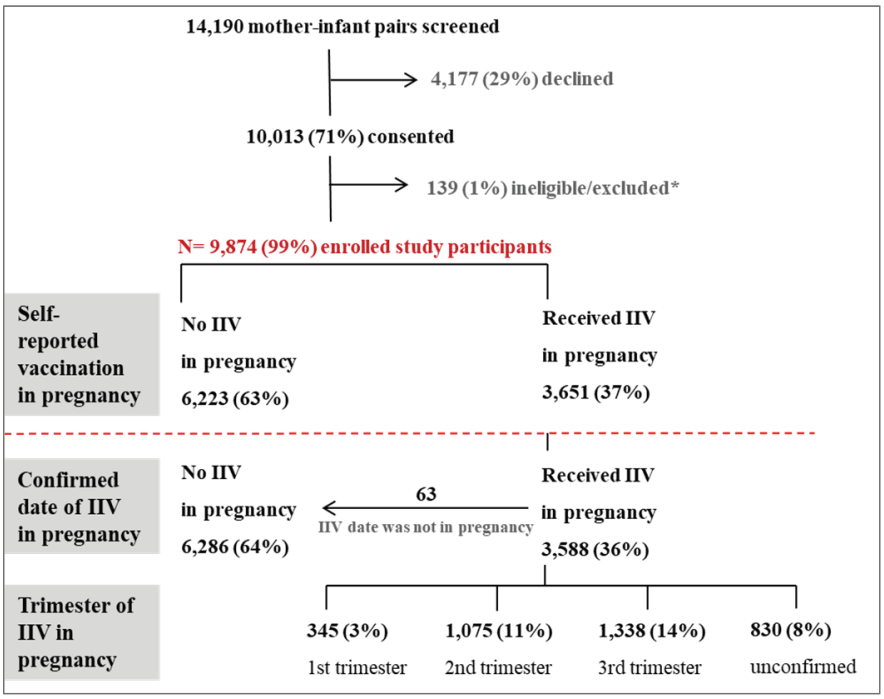
Maternal demographic and pregnancy characteristics were similar between groups, and First Nations status was captured in >99% of study participants (Table 1). Differences between the unvaccinated and vaccinated groups, respectively, included: receipt of IIV within 12 months of the current pregnancy (18% vs. 41%); having received IIV ever (44% vs. 62%); HCP recommendation to have IIV during pregnancy (27% vs. 78%; GP 15% vs. 47%, obstetrician 6% vs. 22%, midwife 9% vs. 18%), and receiving dTpa vaccine during pregnancy (12% vs. 44%).

Influenza vaccination status in pregnancy

Overall, self-reported IIV uptake in pregnancy was 36%, ranging from 30–49% by site (Supplementary Figure 2). Self-reported IIV uptake in pregnancy also varied within study site and between the years for all sites. There was an increasing trend in IIV uptake for the Brisbane site, and the final study year of 2015 showed the highest uptake of IIV in all sites apart from Sydney (Supplementary Figure 3). There was a shift in the median gestational age at the time of IIV in pregnancy for the 2012–2013 study period when compared with 2014–2015 (Figure 2, showing 25% and 75% interquartile ranges). For the years 2012–2013 inclusive, the overall median gestational age at the time of IIV in pregnancy was 25 weeks, with 75% at or before 31 weeks gestation. For the years 2014–2015 inclusive, this increased to 29 weeks, with 75% at or before 34 weeks gestation. The increase in the median gestational age occurred across all sites.

As seen in Figure 2, participants from Darwin (in a tropical zone) received IIV at an earlier median gestational age than those in the temperate climate sites (Brisbane, Sydney, Melbourne, Adelaide and Perth).

Figure 1: Flow diagram of FluMum study participants by maternal vaccination status, Australia, 2012–2015.



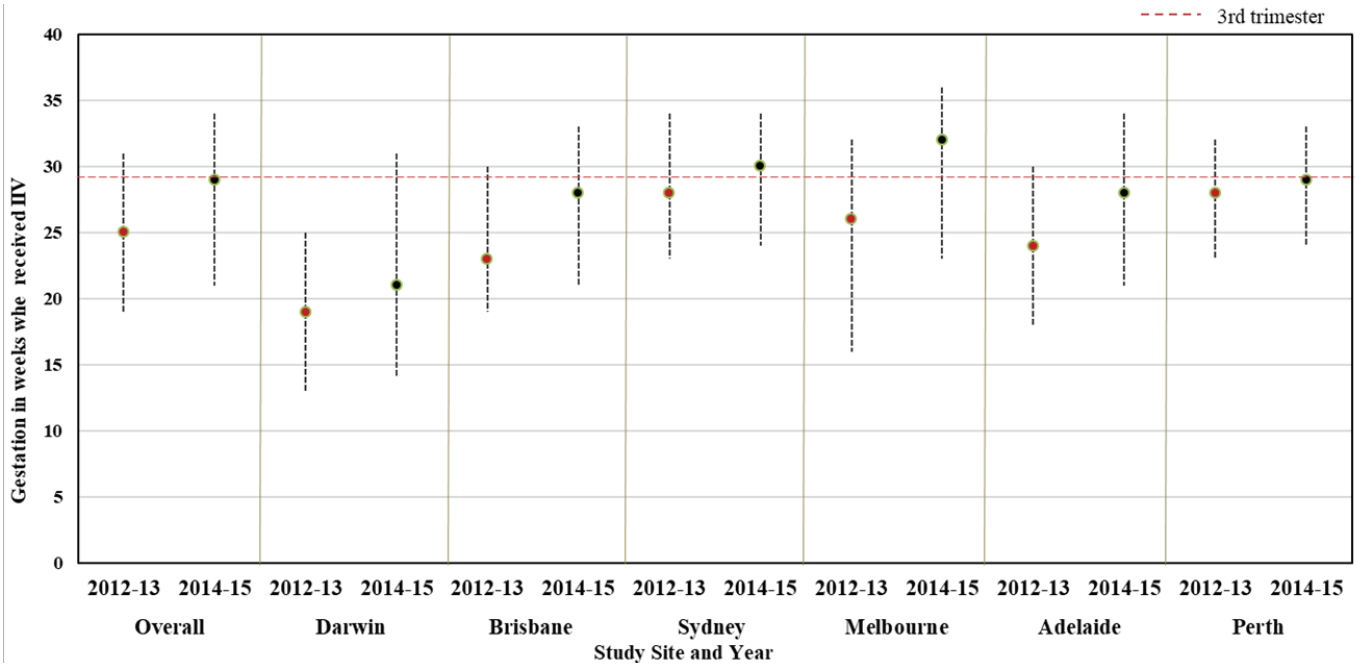
Notes:

Trimester was only calculated where a date of vaccination was available

IIV = Inactivated Influenza Vaccine

^139 ineligible/excluded: 81 IIV status in pregnancy was unknown/missing; 27 withdrew consent; 14 eligibility not confirmed; 6 data duplicates (same pregnancy); 4 data loss; 3 infant deaths; 2 moved overseas; 2 insufficient English

Figure 2: Median gestation in weeks at time of IIV in pregnancy, by study site, Australia, 2012–2013 inclusive, and 2014-2015 inclusive.



Note:

Excludes 830 enrolled participants who self-reported receipt of IIV in pregnancy for which an exact date of vaccination could not be confirmed

Table 1: Demographic characteristics of FluMum study participants overall, and by self-reported influenza vaccine uptake in pregnancy, Australia 2012-2015.

	Total n/N (%)	No IIV in pregnancy n/N (%)	Received IIV in pregnancy n/N (%)
Characteristic n (%)	**N=9,874**	**N=6,286 (64)**	**N=3,588 (36)**
Maternal demographics/ co-morbidities			
Maternal age at infant birth (mean years and IQR)	31.8 (28.5–35.2)	31.6 (28.2–35.2)	32.2 (29.0–35.3)
Mother identified as a First Nations woman	257 (2.6)	162 (2.6)	95 (2.7)
Australian born	6,328 (64)	4,012 (64)	2,316 (65)
Maternal education diploma/higher	5,760 (66)	3,509 (63)	2,251 (71)
English as main language spoken	7,917 (82)	5,013 (82)	2,904 (83)
In paid employment during pregnancy	7,527 (76)	4,621 (74)	2,906 (81)
Median household size (IQR)	4 (3–5)	4 (3–5)	4 (3–4)
Received IIV within 12 months prior to start of current pregnancy	2,553 (26)	1,119 (18)	1,434 (41)
Received IIV ever	4,860 (50)	2,691 (44)	2,169 (62)
Risk factor as an indication for IIV (other than pregnancy)[a]	2,115 (21)	1,279 (20)	836 (23)
Pregnancy			
Attended antenatal care in 1st trimester	8,763 (89)	5,543 (89)	3,220 (90)
Smoking in pregnancy, self report	645 (6.5)	458 (7.3)	187 (5.2)
Regularly exposed to indoor tobacco smoke during pregnancy	244 (2.5)	178 (2.8)	66 (1.8)
Regularly exposed to household smoke during pregnancy	1,860 (19)	1,301 (21)	559 (16)
Children attend day care facility	2,368 (24)	1,575 (25)	793 (22)
Health care provider[b] recommended IIV in pregnancy	4,438 (45)	1,669 (27)	2,769 (78)
GP recommended IIV during pregnancy	2,623/9,801 (27)	939/6,232 (15)	1,684/3,569 (47)
Obstetrician recommended IIV during pregnancy	1,156/9,801 (12)	361/6,232 (5.8)	795/3,569 (22)
Midwife recommended IIV during pregnancy	1,217/9,801 (12)	571/6,232 (9.2)	646/3,569 (18)
Received pertussis-containing vaccine during pregnancy[c]	1,329/5,255 (25)	374/3,087 (12)	955/2,168 (44)
Birth			
Gestation at birth (median weeks and IQR)	39 (38–40)	39 (38–40)	39 (38–40)
Birthweight (mean grams and IQR)	3,343 (3,030–3,702)	3,350 (3,040–3,720)	3,331 (3,019–3,700)
Public hospital birth	6,131 (62)	3,983 (63)	2,148 (60)

Notes:

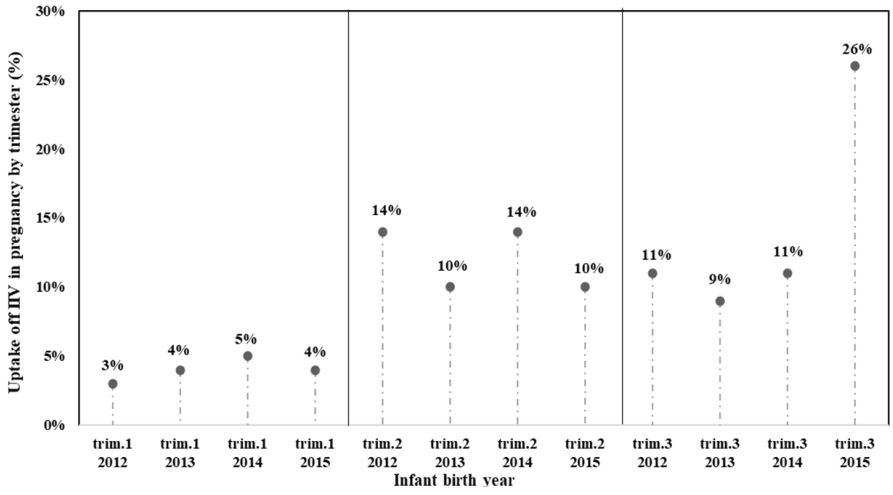
Denominators differ due to missing data.

a: Includes hypertension (essential, gestational and pre- eclampsia), emphysema or severe asthma requiring frequent hospital visits, HIV/AIDS, type 1, type 2 and gestational diabetes

b: Health care provider (GP, obstetrician or midwife)

c: Data collected from 2014-2015 inclusive

Figure 3: IIV uptake in pregnancy by trimester of pregnancy, FluMum study, Australia (2012–2015).



Note:

Excludes 830 enrolled participants who self-reported receipt of IIV in pregnancy for which an exact date of vaccination could not be confirmed

The difference was evident for both the 2012–2013 and 2014–2015-year periods. Participants in the Darwin site, therefore, experienced a longer median gestation/ time from IIV to birth than those from the other sites (20 weeks versus 10–16 weeks in 2012–2013 and 18 weeks versus 7–11 weeks during 2014–2015).

Excluding those with an unconfirmed date of IIV, the uptake of IIV by trimester of pregnancy ranged from 3–5% in the first trimester, and 10–14% during the second trimester, before increasing markedly during the third trimester from 9–11% in 2012–2014 to 26% in 2015 (Figure 3). In 2014, 3% (n=85/2,572) of women self-reported dTpa vaccination in pregnancy, increasing to 46% (n=1,244/2,683) in 2015. Women who reported receiving both IIV and dTpa vaccines in pregnancy increased from 2% in 2014 (n=52/2,572) to 34% (n=903/2,684) in 2015 (data not shown elsewhere).

Predictors of influenza vaccination in pregnancy

Any HCP recommendation for IIV during pregnancy remained statistically significant overall, and across all study years in the multivariable logistic regression model as a predictor of IIV uptake in pregnancy (aOR 7.04 [95%CI 5.83-8.50], $p<0.001$). When run separately, the model for specific HCP recommendations were: GP (aOR 4.12 [95%CI 3.43-4.98], $p<0.001$, obstetrician (aOR 4.41 [95%CI 3.45-5.64], $p<0.001$), and midwife (aOR 1.88 [95%CI 1.51-2.36], $p<0.001$). Women who had received IIV in the 12 months preceding their current pregnancy, and those who received the dTpa vaccine during pregnancy were also predictors of IIV in pregnancy (Table 2a).

Any HCP recommendation for IIV, GP recommendation and dTpa vaccination during the current pregnancy were factors that consistently predicted IIV uptake in pregnancy within each of the study sites (Table 2b). Other variables that predicted IIV uptake in pregnancy, but not necessarily across all years or all sites, were women who: attained an education level of diploma/higher; had ever received an IIV; or had a risk factor as an indication for IIV (excluding pregnancy). For all sites apart from Melbourne, having received IIV within 12 months of the current pregnancy was a predictor variable for receipt of IIV in pregnancy (Table 2b).

Table 2a: Predictors of self-reported influenza vaccine uptake in pregnancy in FluMum study participants by study year, Australia 2012-2015.

Multivariable logistic regression	Overall	2012	2013	2014	2015
Variables from Table 1 remaining in the model	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P
Maternal education diploma/higher				1.40 (1.03–1.89) <0.05	
First Nations mum		4.56 (1.97–10.57) <0.001			
Smoked in pregnancy		0.33 (0.17–0.62) 0.001			
Received IIV within 12mnths of current pregnancy	2.87 (2.36–3.50) <0.001	4.02 (2.91–5.56) <0.001	2.80 (2.11–3.72) <0.001	4.30 (3.28–5.64) <0.001	2.05 (1.57–2.68) <0.001
Received IIV ever	1.53 (1.26–1.85) <0.001	1.54 (1.15–2.05) <0.01	1.35 (1.05–1.73) <0.05		1.79 (1.39–2.30) <0.001
Risk factor as indication for IIV (excl. pregnancy)[a]	1.24 (1.01–1.51) <0.05				1.44 (1.09–1.90) <0.01
Public hospital birth	1.23 (1.03–1.47) <0.05	1.38 (1.04–1.84) <0.05			
HCP[b] recommended IIV during pregnancy	7.04 (5.83–8.50) <0.001	11.31 (5.04–25.35)<0.001	11.45 (6.57–19.96)<0.001	8.62 (4.67–15.90)<0.001	7.04 (4.28–11.59)<0.001
GP recommended IIV during pregnancy	4.12 (3.43–4.98) <0.001	8.28 (6.08–11.28) <0.001	8.67 (6.72–11.20) <0.001	5.00 (3.73–6.70) <0.001	3.76 (2.93–4.84) <0.001
Obstetrician recommended IIV during pregnancy	4.41 (3.45–5.64) <0.001	6.07 (3.93–9.37) <0.001	7.25 (5.07–10.37) <0.001	4.36 (3.04–6.24) <0.001	4.19 (2.98–5.86) <0.001
Midwife recommended IIV during pregnancy	1.88 (1.51–2.36) <0.001	3.47 (2.22–5.42) <0.001	3.16 (2.27–4.41) <0.001	1.98 (1.34–2.92) <0.001	3.15 (2.28–4.34) <0.001
Received pertussis vaccine during pregnancy[c]	4.88 (4.08–5.83) <0.001	Data not collected	Data not collected	2.78 (1.62–4.77) <0.001	7.26 (5.68–9.27) <0.001

Notes:

aORs and 95%CIs not shown when variables did not remain statistically significant in the multivariable logistic regression model

a: Includes hypertension (essential, gestational and pre-eclampsia), emphysema or severe asthma requiring frequent hospital visits, HIV/AIDS, type 1, type 2 and gestational diabetes

b: Health care provider (GP, obstetrician or midwife)

c: Variable restricted to year 2014 and 2015 due to data collection for dTpa for these years only

Table 2b: Predictors of self-reported influenza vaccine uptake in pregnancy in FluMum study participants by study site, Australia 2012-2015.

Multivariable logistic regression	Darwin	Brisbane	Sydney	Melbourne	Adelaide	Perth
Variables from Table 1 remaining in the model	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P	aOR (95% CI) P
Maternal education diploma/higher				1.98 (1.05–3.74) <0.05		
Received IIV within 12mnths of current pregnancy	2.60 (1.74–3.91) <0.001	2.56 (1.64–3.99) <0.001	3.84 (2.10–6.99) <0.001		2.95 (1.77–4.93) <0.001	3.53 (2.31–5.39) <0.001
Received IIV ever	2.14 (1.43–3.21) <0.001	1.68 (1.01–2.79) <0.05		1.75 (1.00–3.05) <0.05		
Risk factor as indication for IIV (excl. pregnancy)*		1.74 (1.08–2.79) <0.05				
Exposed to household smoke during pregnancy		0.55 (0.31–0.98) <0.05				
Children attend day care facility					0.55 (0.32–0.93) <0.05	
HCP recommended IIV during pregnancy[a]	7.96 (3.54–17.90) <0.001	3.60 (1.37–9.51) <0.01	7.17 (2.17–23.70) <0.001	12.21 (3.39–43.99) <0.001	2.39 (1.32–4.31) <0.01	4.71 (2.42–9.16) <0.001
GP recommended IIV during pregnancy	3.06 (2.01–4.68) <0.001	5.12 (3.39–7.71) <0.001	7.22 (4.23–12.34) <0.001	8.71 (5.08–14.94) <0.001	1.96 (1.18–3.27) <0.01	3.79 (2.37–6.05) <0.001
Obstetrician recommended IIV in pregnancy	3.10 (1.76–5.49) <0.001	3.99 (2.26–7.05) <0.001		10.51 (4.78–23.12) <0.001		5.31 (3.47–8.11) <0.001
Midwife recommended IIV in pregnancy	2.96 (1.95–4.49) <0.001	2.99 (1.17–7.61) <0.05	5.40 (2.62–11.11) <0.001	5.22 (2.19–12.42) <0.001		
Received pertussis vaccine in pregnancy[b]	4.26 (2.89–6.28) <0.001	4.00 (2.64–6.06) <0.001	4.16 (2.44–7.11) <0.001	3.31 (1.96–5.57) <0.001	7.60 (4.66–12.40) <0.001	4.70 (3.14–7.03) <0.001

Notes:

a: Health care provider (GP, obstetrician or midwife)

b: Data collected for dTpa from 2014 - 2015 only

Views, attitudes and beliefs about vaccination in pregnancy

Overall, 80% of women considered influenza a serious disease in pregnancy, and 81% thought that IIV in pregnancy reduced the disease severity (Supplementary Table 1). Women who received IIV in pregnancy were twice as likely to have had influenza infection discussed with them during pregnancy compared to unvaccinated women (81% vs. 40%), and more likely to report understanding that IIV also prevented influenza infection in infants (61% vs. 40%). Unvaccinated women were twice as likely to report they were concerned about vaccines in pregnancy (40% vs. 22%), and to believe IIV causes illness (61% vs. 34%) and can harm their unborn baby (27% vs. 5%). An IIV was recommended in pregnancy for 32% of all study participants, and 67% of unvaccinated participants (n=3,652/5,472) stated they would have accepted IIV during pregnancy if it was recommended by their doctor. Also, 10% of unvaccinated participants (n=605/6,194) stated it was recommended they *not* be given IIV during pregnancy, and of these, 25% (n=152/605) were recommendations from HCPs (GP, obstetrician, midwife, immunisation nurse, pharmacist).

Discussion

Over a four-year study period (2012–2015), IIV uptake in pregnancy was low (36%), which – notwithstanding moderate

variation of 30–49% uptake between the six sites – is sub-optimal. Healthcare provider recommendation for IIV in pregnancy, previous vaccination with an IIV, particularly receipt in the previous 12 months, and dTpa vaccination in pregnancy were key factors that consistently predicted the uptake of IIV in pregnancy over time and by study site.

The recommendation of IIV in pregnancy by an HCP is a recognised key driver for acceptance and uptake.[11-13] Most women in our unvaccinated cohort (67%) would have accepted IIV during pregnancy if it had have been offered to them by their HCP. Since IIV in pregnancy is a nationally recommended and publicly funded strategy, this was a missed opportunity by HCPs for many of the women in our study. Based on the perspective of participants, it seems that the intention of HCPs to offer pregnant women vaccines is not translating into practice, despite their awareness of the recommendations.[14] While seasonal IIV is typically available for ~11 months of each calendar year, the window of opportunity to offer IIV in pregnancy appears to have been unnecessarily constrained to a narrow period coinciding with the early months of vaccine availability. In our cohort, 50% of IIV given during pregnancy was administered over a seven-week period in each calendar year. Here the focus appears to be on the early influenza season, rather than an offer of IIV at any time during pregnancy. Very few women in our cohort (3–4%) received IIV in the first trimster, while 11–14% had received IIV in the second trimester. Receipt of IIV in the 12 months preceding the current pregnancy, or ever, was also a strong predictor of uptake during pregnancy. This is consistent with the influence of GP recommendation of IIV in pregnancy,[13,15] and the familiarity of normally getting the seasonal IIV when not pregnant.[16]

We observed an almost whole trimester shift of IIV from the second to the third trimester of pregnancy in 2015. The shift coincided with the introduction of the maternal dTpa program that targeted women during their third trimester of pregnancy. Opportunistic vaccination with the convenience of getting both (IIV and dTpa) vaccines at the one visit may have been one of the major drivers. Possibly, women also felt more accepting of vaccination later in their pregnancy due to concerns around the safety of IIV earlier in pregnancy, given that safety was recognised as a concern for 40% of our unvaccinated study participants. Since morphology screening (ultrasound) is conducted at ~18–22 weeks gestation, and the optimal timing for dTpa is now recommended from 20–32 weeks gestation,[17] it may be more acceptable for women to have both vaccines (IIV and dTpa) at or following the morphology scan, especially for those women who have previously had safety concerns about IIV in the first trimester.

Reported IIV uptake in pregnancy in Australia has varied from ~24 to 61% between jurisdictions[18-20] and influenza seasons,[10] but has consistently been sub-optimal. In 2015, IIV uptake in non-Indigenous pregnant women was 24% in the Northern Territory,[20] 61% and 72%, respectively, for IIV and dTpa in Western Australia,[18] and 62% and 63%, respectively, for Western Australian First Nations women.[21] More recently, IIV uptake in pregnancy was 76% in South Australia[11] and 39% in Victoria.[19] Differences in uptake between jurisdictions are most likely multifactorial; states with shared-care models of antenatal care indicate higher IIV uptake, and areas where English is a second language and with lower socioeconomic status indicate lower IIV uptake.[22] Regardless of the differences, a conversation with pregnant women about the risks associated with influenza infection during pregnancy and infancy and what is known about IIV safety and effectiveness, as well as offering IIV to every pregnant woman, is required. Given our cohort were recruited from major capital cities, not rural or remote-living areas, access to HCPs (and hence vaccinations) should not have been an issue unless the co-payment cost of a GP visit was a factor; however, <2% of women indicated that cost was an issue. Most of those who were unvaccinated believed that influenza in pregnancy was serious (76%) and that IIV reduced the severity of influenza in pregnancy (77%).

Strengths and limitations

We were able to confirm IIV uptake in pregnancy by HCPs for 77% of participants. This, along with our large sample size, broad geographic distribution over multiple study sites and data collection through consecutive influenza seasons are strengths of this study. Although a non-random sample, the study design enabled within-cohort comparisons that are generalisable to the general Australian population during this time period, and our one-on-one participant interviews conducted by trained researchers to capture demographic, pregnancy and birth characteristics and views, attitudes and beliefs about vaccination in pregnancy further strengthen our results.

We acknowledge that our eligibility criteria excluded non-English speaking women, potentially introducing selection bias. Budgetary restraints precluded us from employing interpreters; however, 18% of study participants stated English was not their main spoken language, and this did not differ between women who received IIV and unvaccinated women. Other limitations include non-representation of remote-living women and women who had either a stillbirth, miscarriage or late spontaneous abortion. We cannot know what proportion of these, or women who did not consent to be part of the study, received IIV or pertussis in pregnancy, and these areas require further research.

Conclusions

The uptake of IIV in Australia was poor prior to the introduction of the maternal dTpa vaccination program. Healthcare provider discussions with pregnant women about the risks associated with influenza infection during pregnancy and early infancy and evidence about the safety and effectiveness of IIV are required. Recommending and offering IIV in pregnancy needs to be included in these discussions to improve uptake.

Implications for public health

Although HCP recommendation for IIV in pregnancy remains the strongest predictor of uptake, a national systematic approach to ascertain vaccination status in pregnancy is still required. Key data elements should capture and prioritise: First Nations status, non-English speaking women, and geographic location for remote-living women to identify areas of disparity in vaccine uptake. Meanwhile, education for the public, HCPs and other advocates in healthcare settings are needed, and improving coverage in the general population of women may influence positive vaccine choices during pregnancy.

Acknowledgements

We would like to thank A/Prof Ann Koehler, CDCB, SA Health, Karen Watson, Felicity Hargrave, Sallyanne Le Gros-Wilson, Judith

Zenchyson, Sharon Tan, Elizabeth Clarke, Genevieve Dwyer, Jennifer Murphy, Elizabeth Hayles, Verity Hill, Susan Lee, Kathryn Riley, Caroline Talbot, Heidi Hutton and Daniel Arnold.

Funding

This project was funded via a National Health and Medical Research Council (NHMRC) Project Grant (APP 1020035). Lisa McHugh is funded through the NHMRC Council Centre of Research Excellence (CRE), the Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE APP1116530) as an APPRISE Research Fellow. During the project, Kerry-Ann O'Grady was supported by NHMRC Early Career and Career Development Fellowships (490338 and APP1045157). Helen Marshall is supported by an NHMRC Practitioner Fellowship APP1155066, Nicholas Wood is supported by an NHMRC Career Development Fellowship APP1142783, Kirsten Perrett is supported by a Melbourne Children's Clinician Scientist Fellowship. Paula Binks is supported by an NHMRC postgraduate scholarship (APP1190983). Michael Binks is funded by an NHMRC 'Hot North' Career Development Fellowship (GNT 1131932).

References

1. Rasmussen SA, Jamieson DJ, Bresee JS, Englund JA, Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol*. 2012;207(3 Suppl):S3-8.
2. Beischer NA, Mackay EV. *Obstetrics and the Newborn, An Illustrated Textbook*. 2nd ed. Sydney (AUST): WB Saunders;1986.
3. Anzic Influenza Investigators Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ*. 2010;340:c1279.
4. Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. *N Engl J Med*. 2013;368(4):333-40.
5. Flint S, Davis J, Su J, Oliver-Landry E, Rogers B, Goldstein A, et al. Disproportionate impact of pandemic (H1N1) 2009 influenza on Indigenous people in the Top End of Australia's Northern Territory. *Med J Aust*. 2010;192(10):617-22.
6. Australian Technical Advisory Group on Immunisation National Health and Medical Research Council. *The Australian Immunisation Handbook*. 10th ed. Canberra (AUST): Australian Department of Health and Ageing, 2013.
7. Department of Human Services. *Australian Immunisation Register*. Canberra (AUST): Government of Australia; 2019.
8. Australian Department of Health. *National Immunisation Program (NIP) Schedule*. Canberra (AUST): Government of Australia; 2018.
9. O'Grady KA, McHugh L, Nolan T, Richmond P, Wood N, Marshall HS, et al. FluMum: A prospective cohort study of mother–infant pairs assessing the effectiveness of maternal influenza vaccination in prevention of influenza in early infancy. *BMJ Open*. 2014;4(6):e005676.
10. Australian Department of Health and Aging. *Australian National Notifiable Disease Surveillance System: Influenza (Laboratory Confirmed) Public Dataset 2008-2016*. Canberra (AUST): Government of Australia; 2018.
11. Mohammed H, Clarke M, Koehler A, Watson M, Marshall HS. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. *PloS One*. 2018;13(6):e0197867.
12. Barrett T, McEntee E, Drew R, O'Reilly F, O'Carroll A, O'Shea A, et al. Influenza vaccination in pregnancy: Vaccine uptake, maternal and healthcare providers' knowledge and attitudes. A quantitative study. *BJGP Open*. 2018;2(3):bjgpopen18X101599.
13. Khan AA, Varan AK, Esteves-Jaramillo A, Siddiqui M, Sultana S, Ali AS, et al. Influenza vaccine acceptance among pregnant women in urban slum areas, Karachi, Pakistan. *Vaccine*. 2015;33(39):5103-9.
14. Lu AB, Halim AA, Dendle C, Kotsanas D, Giles ML, Wallace EM, et al. Influenza vaccination uptake amongst pregnant women and maternal care providers is suboptimal. *Vaccine*. 2012;30:4055-9.
15. Kilich E, Dada S, Francis MR, Tazare J, Chico RM, Paterson P, et al. Factors that influence vaccination decision making among pregnant women: A systematic review and meta-analysis. *PLoS One*. 2020;15(7):e0234827.
16. Mak DB, Regan AK, Joyce S, Gibbs R, Effler PV. Antenatal care provider's advice is the key determinant of influenza vaccination uptake in pregnant women. *Aust N Z J Obstet Gynaecol*. 2014;55(2):131-7.
17. Australian Technical Advisory Group on Immunisation. *Changes to the Recommended Use of Pertussis Vaccines in Pregnant Women*. Canberra (AUST): Australian Department of Health; 2019.
18. Mak DB, Regan AK, Vo DT, Effler PV. Antenatal influenza and pertussis vaccination in Western Australia: A cross-sectional survey of vaccine uptake and influencing factors. *BMC Pregnancy Childbirth*. 2018;18(1):416.
19. Rowe SL, Perrett KP, Morey R, Stephens N, Cowie BC, Nolan TM, et al. Influenza and pertussis vaccination of women during pregnancy in Victoria, 2015–2017. *Med J Aust*. 2019;210(10):454-62.
20. Overton K, Webby R, Markey P, Krause V. Influenza and pertussis vaccination coverage in pregnant women in the Northern Territory in 2015 – New recommendations to be assessed. *North Territ Dis Control Bull*. 2016;23(4):1-8.
21. Lotter K, Regan AK, Thomas T, Effler P, Mak DB. Antenatal influenza and pertussis vaccine uptake among Aboriginal mothers in Western Australia. *Aust N Z J Obstet Gynaecol*. 2018;58(4):417-24.
22. Australian Bureau of Statistics. *2076.0 - Census of Population and Housing: Characteristics of Aboriginal and Torres Strait Islander Australians, 2011 - Language Spoken At Home*. Canberra (AUST): ABS; 2012.

Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: Views, attitudes and beliefs of FluMum study participants overall, and by IIV uptake in pregnancy, Australia (2012-2015 inclusive).

Supplementary Figure 1: Month IIV was received in pregnancy, Australia, 2012–2015.

Supplementary Figure 2: FluMum study participants by vaccination status and study site, Australia, 2012–2015.

Supplementary Figure 3: Proportion of FluMum study participants who received IIV by study site and year, Australia, 2012–2015.