



Australian Government
Department of Health

COMMUNICABLE DISEASES INTELLIGENCE

2019 Volume 43
<https://doi.org/10.33321/cdi.2019.43.33>

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Lisa McHugh, Michael J Binks, Yu Gao, Ross M Andrews, Robert S Ware,
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Communicable Diseases Intelligence

ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

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Communicable Diseases Intelligence (CDI) is a peer-reviewed scientific journal published by the Office of Health Protection, Department of Health. The journal aims to disseminate information on the epidemiology, surveillance, prevention and control of communicable diseases of relevance to Australia.

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Communicable Diseases Intelligence is produced by:
Health Protection Policy Branch
Office of Health Protection
Australian Government
Department of Health
GPO Box 9848, (MDP 6)
CANBERRA ACT 2601

Email:

cdi.editor@health.gov.au

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Original article

Influenza vaccination in pregnancy among a group of remote dwelling Aboriginal and Torres Strait Islander mothers in the Northern Territory: The 1+1 Healthy Start to Life study

Lisa McHugh, Michael J Binks, Yu Gao, Ross M Andrews, Robert S Ware, Tom Snelling and Sue Kildea.

Summary

We found uptake of inactivated influenza vaccine (IIV) in pregnancy in remote-living Aboriginal and Torres Strait Islander women from the NT of Australia was 0% for the pre-influenza A(H1N1)pdm09 period (2003 to 2006), and remained unacceptably low (7%) for the post-influenza A(H1N1)pdm09 period (>2009–2011). Although IIV was routinely recommended for pregnant women throughout the entire eight year study period, vaccine uptake was extremely low among the 697 pregnancies in our study, particularly in women with known comorbidities and/or high risk factors.

Abstract

Remote-living Aboriginal and Torres Strait Islander women experience a higher burden of influenza infection during pregnancy than any other Australian women. Despite recommendations of inactivated influenza vaccination (IIV) in pregnancy, uptake and safety data are scarce for this population. We examined uptake of IIV in pregnancy and report adverse birth outcomes amongst a predominantly unvaccinated group of remote-living Aboriginal and Torres Strait Islander women from the Northern Territory (NT), using data from the 1+1 Healthy Start to Life study. Data were deterministically linked with the NT Immunisation Register to ascertain IIV exposure in pregnant women during 2003–2006 and 2009–2011 inclusive. Overall, IIV uptake in pregnancy was 3% (n=20/697 pregnancies); 0% (0/414) pre-influenza A(H1N1)pdm09 and 7% (20/293) post-influenza A(H1N1)pdm09 (2009–2011). Vaccine uptake was poor in this cohort and it is unclear at what stage this policy failure occurred. Women with known comorbidities and/or high risk factors were not targeted for vaccination. Much larger study participant numbers are required to validate between group comparisons but there was no clinically nor statistically significant difference in median gestational ages (38 weeks for both groups), mean infant birthweights (3,001 g unvaccinated vs 3,175 g IIV vaccinated), nor birth outcomes between the few women who received IIV in pregnancy and those who did not. There were no stillbirths in women who received an IIV in pregnancy.

Keywords: Influenza, remote, Northern Territory, pregnancy, birth outcomes, vaccination, uptake, Aboriginal, Australia

Introduction

Pregnant women are a high priority for seasonal inactivated influenza vaccination (IIV) worldwide.¹ Pregnant women and infants bore a disproportionately high burden of illness during the 2009 influenza A (H1N1) pandemic (influenza A(H1N1)pdm09),^{2,3} where 30–50% of women of child-bearing age who died were pregnant.^{4,5} The disease burden from influenza infection was particularly high amongst pregnant Indigenous women in Canada, the Americas and the Pacific, including Australia,^{6–8} where the risk of severe disease and death from influenza A(H1N1)pdm09 was 3–12 times higher than for non-Indigenous populations.^{7,9}

Aboriginal and/or Torres Strait Islander (hereafter respectfully referred to as Aboriginal) women and their infants continue to experience a higher burden of influenza infection during pregnancy and early infancy compared to non-Aboriginal Australians,¹⁰ and are disproportionately over-represented during influenza pandemics with higher rates of hospitalisations and intensive care unit (ICU) admissions.¹¹ Australian infants younger than six months of age incur up to 320 annual hospitalisations per 100,000 population, of which one in 10 are admitted to an ICU.^{12,13} Laboratory-confirmed influenza notifications and average annual notification rates in Northern Territory (NT) women of child-bearing age (15–<50 years) from 2008 to 2012 also showed a marked disproportionate burden of illness in Aboriginal women compared to non-Aboriginal women of the same age group.^{13,14}

In March 2000, a recommendation for seasonal IIV was added to the Australian National Immunisation Program (NIP) for all women who would be pregnant during the influenza season, regardless of trimester of pregnancy, and the program became funded (free) in 2010.¹⁵ The safety of maternal vaccination and vaccine provider recommendation are known to be the key drivers influencing the uptake of IIV in pregnancy.^{16,17} Given there is a disproportionate disease burden from influenza infection amongst Aboriginal Australians,¹⁸ the available

data on seasonal IIV uptake and safety for pregnant Aboriginal women is scarce, particularly for those women living in remote areas where the disease burden may be even greater. A World Health Organization (WHO) report published in 2017, examining the epidemiology of influenza in pregnancy, found robust safety data in the form of randomised controlled trials (RCTs) were still lacking, with birth outcomes reported from observational studies conflicting and at risk of bias.¹⁹ A separate review of the safety of immunisation during pregnancy by the WHO has also recommended that further safety evidence is needed for high-risk groups and local Indigenous populations.²⁰

The primary aim of this study was to ascertain seasonal IIV uptake in pregnancy amongst a cohort of remote-living Aboriginal women in the NT. Subject to adequate IIV uptake, the secondary aim was to compare key birth outcomes between IIV-vaccinated and unvaccinated pregnant women.

Methods

Study design

We conducted retrospective cohort analyses using data collected from the '1+1 Healthy Start to Life' study (1+1HS).²¹ Briefly, the 1+1HS study was designed to examine the utilisation and quality of health services and subsequent maternal and infant health outcomes of Aboriginal women residing in remote communities in the NT over two time periods: before (2003–2006) and after (2009–2011) a significant service redesign. Throughout the study period, pregnant women were routinely transferred to Royal Darwin Hospital (RDH) to birth their baby. Those mothers who were ≥ 20 weeks gestation with a singleton infant that weighed ≥ 400 grams (g) at birth were included. Women who birthed more than one infant within the study period were identified, and women pregnant with twins were excluded from the data analysis on adverse birth outcomes. Maternal and infant community health centre and regional hospital records were manually audited for each study participant,

then linked with demographic, comorbidity and risk factor data, health utilisation and cost and maternal and infant health outcomes. This became the final 1+IHS dataset.

Identifiable 1+IHS data were then deterministically linked with the NT Immunisation Register (NTIR) using the maternal identification number (ID) as the common identifier to confirm and validate maternal vaccination status in pregnancy. The NTIR is a population-based dataset of all immunisations administered in the NT. Clinical record checks were conducted manually for records where discrepancies occurred between the 1+IHS and NTIR datasets. Data cleaning was conducted to identify duplicates, multiple births and repeat birth, non-twin siblings. Missing data were treated as such.

Maternal vaccine exposure

The primary exposure of interest was any influenza vaccination given during pregnancy, defined as a vaccine received between the first day (date) of the last normal menstrual period and the date of birth of the infant. Vaccination status in pregnancy was determined by using the date of vaccination, gestation in weeks at birth of the infant and the date of birth of the infant. Records of IIV obtained from the NTIR were dropped if the dates of IIV did not correlate with IIV during pregnancy or during the 12 months prior. Brand names and dosages of any vaccines received by each woman were ascertained, however batch-specific details were not available. The number of days from receipt of IIV in pregnancy until birth of the infant was recorded.

Birth outcomes

The primary birth outcomes of interest were: pre-term births—infants born >20 weeks gestation, >400 g and <37 completed weeks' gestation;²² low birth weight (LBW)—any infant born >20 weeks and <2,500 g;²³ and small for gestational age (SGA)—infant birthweight <10th percentile calculated using Australian specific national birthweight percentiles by sex and gestational

age.²⁴ Maternal risk factors for adverse birth outcomes were recorded for all study participants (Box 1).

Box 1: Maternal comorbidities and risk factors collected from 1+IHS study participants, 2003–2011.

- Attended antenatal care in the 1st trimester (Y/N)
- Smoking in pregnancy^a (Y/N)
- Pregnancy complication^b
- Previous poor obstetric outcome^c
- Rheumatic heart disease
- Cardiac condition
- Diabetes^d
- Renal disease
- Asthma
- Maternal anaemia

a Recorded at first antenatal visit and at 36 weeks gestation

b Includes threatened preterm labour, preterm rupture of membranes, antepartum haemorrhage, placental abruption, placenta praevia, urinary tract infection (UTI), sexually transmitted infection (STI), gestational hypertension, pre-eclampsia

c Includes previous history of preterm birth, stillbirth, neonatal death (in multiparous women)

d Includes type 1, type 2 and gestational diabetes

Data analysis

Data from the NTIR were merged with the 1+IHS dataset using the maternal identifier to calculate the proportion of women who received an IIV in pregnancy, by study year. Demographic, comorbidity and risk factor characteristics of mother-infant pairs were summarised and compared between women who received an IIV

during pregnancy and mothers who did not. Proportions were calculated; χ^2 analyses for binary and categorical variables; and, depending on the distribution of the data, t-tests and ranksum analyses to calculate means and medians for continuous variables. We conducted Cox proportional-hazard ratio analyses for time-dependent birth outcomes using the continuous variable 'gestational age' as the time-scale variable. Compared to the unexposed group (unvaccinated pregnant women), in the exposed group (women who received IIV in pregnancy), the number of days from receipt of IIV in pregnancy until the birth of the infant was used to calculate effect estimates. Effect estimates are presented as crude hazard ratios (HR) with 95%CI. Data were analysed using Stata v.14.1 (StataCorp, College Station, Texas).

Results

There were 576 women with 697 pregnancies and 697 individual infants who were included in the cohort over the two observation periods: 1 December 2003 – 31 December 2006 and 1 January 2009 – 31 June 2011 (Figure 1). There were 121 mothers (17%) who birthed more than one infant (repeat births).

There were nine women who birthed twins ($n=18$ infants), and none of these women received IIV in pregnancy. These women were henceforth excluded from further data analysis due to known confounding effects for preterm birth, LBW and SGA outcomes. Data linkage with the NTIR found a matching record for all 1+1HS study participants apart from three, who were excluded. A further six women who received dTpa (pertussis) vaccine in pregnancy were also excluded, none of whom had received an IIV in pregnancy.

Uptake

Of the 697 pregnancies, 20 women (3%) received IIV in pregnancy and 677 (97%) women were unvaccinated. The median time from receipt of IIV until birth of the baby was 9 weeks (range 1.9–22.6), or in days 63 (range 13–158).

Ten women received IIV in the third trimester of pregnancy, all of whom were vaccinated approximately two weeks before the birth of the infant. Nine women received IIV in the second trimester and one in the first trimester. Seasonal IIV uptake in pregnancy during 2003–2006 inclusive (pre influenza A(H1N1)pdm09) was zero (0/414). In 2009, six IIVs were given from July to November, commencing two months after the first case of influenza was detected in the NT. During 2009–2011 inclusive (post-influenza A(H1N1)pdm09), uptake was 20/293 (7%). There were no data collected in 2007 and 2008 (Table 1).

Maternal characteristics, comorbidities and risk factors

The median maternal age of study participants at birth of their infant was 24 years for women who received IIV in pregnancy (range in years 13–41) and unvaccinated pregnant women (range in years 18–41); 31% were primiparous women and 53% of infants born were male. There were 281 women (42%) who presented for antenatal care in the first trimester, with 11 (4%) of these receiving IIV in pregnancy. The median gestation in weeks at first presentation for antenatal care was 13 (range 7–28) for women who received IIV in pregnancy and 16 (range 0–40) for unvaccinated pregnant women. Overall, 22% of multiparous women had a prior history of a poor obstetric outcome (either preterm birth, stillbirth or neonatal death) with six (4%) of these having received IIV in pregnancy. Other differences in maternal demographics, comorbidities and risk factors between women who received IIV in pregnancy are shown in Table 2.

Birth outcomes

Low uptake of IIV during pregnancy limited the capacity for meaningful comparisons of birth outcomes between unvaccinated women (the referent group) and the small number of women who were vaccinated in pregnancy. The median gestational age at birth of the infant was 38 weeks (range 21–42 weeks) for both the unvaccinated and vaccinated pregnant women,

Figure 1: Study participants from 1+1 Healthy Start study, by IIV vaccination status, Northern Territory, Australia, 2003–2012.

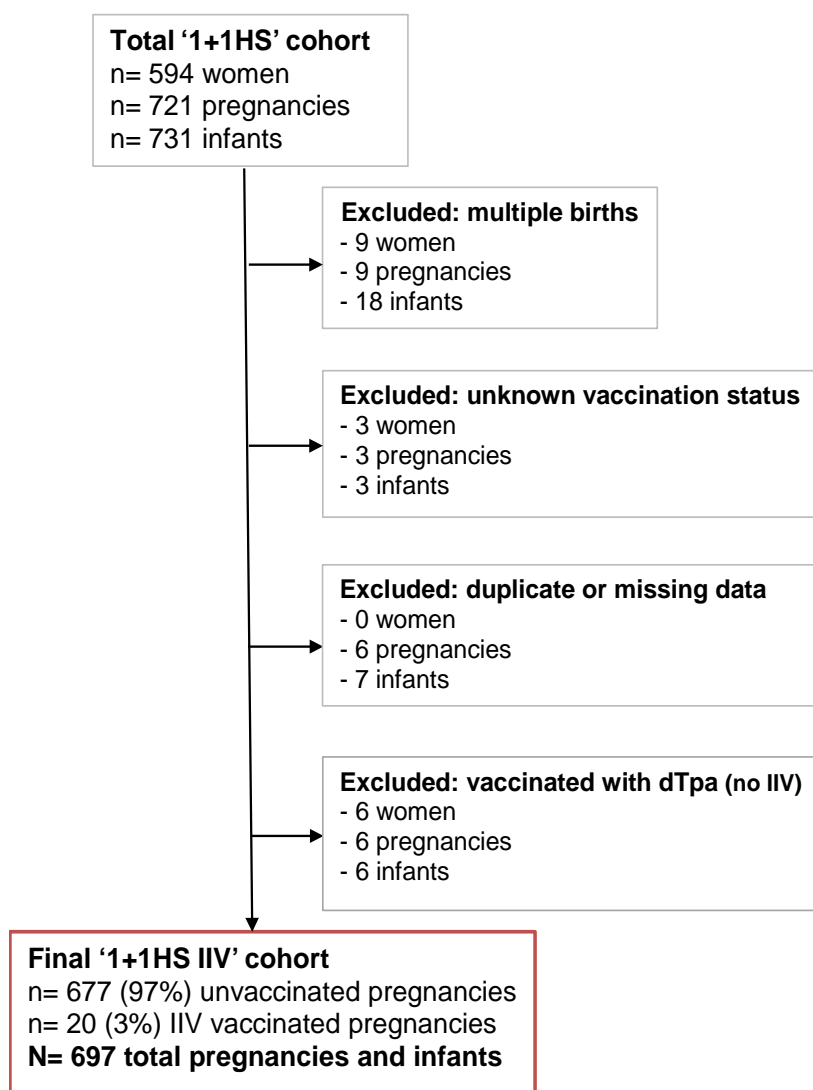


Table 1: IIV uptake pre- and post-influenza A(H1N1)pdm09 in 1+1HS study participants, Northern Territory, Australia, 2003–2011.

Year of birth	Number of births	N vaccinated with IIV in pregnancy	%
2003	1	0/1	(0%)
2004	122	0/122	(0%)
2005	142	0/142	(0%)
2006	139	0/139	(0%)
2007	Data not collected	n/a	
2008	Data not collected	n/a	
2009	44	6/44	(14%)
2010	153	1/153	(<1%)
2011	96	13/96	(14%)
Total	697	20/697	(3%)

Table 2: Maternal characteristics, comorbidities and risk factors of 1+IHS study participants, and percentage who received IIV in pregnancy, Northern Territory, Australia, 2003–2012.

Characteristics	Total n (%)	Vaccinated ^a influenza n (%)
Twin pregnancy	9/594 (2%)	0/9 (0%)
Parity (primiparous)	217/697 (31%)	5/217 (2%)
Antenatal care 1st trimester (Y/N) ^b	281/697 (42%)	11/281 (4%)
Smoking in pregnancy when recorded, (Yes) at 36wks	113/199 (57%)	6/113 (5%)
Previous poor obstetric outcome^c	152/697 (22%)	6/152 (4%)
Rheumatic heart disease	41/697 (6%)	3/41 (7%)
Cardiac condition	62/697 (9%)	1/62 (2%)
Diabetes^d	46/697 (7%)	2/46 (4%)
Renal disease	20/697 (3%)	0/20 (0%)
Asthma	9/697 (1%)	0/9 (0%)
Maternal anaemia	414/697 (59%)	13/414 (3%)
Pregnancy complication^e	374/697 (54%)	11/374 (3%)

Note: denominators differ due to missing data.

a number n (%) who received IIV in pregnancy that had comorbidity/risk factor

b Self-reported response at 1st antenatal visit

c Includes previous history of preterm birth, stillbirth, neonatal death (in multiparous women)

d Includes type 1, type 2 and gestational diabetes

e Includes threatened preterm labour, preterm rupture of membranes, antepartum haemorrhage, placental abruption, placenta praevia, UTI, STI, gestational hypertension, pre-eclampsia

with a small and neither clinically relevant or statistically significant difference in mean birth-weights (3,001 g vs 3,175 g [95%CI -467 g, 119 g, $p=0.24$]). Proportions of preterm births and LBW were similar between the unvaccinated and vaccinated group (Table 3), though there were proportionally more than three times as many infants born SGA in unvaccinated pregnancies, 17% (111/660), compared to 5% (1/19) of IIV vaccinated pregnancies. Our time-dependent analysis found no evidence of an increased risk of preterm births, LBW or SGA infants when comparing women who received an IIV in pregnancy with unvaccinated pregnancies (Table 3). Adjusted HRs were not conducted due to insufficient numbers of vaccinated women for the model to support adjustment on multiple factors.

Discussion

Despite a nationally-funded seasonal IIV program targeting Aboriginal pregnant women being recommended since 2000, only 3% of the Aboriginal women in our study received an IIV vaccination during their pregnancy during 2003–2006 and 2009–2011. This very low coverage was particularly disconcerting given our study participants were women living in a remote setting with high rates of poverty and markedly high rates of smoking, comorbidities, birthing at a younger age, and pregnancy, birth and postnatal complications, similarly reported in remote-living Aboriginal women from the NT.^{25,26} Aboriginal women continue to incur significantly more adverse perinatal outcomes compared to other Australian women, particularly stillbirths, preterm births, SGA and LBW infants.^{25,27} These infants experience higher rates of morbidity and mortality and are more

Table 3: Cox proportional-hazard ratios for birth outcomes in I+IHS study participants, Northern Territory, Australia, 2003–2011.

Birth outcome	Unvaccinated Referent group 677/697	% (97%)	Vaccinated ^a Influenza 20/697	%(3%)	HR ^b (95%CI)
Gestation ^c (range) differences (95% CI)	38wks (21–42 wks)		38 wks (29 – 41 wks); 0 wks (-0.9, 1.39 wks)		
Birthweight ^d (range) differences (95% CI)	3001g (400 g – 5080 g)		3175 g (1371 g – 4715 g); +174 g (-468 g, 118 g)		
Preterm birth (<37 completed weeks)	126/677	(19%)	4/20	(20%)	1.35 (0.50, 3.67)
Low birthweight (<2500 g)	113/677	(17%)	4/20	(20%)	1.41 (0.52, 3.83)
Small for gestational age (<10th percentile)	111/660	(17%)	1/19	(5%)	0.28 (0.04, 2.02)

Note: denominators differ due to missing data.

a Results compared to referent (unvaccinated) group

b Hazard ratio: results are compared to referent (unvaccinated) group

c Median gestation at birth of infant

d Mean infant birthweight

susceptible to vaccine-preventable infections compared to infants born at term.^{25,28} The long-term sequelae for Aboriginal infants who are born preterm or LBW comprises substantially higher rates of chronic diseases and hospitalisations compared to non-Aboriginal adults.^{25,29}

The first NT case of influenza A(H1N1)pdm09 was detected on 29 May 2009.²⁹ Coverage of IIV uptake in pregnancy was 0% in a pre influenza A(H1N1)pdm09 era (<2009). We expected uptake to be substantially higher than observed, and saw no evidence of improved or sustained vaccination coverage after a small increase during the pandemic (14%) and post pandemic (14%). It is not possible to determine whether this was a failure to report, under-ascertainment or refusal of vaccination, however similar studies have also reported low IIV uptake in pregnant Aboriginal women.³⁰ Further, an existing vaccination record from the NTIR was detected for >98% of the participants in our study, and immunisation coverage is known to be high among Aboriginal infants from the NT.³¹ One study nested within a RCT examined pre- and post-influenza A(H1N1)pdm09 IIV uptake in different Aboriginal communities in the NT over a similar time period (2006–2011).³⁰ This study found very low rates of seasonal IIV uptake (~4% verified) in pregnant Aboriginal women in a pre-influenza A(H1N1)pdm09 period (n=3/71), with verified coverage increasing to ~42% (n=28/67) in the intra-influenza A(H1N1)pdm09 period (2009–2010). Participant numbers for that study were small (N=138), with a relatively higher level of education and less high-risk factors compared to remote-living Aboriginal women from the NT.²⁶ A NT bulletin showed IIV uptake in Aboriginal pregnant women during 2013 was ~30% (n=585/1,930) for those who birthed at RDH,³² which is where our study population birthed. Whilst this shows a substantial increase in IIV uptake in pregnancy for Aboriginal women, the breakdown of remote- and very-remote-living status was not reported, therefore uptake of IIV in pregnancy is potentially not generalisable for the whole Aboriginal population who live in the Top End, and potentially an artefact of healthy, urban and outer-regional-living Aboriginal

pregnant women accessing antenatal health care programs. A small survey in 2017 from Western Australia (WA) reported 37% (n=35/94) of Aboriginal women with a known vaccination status received an IIV in pregnancy.³³ The women in the WA study were largely metropolitan/urban living, and it is unclear what proportion, if any, were remote-and very remote-living. Maternal demographic characteristics, comorbidities, risk factors and adverse birth outcomes were not reported in the WA survey.

Australian literature has demonstrated that advice on maternal vaccination from a pregnant woman's healthcare provider is the key influencer of vaccination uptake in pregnancy,¹⁷ and that if given the opportunity, Aboriginal women are accepting of IIV in pregnancy,³³ particularly if community consultation and engagement with local communities is a priority.³⁴ Providing evidence of IIV uptake, safety and effectiveness in pregnancy in a consistent, appropriate and culturally acceptable way for Aboriginal women and their families is also essential.³⁵ Providing local support of maternal vaccination programs to antenatal healthcare workers may be critical in order to give remote-living pregnant Aboriginal women an informed, positive recommendation regarding maternal vaccination.

The 2017 Aboriginal and Torres Strait Islander Health Performance Framework report of the NT³⁶ highlighted an important aim was to map the health needs of remote Aboriginal women and infants to the health services available, in order to address low birthweight, smoking during pregnancy and low antenatal care attendance. Addressing the high burden of respiratory illness in pregnancy, in women of childbearing age, and in young infants is also warranted in this population. Acknowledging the poor uptake of IIV we observed in our study, increasing IIV coverage in pregnancy would be a step forward, provided safety and effectiveness can be demonstrated.

The international literature on the safety of IIV in pregnancy are encouraging,^{37,38} but there are persistent gaps in the evidence for high-risk

populations, such as remote-living Indigenous peoples, that need to be addressed. Data are lacking on the safety of vaccination in the first trimester of pregnancy, and on safety endpoints such as miscarriage, preterm births, stillbirths, LBW and SGA infants. One Australian study published in 2018 found no increased risk in preterm births, low birthweight or SGA infants in pregnant women who received a seasonal IIV compared to unvaccinated pregnant women,³⁹ however only 3% of this national cohort (N=8,827 mother-infant pairs) were Aboriginal women. Prior to 2015, analyses were largely limited to specific vaccines used during the influenza A(H1N1) pandemic,⁴⁰ and observational studies used in a meta-analysis³⁸ were non-Indigenous women living in well-resourced populations of North America and Europe.

Strengths and limitations

A strength of this study lies in the rich, rigorous data collection methodologies and the ability to ascertain maternal vaccination status for all study participants. Our sample size of 697 pregnancies among 582 remote-living Aboriginal women is larger than other available studies, and through data linkage rather than self-report, we were able to establish seasonal IIV uptake based on confirmed dates of vaccination. Data linkage also enabled us to improve the internal validity of the study sample. We were able to retrieve missing maternal and infant data, enabling us to identify duplicate entries and to correct illogical dates of maternal and infant births. Our small numbers of vaccinated pregnancies were unexpected and as such, are a limitation, as was the inability to report on women who suffered miscarriages <20 weeks gestation. We did however, reduce the risk of introducing immortal time bias by applying the recommended methodology for conducting time-dependent analyses.

There are currently no programs to systematically monitor the uptake, safety and effectiveness of IIV in pregnancy, so it is difficult to determine where the procedural gaps exist for remote-living Aboriginal pregnant women of the NT. Until such programs are in place, well-

conducted observational studies and data linkage studies remain important, particularly for planning and in preparation for future influenza pandemics.

Conclusion

In Australia, an operational period of a nationally recommended seasonal IIV has been in place for almost 20 years. Despite the funded IIV program targeting pregnant Aboriginal women, vaccine uptake remained <4% in our participants from remote and very remote communities in the NT across 2003–2006 and 2009–2011. Reasons for this policy failure during this time period are unknown, with further research needed. Providing evidence of the safety and effectiveness of IIV in pregnancy may contribute to the willingness of women and health care providers to implement this policy.

Declarations

Ethics approval and consent to participate

This project was approved by the Menzies School of Health Research Human Research Ethics Committee (reference number 2016-/2710) and the Northern Territory Government Department of Health (project number 2016-0377).

Conflict of interest

The authors declare that they have no competing interests.

Funding

The 1+1 Healthy Start to Life study was funded by a National Health and Medical Research Council and NT Government Research and Innovation Board Project Grant (number: 422503). LMCh was supported by an Australian Postgraduate Award scholarship provided by Charles Darwin University of the Northern Territory and an Enhanced Living scholarship provided by Menzies School of Health Research as part of the Doctor of Philosophy (PhD) program.

Authors' contributions

LMcH cleaned and analysed the linked NTIR data and 1+1HS data, calculated influenza notification rates and wrote all drafts of the manuscript. SK contributed to the overall supervision of the development of the paper. SK and YG were investigators on the 1+1HS project. LMcH, SK and YG contributed substantially to the preparation of the data for analysis. SK contributed to data collection. RMA contributed to all drafts of the manuscript, data analysis, influenza notification rates and cross checking results. RW, TS and MJB contributed to the methods, interpretation of results and editing of manuscripts. All authors contributed to and approved the final manuscript. All authors attest they meet the ICMJE criteria for authorship.

Acknowledgements

We would like to acknowledge the chief investigator team from the original '1+1HS' study, in particular; Professor Lesley Barclay as lead CIA, Dr Sarah Bar Zeev and Dr Cath Josif for data collection and analysis, and Dr Karen Dempsey for assistance with data linkage with the NTIR.

Author details

Ms Lisa McHugh¹
Dr Michael J Binks²
Dr Yu Gao³
Prof Ross M Andrews⁴
Prof Robert S Ware⁵
Dr Tom Snelling⁶
Prof Sue Kildea⁷

1. PhD scholar, Menzies School of Health Research, Charles Darwin University, Tiwi, Northern Territory, Australia.
2. Senior Research Fellow, Menzies School of Health Research, Charles Darwin University, Tiwi, Northern Territory, Australia.
3. Senior Research Fellow, Mater Midwifery Research Unit – University of Queensland, Women's Health and Newborn Services

(Maternity) Mater Health Service; School of Nursing, Midwifery and Social Work, University of Queensland, Brisbane, Queensland, Australia.

4. Senior Epidemiologist, Menzies School of Health Research, Charles Darwin University, Tiwi, Northern Territory, Australia. Head of Master of Philosophy in Applied Epidemiology Program, National Centre for Epidemiology & Population Health, Australian National University, Canberra, Australian Capital Territory, Australia.
5. Senior Biostatistician, Menzies Health Institute Queensland, Griffith University, Brisbane, Queensland, Australia.
6. Head, Infectious Disease Implementation Research, Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia; Perth Children's Hospital, Perth, Western Australia, Australia; Curtin University, School of Public Health, Perth, Western Australia, Australia.
7. Director, Mater Research Institute – University of Queensland, Women's Health and Newborn Services (Maternity) Mater Health Service; School of Nursing, Midwifery and Social Work, University of Queensland, Brisbane, Queensland, Australia

Corresponding author

Dr Lisa McHugh
Menzies School of Health Research/Charles Darwin University.
Level 1,147 Wharf Street Spring Hill
Brisbane QLD, 4000.
Telephone: +61 7 418 200 553.
Email: lisa.mchugh@menzies.edu.au

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