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'Links2HealthierBubs' cohort study: protocol for a record linkage study on the safety, uptake and effectiveness of influenza and pertussis vaccines among pregnant Australian women

Mohinder Sarna,[1] Ross Andrews,[2,3] Hannah Moore,[4,5] Michael J Binks,[6] Lisa McHugh,[7] Gavin F Pereira,[1] Christopher C Blyth,[8,9] Paul Van Buynder,[10] Karin Lust,[11] Paul Effler,[12] Stephen B Lambert,[13] Saad B Omer,[14] Donna B Mak,[15,16] Thomas Snelling,[17,18,19,20] Heather A D'Antoine,[21] Peter McIntyre,[22] Nicholas de Klerk,[23,24] Damien Foo,[25] Annette K Regan[25,26,27]

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For numbered affiliations see end of article.

Correspondence to
Dr Annette K Regan;
Annette.Regan@curtin.edu.au

ABSTRACT

Introduction Pregnant women and infants are at risk of severe influenza and pertussis infection. Inactivated influenza vaccine (IIV) and diphtheria-tetanus-acellular pertussis vaccine (dTpa) are recommended during pregnancy to protect both mothers and infants. In Australia, uptake is not routinely monitored but coverage appears sub-optimal. Evidence on the safety of combined antenatal IIV and dTpa is fragmented or deficient, and there remain knowledge gaps of population-level vaccine effectiveness. We aim to establish a large, population-based, multi-jurisdictional cohort of mother-infant pairs to measure the uptake, safety and effectiveness of antenatal IIV and dTpa vaccines in three Australian jurisdictions. This is a first step toward assessing the impact of antenatal vaccination programmes in Australia, which can then inform government policy with respect to future strategies in national vaccination programmes.

Methods and analysis 'Links2HealthierBubs' is an observational, population-based, retrospective cohort study established through probabilistic record linkage of administrative health data. The cohort includes births between 2012 and 2017 (~607 605 mother-infant pairs) in jurisdictions with population-level antenatal vaccination and health outcome data (Western Australia, Queensland and the Northern Territory). Perinatal data will be the reference frame to identify the cohort. Jurisdictional vaccination registers will identify antenatal vaccination status and the gestational timing of vaccination. Information on maternal, fetal and child health outcomes will be obtained from hospitalisation and emergency department records, notifiable diseases databases, developmental anomalies databases, birth and mortality registers.

Ethics and dissemination Ethical approval was obtained from the Western Australian Department of Health, Curtin University, the Menzies School of Health Research, the Royal Brisbane and Women's Hospital, and the West Australian Aboriginal Health Ethics Committees. Research findings will be disseminated in peer-reviewed journals, at scientific meetings, and may be incorporated into communication materials for public health agencies and the public.

Strengths and limitations of this study

- Record linkage allows the generation of a large, rich population-based dataset from multiple sources at low cost.
- Linked data from three jurisdictions will establish a cohort with sufficient sample size to enable the examination of uncommon or rare outcomes (eg, neonatal mortality), the evaluation of antenatal vaccines among subgroup populations (eg, infants with risk factors such as preterm infants, Aboriginal and/or Torres Strait Islander peoples), and allows follow-up of mother-infant pairs in the cohort over an extended period of time.
- Inclusion of a geographically and socioeconomically diverse, population-based sample will help to minimise selection bias in the cohort.
- Analytic techniques will be employed to minimise potential bias from differential health-seeking behaviour of vaccinated women.
- As a retrospective, observational cohort study using linked administrative data, vaccination cannot be randomly assigned; however, it allows whole-of-population assessment and maximises follow-up of the cohort.

INTRODUCTION

Pregnant women, as a result of their changed immunological status, are particularly susceptible to severe infection. Data from studies conducted during influenza pandemics have shown pregnant women to be at elevated risk of severe influenza infection and its complications.[1 2] Furthermore, the risk of hospitalisation from influenza or pneumonia increases progressively throughout the pregnancy.[3 4] Deaths among pregnant women and perinatal mortality in infants born to infected

women during the 2009 H1N1 influenza pandemic highlighted the disease risk.[5]

Respiratory infections during critical periods of lung development and immune maturation are one of the most common causes of death in early infancy.[6] Infants aged 1–5 months, an age when they are ineligible for influenza vaccine, have the highest rates of influenza.[7] In Australia, hospitalisation rates of acute lower respiratory infection among Aboriginal and/or Torres Strait Islander children are nearly six times that of non-Aboriginal children.[8] Influenza and pertussis infections account for one in every four of these hospital admissions.[9]

In the absence of a licensed and effective vaccine for newborns,[5] influenza and pertussis vaccination during pregnancy has been recommended as a means to safeguard newborns during their first few months of life. Randomised controlled trials suggest that maternal immunisation against influenza prevents infection in both the mother and their infant.[10 11] Data from the USA and the UK have shown that vaccination during pregnancy can reduce influenza by 71% and pertussis by 91% in young infants.[12 13] In 2012, the WHO released a position paper on influenza vaccination recommending that pregnant women should have the highest priority for countries considering expansion of their seasonal influenza vaccination programme.[14]

Inactivated influenza vaccine (IIV) in pregnancy has been a long-standing policy recommendation in Australia[15] and is offered free of charge funded by the government. Following the success of maternal vaccination to prevent pertussis in early infancy in the UK,[12] low dose diphtheria-tetanus-acellular pertussis vaccine (dTpa) became the second vaccine recommended routinely during pregnancy in Australia in April 2015 and funded by state and national immunisation programmes.[15]

Despite the importance to health and significant programmatic costs, Australia currently lacks a coordinated approach to maternal vaccination. Uptake of routinely recommended vaccines in pregnancy is suboptimal and not systematically monitored.[16–19] Pregnancy status is not collected as part of the national whole-of-life immunisation register, the Australian Immunisation Register (AIR), making antenatal immunisation impossible to measure using AIR alone. In Western Australia (WA), Queensland (QLD) and the Northern Territory (NT), antenatal immunisation status is routinely collected via either state-based immunisation registers or through perinatal data collections. These collections offer the opportunity to conduct high-quality, population-level evaluation of the health effects of antenatal vaccination programmes in these jurisdictions.

The 'Links2HealthierBubs' project is a vital first step toward national evaluation of antenatal vaccination in Australia. Identification of factors associated with under-immunisation will enable more targeted vaccine promotion. Study results will inform antenatal vaccine programmes and Australian governmental policy. Improved antenatal vaccination programme monitoring and delivery is essential in reducing influenza and pertussis-related illness in pregnant women and infants. With the establishment of the AIR in 2016, the analyses performed here could be applied to a national dataset through AIR linkage in future.

AIMS

The 'Links2HealthierBubs' study combines health information from multiple sources at an individual-level designed to improve our understanding of the risks and benefits of antenatal immunisation. We will use existing record linkage infrastructure to generate a large cohort of pregnancies and establish a population-based mother-infant cohort sufficiently powered to estimate rare or uncommon outcomes that have not been possible with individual state-based data to date to address three aims (figure 1).

Aim 1: Measure the effectiveness of IIV and dTpa against laboratory-confirmed infections in pregnant women and their infants

Although this is a rapidly growing area of research, there remain several gaps in our knowledge of antenatal vaccination (table 1). First, limited data have been published evaluating effectiveness against disease severity (such as hospitalisation).[20–23] Few studies have evaluated the influence of gestational timing of influenza vaccine administration on disease prevention in mothers and infants,[24–26] or the safety and effectiveness of repeat doses, particularly with regard to the currently recommended pertussis vaccine that also contain tetanus and diphtheria. The interval between influenza vaccination and birth is associated with changes in the level of protective antibody present in newborns.[27] Longer intervals between influenza vaccination and delivery, as well as intervals too close to delivery, have been shown to result in lower cord-blood titres in infants, potentially reducing vaccine effectiveness.[27] Although known to influence transplacental antibody transfer, few studies have measured the impact of these factors on clinical end-points, such as hospitalisation of mothers and infants with respiratory illness. Second, few studies have evaluated the role that antenatal vaccination may have on the performance of childhood vaccines. Immunological evidence of 'blunting' of infant responses to pertussis vaccines due to interference by maternal antibodies has been observed.[28–30] Finally, despite the disproportionate burden of respiratory infections among Aboriginal and/or Torres Strait Islander infants, the effectiveness of vaccination in pregnancy for this population group has not yet been measured in Australia. Such data are important for informing future prevention programmes.

This cohort study aims to address these gaps by:

1. Measuring the effectiveness of antenatal IIV and dTpa vaccines on laboratory-confirmed influenza and pertussis infections among mothers and their infants in the first 6 months of life, with subgroup analyses by: (1) trimester of vaccination and (2) among infants with risk factors for infection (eg, preterm birth, small for

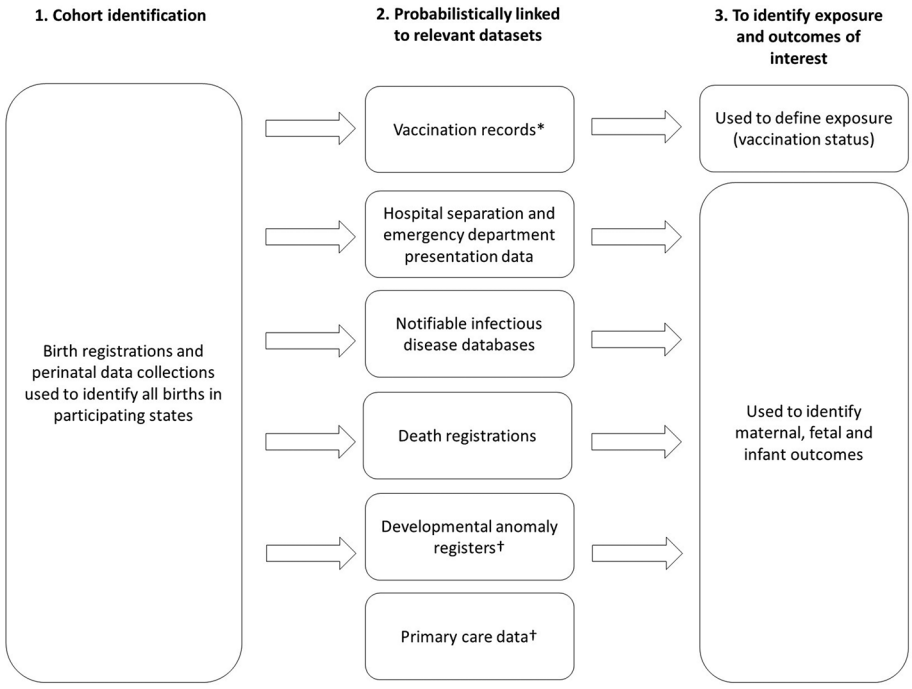

Figure 1 Establishment of study cohort using record linkage: Western Australia (WA), Queensland (QLD), and the Northern Territory (NT), 2012–2017. *Vaccination records were obtained from state-wide registers in each participating jurisdiction; in WA, this register was restricted to pregnant women; in the NT and QLD, these registers included all vaccinations administered to individuals in the state. †Developmental anomaly data available in WA and QLD; primary care data available in NT only.

gestational age (SGA) and Aboriginal and/or Torres Strait Islander infants).
2. Assessing the impact of antenatal pertussis vaccination on the effectiveness of other childhood vaccines routinely offered on the immunisation schedule by comparing disease notifications in the first 6 months of life in fully vaccinated infants of mothers who did and did not receive maternal pertussis vaccination.

Aim 2: Assess the safety of IIV and dTpa given antenatally in mothers and infants

A number of studies, including several systematic reviews,[31–33] have found no evidence that IIV or dTpa adversely impacts the fetus; however, there is a dearth of postimplementation data evaluating the safety of combined administration of IIV and dTpa during pregnancy in terms of adverse events for mothers and differences in birth outcomes following IIV and dTpa vaccination during pregnancy. Large, comprehensive datasets are required to compare outcomes such as preterm birth, birth weight, SGA, birth defects, stillbirth and neonatal death (<1 month of age) between women who have received IIV and dTpa during pregnancy and unvaccinated pregnant women.[16] Furthermore, few studies have evaluated the potential health impact of antenatal IIV and dTpa administration on the health of infants beyond 6 months of age.[22 34 35]

This cohort study will assess the safety of IIV and dTpa vaccination during pregnancy on:

1. Health outcomes in the perinatal period and early childhood (up to 5 years), including (but not restricted to) preterm birth, birth weight, SGA, birth defects and cerebral palsy, stillbirth, and neonatal death (<1 month of age).
2. Maternal health, including severe adverse events resulting in hospitalisation or admission to the intensive care unit (ICU).

Aim 3: Evaluate antenatal vaccine coverage in Australia

A number of studies have identified predictors of antenatal vaccination, including maternal age, pre-existing medical conditions and socioeconomic status.[36] As vaccine coverage in pregnant women is not routinely monitored in Australia, the influence of other demographic and health factors, including geographic variation, is not well understood. Limited data are available by remoteness, geographic area and level of socioeconomic deprivation.[17 37] Moreover, uptake in Aboriginal and/or Torres Strait Islander mothers is poorly defined.[17 38] Disparities between Aboriginal and non-Aboriginal children in the childhood immunisation schedule have shown lower vaccine coverage in the first year of life in Aboriginal and/or Torres Strait Islander children compared with non-Aboriginal infants as a result of greater delay in the receipt of vaccines,[39] although these trends may not be reflected in the uptake of maternal vaccines.

To address this, the 'Links2HealthierBubs' cohort study aims to:

1. Identify geographic, sociodemographic (including by Aboriginal status) and other risk factors associated with uptake of IIV and/or dTpa vaccine during pregnancy.
2. Evaluate trends in vaccine uptake among pregnant women in Australia.

Table 1 Summary of project aims and knowledge gaps addressed by the Links2HealthierBubs cohort study

Knowledge gap	Component of the Study
AIM 1: Vaccine effectiveness	
Few studies have measured the effectiveness of antenatal influenza and pertussis vaccines in preventing maternal and infant laboratory-confirmed infection	Measure effectiveness of antenatal IIV and dTpa on laboratory-confirmed infection in mothers and in the first 6 months of life in infants
There is limited evidence evaluating whether antenatal vaccination protects against severe disease in mothers and infants	Measure effectiveness against hospitalised infection and infections required admission to intensive care unit
Few studies have been sufficiently powered to assess the potential influence of gestational timing of vaccination on vaccine effectiveness	Assess the potential influence of trimester of the effectiveness of vaccination
No studies have measured the effectiveness of antenatal vaccination among infants with risk factors for severe disease	Measure effectiveness among infants with risk factors for infection (ie, preterm infants, Indigenous infants, infants with developmental anomalies)
Despite clinical evidence suggesting the presence of maternal antibodies may inhibit infant response to primary pertussis vaccination, population-level data evaluating this are limited	Assess the potential influence of maternal pertussis immunisation on childhood vaccine effectiveness
AIM 2: Vaccine safety	
Limited data exist evaluating the impact of concomitant administration of influenza and pertussis vaccines	Assess the safety of IIV and dTpa on maternal and infant health
Few studies have been sufficiently powered to assess safety end-points by trimester of vaccination	Consider the trimester of vaccination in the assessment of safety end-points for IIV and dTpa
Few studies have evaluated outcome measures associated with antenatal vaccination beyond 6 months of age	Assess the impact of IIV and dTpa in terms of neonatal, infant and child health up to 5 years of age
AIM 3: Vaccine coverage	
There are limited data on antenatal uptake of vaccines across multiple jurisdictions in Australia including sub-analyses based on sociodemographic factors	Estimate the uptake of IIV and dTpa; IIV only and dTpa only in the three jurisdictions and special population groups (ie, low-income, remote, CALD, by maternal country of birth)
Few longitudinal studies exist which have evaluated trends in vaccine coverage in multiple Australian jurisdictions	Assess trends in vaccine coverage in multiple Australian jurisdictions using population-level data for both IIV and dTpa
No study in Australia has assessed the importance of residence or performed spatial analyses in relation to maternal vaccination	Identify whether there are geographic, regional, and other sociodemographic predictors of vaccination during pregnancy

CALD: culturally and linguistically diverse; dTpa; diphtheria-tetanus-acellular pertussis vaccine; IIV; inactivated influenza vaccine.

METHODS AND ANALYSIS

Study design and setting

'Links2HealthierBubs' is an observational, population-based cohort study using retrospective data collected in administrative health registers from three jurisdictions of Australia (WA, QLD and the NT) where antenatal vaccination data are currently available at a population-level and can be linked to other health information. Together these three jurisdictions account for 33% of Australia's annual birth cohort, of which Aboriginal and/or Torres Strait Islander births comprise 8.0%, 8.9% and 35.8% of total births in each jurisdiction, respectively (table 2).[40] Infants will be identified through jurisdictional birth or perinatal registers. All infants born between 1 January 2012 and 31 December 2017 and their mothers will be included as participants in the study. This time period was selected as it includes a baseline period when IIV was available and routinely recommended,[18] but prior to the introduction of funded dTpa (2012–2014) and an intervention period following the introduction of dTpa in jurisdictions (2015–2017). Within each jurisdiction, the cohort of mothers and infants will be linked to vaccination and health data, including emergency department presentation, hospital separations, birth records, notifiable diseases register and mortality data (table 2). With the exception of antenatal vaccination registers, these registers are nationally mandated and provide data to the Australian Institute of Health and Welfare (AIHW), and the quality of data is considered to be high.[41] Data from developmental anomalies registries and primary care will also be obtained in jurisdictions where these are available.

Exposure measurement

Individual-level data on antenatal vaccination will be obtained from jurisdictional perinatal data collections (QLD: 2015–2017, WA: 2016–2017) and immunisation registries (NT: 2012–2017, QLD: 2012–2017, WA: 2012–2016). These data collections have state-wide coverage of

Table 2 Population profile, estimated vaccine coverage and data sources, by participating jurisdiction

	Western Australia	Queensland	Northern Territory
Population profile			
Total number of births*	208 608	375 001	23 996
Number of births to Aboriginal and/or Torres Strait Islander women	16 748 (8.0%)	33 334 (8.9%)	8592 (35.8%)
Median age of mothers (years)	30.6	30.1	29.0
Estimated maternal vaccine coverage†			
Influenza	31%	31%	31%
Pertussis	17%	17%	17%
Both vaccines	9%	9%	9%
Data sources			
Exposure			
Vaccination	WA Antenatal Vaccination Database‡	Vaccination Information and Vaccination Administration System	NT Immunisation Register
Outcomes			
Perinatal outcomes	WA Midwives Notification System, WA Birth Registrations, WA Register of Developmental Anomalies	QLD Perinatal Data Collection, Registrar General Births	NT Perinatal Trends, NT Birth Registry
Respiratory infections	WA Notifiable Infectious Disease Database, WA Hospital Morbidity Data Collection, WA Emergency Department Data Collection	QLD Notifiable Conditions, QLD Hospital Admitted Patient Data Collection, QLD Emergency Departments	NT, Notifiable Conditions, NT Inpatient Activity, Hospital, NT Emergency, NT Primary Healthcare Collection
Other childhood conditions	WA Hospital Morbidity Data Collection, WA Emergency Department Data Collection, WA Register of Developmental Anomalies	QLD Hospital Admitted Patient Data Collection, Emergency Department Data Collection, Congenital Anomalies Linked File	NT Inpatient Activity, Hospital, NT Emergency, NT Primary Healthcare Collection
Deaths	WA Death Registry	Registrar General Deaths	NT Deaths Registry

*Estimated for the years 2012–2017; Data sources: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3301.02016?OpenDocument.
†R Andrews, personal communication based on FluMum study unpublished data, 2012–2015.
‡Data available for mothers only (no childhood immunisation data available).
NT, Northern Territory; QLD, Queensland; WA, Western Australia.

pregnant women and will be used to provide information on IIV and dTpa vaccines administered during pregnancy and either (1) the gestation of the woman at vaccination, or (2) the date of vaccination, which will be used together with gestational age and date of birth to extrapolate gestational age at time of vaccination.

In NT and QLD, where there are immunisation registers covering the study period, information on childhood vaccines will also be obtained, including the vaccine administered and the date of administration. Whole-of-life immunisation data were not available for linkage in WA.

Outcome measurement

Pregnancy and birth outcomes

Information on the pregnancy, labour and birth will be obtained from jurisdictional perinatal data collections, hospital separation and emergency department data. Such information will include complications diagnosed during pregnancy, episodes of care during pregnancy, onset of labour and the method of delivery. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes will be used to obtain conditions from hospital separation and emergency department data.

Health outcomes at birth include preterm birth (birth <37 weeks), low birth weight (<2500 g), SGA (lowest 10th percentile of birth weight for gestation) and stillbirth (fetal death ≥20 weeks). The variables needed to measure these outcomes have >95% accuracy.[42] Other available information will include date of birth, APGAR scores, measures of head circumference and body length, and days of specialised newborn care required.

Healthcare utilisation and severity of illness

Laboratory-confirmed influenza and pertussis infections in the first 6 months of life will be identified through the notifiable diseases databases in each jurisdiction, based on medical and laboratory notifications made to respective departments of health. The date of notification and laboratory testing result will be used to determine the age of the infant and gestation of mothers at the time of infection.

Hospital separations and emergency department data from each jurisdiction will be used to identify presentations and admissions to hospital for infants and children in the cohort. Length of stay in hospital, admission to ICU and requirement for mechanical ventilation will also be available from these records.

Access to the NT Primary Care Database will provide information on episodes of community clinic presentations for mothers and their children in the NT cohort, including reasons for and the date of the visit.

Mortality

We will use death registrations from all three jurisdictions to identify deaths occurring among mothers and infants in the cohort during the neonatal period. Death registrations provide the date and cause of death for participants in the cohort.

Developmental anomalies: WA and QLD

Developmental anomalies will be assessed using information in the WA Register of Developmental Anomalies (WARDA) and the Congenital Anomaly Linked File (CALF) register in QLD. These state-wide registers maintain all diagnosed developmental anomalies for children up to the age of 5 years, using the same classification categories.[43] Only the WARDA is legislated by WA state law. The WARDA and CALF registers include diagnostic information for up to 10 developmental anomalies, the former coded using the British Paediatric Association International Classification of Diseases version 9 (BPA-ICD-9), and the latter using the ICD-10-AM coding system.

Measurement of covariates and risk factors

Information on potential confounders and factors required for subgroup analysis will be obtained from jurisdictional perinatal data collections and birth registers. These data collections include information on the mother's residence at the time of delivery, which can be used to determine her geographical location and the proximity to immunisation services. The mother's residence will also be used to determine her socioeconomic level based on Socioeconomic Indexes for Areas, a collection of four indices developed by the Australian Bureau of Statistics. For this analysis, we will use the Index of Relative Advantage and Disadvantage at the area level of collector's district, the smallest level available for population-wide analyses.[44] The mother's Indigenous status will be determined based on the Indigenous status recorded in all available health records. As Indigenous status is not always accurately captured in health data collections in WA and QLD, an algorithm developed in WA which uses all available health records will be applied to make a determination of whether the mother is likely to be Indigenous.[45] Indigenous status is considered to be highly accurate (>99%) for mothers and infants in the NT, and is based on national best practice guidelines for data linkage activities relating to Aboriginal and Torres Strait Islander people, developed by the AIHW and methodology developed in the NT for defining Indigeneity.[46] The mother's medical history will be obtained using look-back through hospital separations data 1 year prior to conception, as well as medical information recorded in the perinatal data collection.

Record linkage

Individual information from each dataset will be linked using jurisdictional record linkage services. Record linkage uses identifiable demographic data to probabilistically link an individual's clinical data from different data repositories. Deidentified datasets with a unique linkage key for each individual will be provided to the researchers for analysis. In WA, the Data Linkage Branch of the Department of Health[47] will establish the study cohort and extract and link relevant data sources. In the NT, extraction and linkage will be led by SA-NT DataLink,[48] and in QLD by the Statistical Services Branch at QLD Health.[49]

Power calculation

Cohort data will be aggregated to permit pooled, multi-jurisdictional analyses. We anticipate the total cohort of ~607 605 mother-infant pairs from three jurisdictions will include ~208 608 pregnancies from WA, 375 001 from QLD and 23 996 from the NT (table 2).

The number of mother-infant pairs required for influenza and pertussis-related outcomes, and adverse fetal and neonatal outcomes, under consideration with different observed vaccine coverage (for α=0.05 and β=0.80) are listed in table 3. Based on the anticipated total cohort size and expected vaccine coverage, the overall study will be powered to detect at least 30% effectiveness against the majority of infection-related end-points, with the exception of ICU admission for influenza (45%). For most safety end-points, the anticipated cohort size will be powered to detect a 10% increase in the approximated relative risk for vaccinated compared with unvaccinated mothers and infants, with the exception of stillbirth (15%) and infant mortality (20%) (table 3).

Data analysis strategy

Using vaccination records, we will measure vaccination status and gestational timing of vaccination in the cohort. Among the ~607 605 women to be included in the study cohort, we anticipate ~30% will be vaccinated against influenza and <5% against pertussis during the 2012–2015 time period; ~35% will be vaccinated against influenza only, ~60% against pertussis only and ~30%

Table 3 Number of mother-infant pairs required to achieve 80% power with 5% probability of type I error

Aim	Outcome (estimated incidence)	Relative risk	Observed vaccine coverage				
			10%	15%	20%	25%	30%
1	Laboratory-confirmed influenza (1%)	1.30	105 370	74 827	59 975	51 472	46 216
	Laboratory-confirmed pertussis infection (0.5%)	1.30	211 930	150 494	120 630	103 528	92 959
	Hospitalised influenza (0.3%)	1.30	354 000	251 381	201 500	172 940	155 285
	Hospitalised pertussis (0.4%)	1.30	265 210	188 328	150 955	129 556	116 332
	Influenza-associated ICU admission (0.1%)	1.45	493 720	351 635	282 655	243 248	218 984
	Pertussis-associated ICU admission (0.2%)	1.30	531 600	377 495	302 590	259 700	233 191
2	Stillbirth (0.7%)	1.15	577 410	408 802	326 725	279 624	250 384
	Preterm birth (9%)	1.10	90 850	64 247	51 290	43 844	39 216
	Small-for-gestational age (10%)	1.10	80 830	57 160	45 630	39 008	34 889
	Birth defects (5%)	1.10	171 000	120 934	96 555	82 548	73 839
	Infant mortality (0.4%)	1.20	579 100	410 415	328 340	281 272	252 101

ICU, intensive care unit.

for both vaccines from 2015 onwards.[16] Three separate comparisons will be made: IIV-vaccinated versus unvaccinated, dTpa-vaccinated versus unvaccinated and IIV/dTpa-vaccinated versus unvaccinated. Cox proportional hazard models will be used to approximate the relative risk (hazard ratio, HR) of adverse birth outcomes in vaccinated and unvaccinated mothers and infants. For assessment of birth outcomes, these models will incorporate the timing of vaccination into exposure assessment in order to minimise immortal time bias, similar to previous analyses conducted.[50] Gestational/post-conceptional age will be the time axis. The interval between vaccination and birth will also be included as an interaction term in the model.

Vaccine effectiveness of antenatal IIV and dTpa vaccines on laboratory-confirmed influenza and pertussis infections among mothers and their infants will be calculated as 1-HR. To minimise confounding in the study results, we plan to consider inverse probability of treatment weighting and propensity score matching approaches into analyses, where appropriate. Propensity scores will be calculated which will estimate each mother's individual probability of vaccination. Stratified models will be used to estimate vaccine effectiveness for sub-groups (ie, by trimester of vaccination, Aboriginal and/or Torres Strait Islander infants, preterm infants).

Data management

To facilitate secure data-sharing and analysis of a pooled dataset across the three sites, information transfer between SA-NT DataLink, Curtin University, and the Menzies School of Health Research in Queensland will be facilitated through secure transfer using the SUFEX system using AES 128-bit encryption. Safety and security measures are in place at these locations (restricted staff access, password protection, firewall, virus spyware protection).

Patient and public involvement

As this is a retrospective study of deidentified, linked data, patients cannot be involved in the design, recruitment, or conduct of the study. Consumer and community input into the project will be regularly sought by the WA Healthy Pregnancies Reference Group at Curtin University. Research findings will be incorporated into communication materials for the community in participating jurisdictions.

ETHICS AND DISSEMINATION

In Australia, health legislation is state-based and protected by state-based privacy laws. Appropriate ethics committee approvals have been sought. As this research project involves or may impact on Aboriginal and/or Torres Strait Islander people, particularly in the NT, ethics approval has also been sought from state-based Aboriginal ethics committees. Approval has been granted from the Western Australian Department of Health (HREC 2016/56), Curtin University (HRE2017-0808), the Menzies School of Health Research (HREC 2018-3199), and the Royal Brisbane and Women's Hospital (HREC/2018/QRBW/47660) Human Research Ethics Committees, and the West Australian Aboriginal Health Ethics Committee (HREC 889). Approval from all data custodians has also been received.

Results will be disseminated to relevant stakeholders within each participating state and territory. Research findings will be published in peer-reviewed journals and presented at scientific meetings.

Author affiliations
[1]School of Public Health, Curtin University, Perth, Western Australia, Australia
[2]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia

[3]National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory, Australia
[4]School of Public Health, Curtin University, Bentley, Western Australia, Australia
[5]Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia
[6]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia
[7]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia
[8]Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia
[9]Perth Children's Hospital, Perth, Western Australia, Australia
[10]Griffith University, Southport, Queensland, Australia
[11]Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
[12]Communicable Disease Control Directorate, Department of Health Government of Western Australia, Perth, Western Australia, Australia
[13]Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia
[14]Rollins School of Public Health, Emory University, Atlanta, Georgia, United States of America
[15]Communicable Disease Control Directorate, Department of Health Government of Western Australia, Perth, Western Australia, Australia
[16]Notre Dame University, Perth, Western Australia, Australia
[17]Princess Margaret Hospital for Children, Perth, Western Australia, Australia
[18]Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, Perth, Western Australia, Australia
[19]School of Public Health, Curtin University, Bentley, Western Australia, Australia
[20]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia
[21]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia
[22]National Centre for Immunisation Research and Surveillance, Sydney, New South Wales, Australia
[23]Telethon Kids Institute, West Perth, Western Australia, Australia
[24]The University of Western Australia, Perth, Western Australia, Australia
[25]School of Public Health, Curtin University School of Public Health, Perth, Western Australia, Australia
[26]School of Public Health, Texas A&M University, College Station, Texas, United States of America
[27]Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, Perth, Western Australia, Australia

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Contributors Designed the study: AKR led development of the original proposal in collaboration with RMA, HCM, MJB, LM, GFP, CCB, PVB and KL. AKR, RMA, HCM, MJB, LM, GFP, CCB, PVB, KL contributed to the development of the common protocol and procedures. Coordination of the study: AKR, MS, MJB, RA, LM. Wrote the manuscript: MS and AKR wrote the first draft. MS, RA, HCM, MJB, LM, GFP, CCB, PVB, KL, PVE, SBL, SBO, DM, TS, HAD, PM, NdK, DF and AKR contributed to subsequent drafts, read and approved the final manuscript.

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